Module 2.7.4

Summary of Clinical Safety
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<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>AA/AH</td>
<td>African American/African Heritage</td>
</tr>
<tr>
<td>ABC</td>
<td>Abacavir</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AESI</td>
<td>Adverse events of special interest</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATV</td>
<td>Atazanavir</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the concentration-time curve</td>
</tr>
<tr>
<td>AUC(0-τ)</td>
<td>Area under the concentration-time curve over the dosing interval</td>
</tr>
<tr>
<td>BA</td>
<td>Bioavailability</td>
</tr>
<tr>
<td>BCRP</td>
<td>Breast cancer resistance protein</td>
</tr>
<tr>
<td>BE</td>
<td>Bioequivalence</td>
</tr>
<tr>
<td>BID</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BR</td>
<td>Background regimen</td>
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<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>Cτ</td>
<td>Trough concentration at the end of the dosing interval</td>
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<tr>
<td>c/mL</td>
<td>Copies per millilitre</td>
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<td>C0_avg</td>
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<td>DILI</td>
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<td>Evaluation of drug-induced serious hepatotoxicity</td>
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<td>Erythema multiforme</td>
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<td>Food and Drug Administration</td>
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<td>Emtricitabine</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastro oesophageal reflux disease</td>
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<td>GFR</td>
<td>Glomerular filtration rate</td>
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<td>GHO</td>
<td>Global heath outcomes</td>
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<td>GI</td>
<td>Gastrointestinal</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
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<td>Hepatitis B virus</td>
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<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HIV-1</td>
<td>Human immunodeficiency virus, type 1</td>
</tr>
<tr>
<td>HSR</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent data monitoring committee</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
</tr>
<tr>
<td>INI</td>
<td>Integrase inhibitor</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational product</td>
</tr>
<tr>
<td>IRIS</td>
<td>Immune reconstitution inflammatory syndrome</td>
</tr>
<tr>
<td>ISO</td>
<td>Integrated safety output</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>LMP</td>
<td>Last menstrual period</td>
</tr>
<tr>
<td>LPV</td>
<td>Lopinavir</td>
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<tr>
<td>LTFU</td>
<td>Lost to follow-up</td>
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<td>m (e.g., m2.4)</td>
<td>Module (e.g., Module 2.4)</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>mm³</td>
<td>Cubic millimetre</td>
</tr>
<tr>
<td>MRP</td>
<td>Multidrug resistance-associated protein</td>
</tr>
<tr>
<td>MVC</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>NHL</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>NIA</td>
<td>National Institute on Aging</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NSVT</td>
<td>Non-sustained ventricular tachycardia</td>
</tr>
<tr>
<td>OAT</td>
<td>Organic anion transporter</td>
</tr>
<tr>
<td>OBR</td>
<td>Optimized background regimen</td>
</tr>
<tr>
<td>OCEANS</td>
<td>Operating Company Event Accession and Notification</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>OI</td>
<td>Opportunistic infection</td>
</tr>
<tr>
<td>PAH</td>
<td>Para-aminohippurate</td>
</tr>
<tr>
<td>PBO</td>
<td>Placebo</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>PDVF</td>
<td>Protocol-defined virologic failure</td>
</tr>
<tr>
<td>Pgp</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PML</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>QTcB</td>
<td>Bazette’s corrected QT interval</td>
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<tr>
<td>QTcF</td>
<td>Fridericia’s corrected QT interval</td>
</tr>
<tr>
<td>RAG</td>
<td>Recombinase activating gene</td>
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<tr>
<td>RAL</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>RSI</td>
<td>Reference Safety Information</td>
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<tr>
<td>RTV</td>
<td>Ritonavir</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SAS</td>
<td>Statistical analysis software</td>
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<tr>
<td>SDAP</td>
<td>Summary Document Analysis Plan</td>
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<td>SJS</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>SOC</td>
<td>System organ class</td>
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<tr>
<td>TDAR</td>
<td>T cell-dependent antibody response</td>
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<tr>
<td>TDF</td>
<td>Tenofovir disoproxil</td>
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<tr>
<td>TdP</td>
<td>Torsades de Pointes</td>
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<tr>
<td>TEN</td>
<td>Toxic epidermal necrolysis</td>
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<tr>
<td>TPV</td>
<td>Tipranavir</td>
</tr>
<tr>
<td>TRDF</td>
<td>Treatment-related discontinuation equals failure</td>
</tr>
<tr>
<td>TTO</td>
<td>Time to onset</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Uridine diphosphate glucuronosyltransferase isozyme 1A1</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
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</table>

**Trademark Information**

**Trademarks of the ViiV Healthcare**

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<thead>
<tr>
<th>Trademark</th>
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<td>EPZICOM</td>
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**Trademarks not owned by ViiV Healthcare**

<table>
<thead>
<tr>
<th>Trademark</th>
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<tr>
<td>Atripla</td>
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<td>Naprosyn</td>
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<td>Truvada</td>
</tr>
<tr>
<td>Dianabol</td>
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<tr>
<td>Avelox</td>
</tr>
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</table>
1. **EXPOSURE TO THE DRUG**

1.1. **Overall Safety Evaluation Plan and Narratives of Safety Studies**

Dolutegravir (DTG, GSK1349572), a 2-metal-binding integrase inhibitor (INI), is a new chemical entity in development for the treatment of human immunodeficiency virus type-1 (HIV-1) infection, as part of combination antiretroviral therapy (ART). Dolutegravir is owned by ViiV Healthcare, who are working with GlaxoSmithKline (GSK) to develop the product.

The safety of DTG has been well characterized in a comprehensive battery of nonclinical studies [Module 2.4 (m2.4), Nonclinical Overview]. The overall nonclinical safety data are supportive of the clinical use of DTG in the treatment of ART-naïve and ART-experienced (INI-naïve) adults and children (≥12 to <18 years of age) at the recommended dose of 50 milligrams (mg) once daily, and at the recommended dose of 50 mg twice daily for ART-experienced (INI-resistant) adults.

The antiretroviral activity of DTG and safety profile in human subjects has been demonstrated in a broad spectrum of clinical trials conducted as part of the development program.

The proposed indication for this application is for the treatment of HIV infection (in combination with other approved antiretroviral agents) in the following populations:

- ART-naïve adults;
- ART-experienced (INI-naïve) adults;
- ART-experienced (INI-resistant) adults; and
- ART-naïve and ART-experienced INI-naïve children (≥12 to <18 years old, weighing ≥40 kilograms).

1.1.1. **Nonclinical Data Relevant to Human Safety**

The safety of DTG has been well characterized in a comprehensive battery of nonclinical studies [Module 2.4 (m2.4), Nonclinical Overview]. The overall nonclinical safety data are supportive of the clinical use of DTG in the treatment of ART-naïve and ART-experienced (INI-naïve) adults and children (≥12 to <18 years of age) at the recommended dose of 50 milligrams (mg) once daily, and at the recommended dose of 50 mg twice daily for ART-experienced (INI-resistant) adults.

The effect of daily treatment with high doses of DTG has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 39 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 32 and 1.2 times the 50 mg human clinical exposure based on AUC, respectively. Because GI intolerance is considered to be due to local drug administration, mg/kg or mg/m\(^2\) metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 30 times the human mg/kg equivalent dose (based on 50 kg human), and 10.5 times the human mg/m\(^2\) equivalent dose for a total daily clinical dose of 50 mg.
The overall nonclinical reproductive and developmental toxicity profile for DTG in rats and rabbits suggests that DTG is not teratogenic and has a low potential for fetal risk. DTG did not affect embryofetal development in rats or rabbits. DTG administration resulted in suppressed body weight gain and decreased food consumption during the lactation period in a pre- and postnatal development study in rat dams (F0) receiving 1000 mg/kg/day. Associated with the maternal toxicity, decreased body weights were noted in the offspring (F1) in the 1000 mg/kg group from pre-weaning until adolescence. There were no effects on pregnancy, parturition or nursing behavior. Due to the decreased body weights of the offspring observed at higher doses the NOAEL for postnatal development of the offspring (F1) was 50 mg/kg/day. At this dose the anticipated human exposure is approximately 25X or 18X a 50 mg once daily or BID dose, respectively. Based on the fact that effects on offspring body weights were noted at doses where maternal toxicity was observed, and the presence of considerable safety margins expected at the proposed clinical doses, there is minimal risk for adverse effects on postnatal development in offspring of mothers receiving DTG. In summary, there have been no demonstrable risks to the developing fetus exposed to DTG.

Of note, the exposure margins presented above for GI toxicity and reprotoxicity were recalculated after finalisation of the integrated summary of safety (ISS), therefore, these exposure margins should be reviewed instead of those presented in the ISS [see m5.3.5.3].

DTG showed no genotoxic risk as assessed in a standard battery of in vitro and in vivo genotoxicity studies. An assessment of the route of synthesis showed no impurities, intermediates, solvents or other agents that may suggest a genotoxic risk. Overall, there is not believed to be a genotoxicity risk with DTG drug substance. DTG has also shown no carcinogenic potential in two carcinogenicity studies (standard 2-year mouse and rat studies).

Nonclinical assessment of potential developmental immunotoxicologic effects suggests no unusual drug specific risk of developmental immunotoxicity in juvenile animals. No new target organ toxicities were observed in the definitive juvenile rat toxicology study. The NOAEL for DTG in juvenile rats is considered to be 2 mg/kg/day. No safety signals specific to paediatric subjects have been identified from preclinical studies with DTG to date.

In summary, the toxic potential of DTG has been well characterized in a comprehensive nonclinical development program. These data are considered adequate to support the proposed clinical use as a treatment of HIV.

1.1.2. Clinical Development Program Overview

The clinical development program for DTG was designed to assess the safety and efficacy of DTG in HIV-infected adult and paediatric subjects. Safety data is included from each of the 30 Phase I, 4 Phase II, 7 Phase III/IIIb clinical trials, as well as the compassionate use program, as listed below in Table 1. Also refer to Appendix Table 1 for a detailed tabular listing of all clinical efficacy and safety studies.
## Table 1  Listing of Clinical Studies Providing Safety Information for DTG

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Status of Study</th>
<th>Type of Study</th>
<th>Location of CSR, CPSR, or Brief Study Summary</th>
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<td>Pharmacokinetic (PK) and Biofarmaceutic Studies</td>
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</tr>
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<td>Extrinsic Factor PK</td>
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<td>5.3.3.4</td>
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<td>Pharmacodynamic (PD) Studies</td>
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<tr>
<td>ING111856</td>
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<td>Healthy Subject PD and PD/PK</td>
<td>5.3.4.1</td>
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<td>ING114819</td>
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<td>Healthy Subject PD and PD/PK</td>
<td>5.3.4.1</td>
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<td>ING111521</td>
<td>Complete</td>
<td>Patient PD and PD/PK</td>
<td>5.3.4.2</td>
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<td>ING116070</td>
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<td>Patient PD and PD/PK</td>
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<tr>
<td>Controlled Clinical Studies Pertinent to the Claimed Indication</td>
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<td>ING112276</td>
<td>Ongoing</td>
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<tr>
<td>ING111762</td>
<td>Ongoing</td>
<td>Efficacy and Safety</td>
<td>5.3.5.1</td>
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<td>ING113086</td>
<td>Ongoing</td>
<td>Efficacy and Safety</td>
<td>5.3.5.1</td>
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<tr>
<td>ING114467</td>
<td>Ongoing</td>
<td>Efficacy and Safety</td>
<td>5.3.5.1</td>
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<td>Uncontrolled Clinical Studies</td>
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<td>ING112574</td>
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<td>Efficacy and Safety</td>
<td>5.3.5.2</td>
</tr>
<tr>
<td>ING112578 (P1093)a</td>
<td>Ongoing</td>
<td>Efficacy and Safety, Paediatric PK</td>
<td>5.3.5.2</td>
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<td>Other Clinical Study Reports</td>
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<td>Ongoing</td>
<td>Efficacy and Safety</td>
<td>5.3.5.4</td>
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<td>Ongoing</td>
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<td>ING115502a</td>
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<td>Named Patient Program</td>
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</table>
Safety data are presented throughout this module in the following groupings:
<table>
<thead>
<tr>
<th>Study Grouping</th>
<th>Analyses Available within Each Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies in ART-Naïve Adults</td>
<td>ING112276(^a) individual study safety analyses; ING113086(^b) individual study safety analyses; ING114467(^a) individual study safety analyses; ING112276(^a), ING113086(^b), and ING114467(^a) pooled safety analyses of DTG treatment arms</td>
</tr>
<tr>
<td>Studies in ART-Experienced (INI-Naïve) Adults</td>
<td>ING111762(^b) individual study safety analyses</td>
</tr>
<tr>
<td>Studies in ART-Experienced (INI-Resistant) Adults</td>
<td>ING112961(^a) (Cohort I and Cohort II) individual study safety analyses; ING112574(^b) individual study safety analyses; ING112961(^a) Cohort 2 and ING112574(^b) pooled safety analyses of DTG BID treatment arms</td>
</tr>
<tr>
<td>Other Completed and Ongoing Studies in Adults(^c)</td>
<td>ING114915(^d) individual study safety analyses; ING116070(^d) individual study safety analyses; ING116529(^a) SAE and pregnancy reports; ING114916(^d) SAE and pregnancy reports; ING115502(^d) SAE and pregnancy reports</td>
</tr>
<tr>
<td>Clinical Development Program in Paediatric Subjects</td>
<td>ING112578 individual study analyses</td>
</tr>
<tr>
<td>Integrated Clinical Pharmacology Studies</td>
<td>Pooled safety analyses(^f) from ING111207, ING111322, ING111405, ING111602, ING111603, ING111604, ING111853, ING111854, ING111856, ING112934, ING112941, ING113068, ING113096, ING113097, ING113099, ING113674, ING114005, ING114819, ING114556, ING114581, ING115381, ING115696, ING115698, ING111855, ING111521, and LAI116181 (DTG arm)</td>
</tr>
<tr>
<td>Clinical Pharmacology Studies Completed or Ongoing after Integrated Analysis (i.e., after the cut-off)(^h)</td>
<td>Completed reports: ING113125, ING115697, ING115465, and ING116195; Ongoing at the cut-off: ING114580</td>
</tr>
</tbody>
</table>

BID, twice daily; SAE, serious adverse event

- a. Supportive Phase IIb trial
- b. Pivotal Phase III clinical trial
- c. This includes the compassionate use program; overall, data from these studies/programs are limited, but are presented whenever available
- d. Study population comprises ART-naïve, HIV-infected adults
- e. Study/program population comprises ART-experienced (INI-resistant) HIV-infected adults
- f. Comprises 24 completed Phase I studies in healthy adults, 1 Phase I study in hepatically-impaired subjects, and 1 Phase IIa study in ART-naïve, HIV-infected adult subjects (ING111521).
- g. Key clinical pharmacology study (i.e., investigates specific safety outcomes); ING111856 is the definitive QTc study, and ING114819 is the renal function study.
- h. These are grouped in m2.7.4 under "Other Completed and Ongoing Studies in Adults" sections; however, as there were no SAEs, pregnancies or fatalities in these studies, no safety findings for these studies are presented

### 1.1.3. Data Cut-off Dates

This submission contains data collected through [redacted]. The final data cut-off dates for individual studies are listed below:
# Table 3  Data Cut-off Dates for Studies Included in m2.7.4

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Time Point of Analysis</th>
<th>Data Cut-off Date</th>
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</thead>
<tbody>
<tr>
<td><strong>Pivotal and Supportive Clinical Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies in ART-Naive Adults</td>
<td>ING112276</td>
<td>Post Week 96&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ING113086</td>
<td>Post Week 48&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ING114467</td>
<td>Week 48&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Studies in ART-Experienced (INI-Naive) Adults</td>
<td>ING111762</td>
<td>Week 24&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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<td>Studies in ART-Experienced (INI-Resistant) Adults</td>
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<td>Post Week 96&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ING112574</td>
<td>Week 24&lt;sup&gt;c-d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Integrated Clinical Pharmacology Studies</strong></td>
<td>25 Phase I studies and Phase IIa study ING111521</td>
<td>Variable&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Other Completed and Ongoing Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART-Naive Adults</td>
<td>ING114915</td>
<td>Not applicable&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ING116070</td>
<td>Week 2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ART-Experienced (INI-Resistant) Adults</td>
<td>ING116529</td>
<td>Not applicable&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ING114916</td>
<td>Not applicable&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ING115502</td>
<td>Not applicable&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clinical Pharmacology Studies Completed or Ongoing after Integrated Analysis (i.e., after the cut-off)</td>
<td>ING113125</td>
<td>Final</td>
</tr>
<tr>
<td></td>
<td>ING115697</td>
<td>Final</td>
</tr>
<tr>
<td></td>
<td>ING115465</td>
<td>Final</td>
</tr>
<tr>
<td></td>
<td>ING116195</td>
<td>Final</td>
</tr>
<tr>
<td></td>
<td>ING114580</td>
<td>Final</td>
</tr>
<tr>
<td>Paediatric Subjects</td>
<td>ING112578 (P1093)</td>
<td>Week 24&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a. This data cut-off date is the date when the data used in the analysis was extracted. This could either be Database Freeze (DBF) or Database Release (DBR), depending whether a new extraction was needed at DBF.

b. The completed interim statistical analysis was more than six months prior to the planned submission date, so a new safety data cut was taken for reporting in this submission; thus, the data reported individually for these studies is not represented in a clinical study report.

c. Safety data for this submission are reported based on the latest Clinical Study Report available.

d. The interim analysis was planned to assess the first approximately 100 subjects that completed 24 weeks on study, and recruitment continued to allow enrolment of a further 50 to 100 subjects, as per protocol. All available safety data, as of the data cut, from all subjects enrolled contributed to the safety analysis. Thus, the planned interim analysis data cut was based on 114/183 subjects through Week 24.

e. Individual studies and study durations are listed in APPENDIX 1: Tabular Listing of Studies.

f. Appendix Table 1: Tabular Listing of Studies.

g. No completed interim analysis is available so a data cut was taken for the purposes of safety reporting in this submission, with a minimal set of safety outputs produced to adequately report the safety data.

h. Not applicable as study is ongoing.

i. Not applicable as this is the named patient program.

j. The analysis was conducted for inclusion in this submission once all subjects in Cohort I, Stage 1 were through Week 24.

An additional cut-off date for SAEs and pregnancies (which aligns with the Data Lock Point for the DTG Development Safety Update Report) was applied to all ongoing studies for complete disclosure of safety information.

These data were obtained from the Sponsor’s global safety database, maintained on GSK’s Operating Company Event Accession and Notification System (OCEANS), which is separate from the clinical trials databases for these studies. OCEANS was searched, for SAE and pregnancy cases that were initially reported to GSK’s Global Safety and Pharmacovigilance department, for each individual study, from the
data of last analysis (i.e., Data Cut-Off Date denoted in Table 3) through to 18. For compassionate use program ING114916 and clinical trial ING116529, this was a cumulative search to 18. It is important to note that no reconciliation was performed between OCEANS and the clinical trials’ databases prior to retrieving these data. Also, as these studies are still ongoing, these cases are still subject to change. These data were not integrated, but are reported separately.

1.1.4. Description of Studies

A tabular listing to describe the enrolment status, objectives, design, key inclusion criteria, treatment details, number of patients by treatment group, key demographics, and primary endpoints for each study contributing safety information in this submission is provided in Appendix Table 1. Further descriptions of the study designs are provided as follows:

- Descriptions of completed studies categorized as “Efficacy and Safety” in Table 1 above are provided in m2.7.3 (Summary of Clinical Efficacy).
- Descriptions of pharmacokinetic and/or pharmacodynamic studies, including paediatric study ING112578 and two studies that investigated specific safety outcomes (i.e., thorough QT study ING111856, and renal function study ING114819), are provided in m2.7.2 (Summary of Clinical Pharmacology).
- Descriptions of completed studies categorized as bioavailability/bioequivalence “BA/BE” in Table 1 above are provided in m2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods).
- A description for the ongoing study categorized as “BA/BE” in Table 1 above (i.e., ING114580) is provided in m5.3.5.4.
- Descriptions for the two ongoing safety and efficacy clinical studies (i.e., ING116529 and ING114915) and for the two patient programs (i.e., ING114916 and ING115502) that did not provide efficacy data for m2.7.3 have been provided below.

1.1.4.1. ING116529 (VIKING-4)

**Title:** A Phase III Randomized, Double-blind Study to Demonstrate the Antiviral Activity of Dolutegravir (DTG) 50 mg Twice Daily Versus Placebo Both Co-Administered with a Failing Antiretroviral Regimen over Seven Days, Followed by an Open Label Phase with All Subjects Receiving DTG 50 mg Twice Daily Co-Administered with an Optimised Background Regimen (OBR) in HIV-1 Infected, Integrase Inhibitor Therapy-Experienced and Resistant, Adults

**Location of Report:** m5.3.5.4, ING116529

**Study Design:** ING116529 is an ongoing Phase III, multicenter, randomized, double-blind study with an initial 7-day, placebo-controlled, functional monotherapy phase to quantify the antiviral activity attributable to DTG in HIV-1 infected, ART-experienced adults who are experiencing virological failure on an INI-containing regimen [i.e., current raltegravir (RAL) or elvitegravir (EVG) failures], and have evidence of genotypic resistance to RAL or EVG at study entry. DTG or placebo are co-administered initially
with the current failing regimen over seven days (RAL or EVG are discontinued prior to dosing with DTG). At Day 8, subjects from both arms enter an open-label phase and receive open-label DTG 50 mg twice daily, co-administered with an optimized background regimen (OBR).

Subjects must have documented genotypic and/or phenotypic resistance to at least one compound in two or more of the other approved classes of ART, but must also be able to include at least one active drug in the OBR to be commenced at Day 8.

The primary objective is to quantify the antiviral activity of DTG 50 mg twice daily compared to placebo when administered with failing background therapy for 7 days in HIV-infected adult subjects with virological failure on a prior INI-containing regimen and INI resistance at Screening.

Day 8 (primary endpoint) interim analysis data (clinical study report) is expected to be available 1Q.

1.1.4.2. ING114915 (FLAMINGO)

**Title:** A Phase IIIb, Randomized, Open-Label Study of the Safety and Efficacy of GSK1349572 (Dolutegravir, DTG) 50 mg Once Daily Compared to Darunavir/Ritonavir (DRV/RTV) 800 mg/100 mg Once Daily each Administered with Fixed-Dose Dual Nucleoside Reverse Transcriptase Inhibitor Therapy over 96 Weeks in HIV-1-Infected Antiretroviral-Naïve, Adult Subjects

**Location of Report:** m5.3.5.4, Study ING114915

**Study Design:** ING114915 is an ongoing Phase IIIb, randomized, open-label, active-controlled, multicentre, parallel group, fully-powered non-inferiority study. The study is being conducted in HIV-1-infected, ART-naïve subjects. Subjects were randomized 1:1 to receive DTG 50 mg once daily (approximately 234 subjects) or DRV/RTV 800 mg/100 mg once daily (approximately 234 subjects), each in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) therapy [either abacavir (ABC)/lamivudine (3TC) or tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)]. Subjects were stratified by screening HIV-1 ribonucleic acid (RNA) and background NRTI selection. The primary objective is to demonstrate the non-inferior antiviral activity of DTG 50 mg administered once daily compared to DRV/RTV 800 mg/100 mg once daily over 48 weeks in HIV-1 infected, ART-naïve subjects.

The primary analysis will take place after the last subject completes Week 48 on study, and an additional analysis will be conducted after the last subject completes Week 96. Week 48 (primary endpoint) results (clinical study report) are expected 3Q.

1.1.4.3. ING114916 (Expanded Access Program)

ING114916 is an open-label, multi-centre, non-randomized, expanded access protocol (EAP) to allow access to patients with HIV-1 infection who have documented RAL or EVG resistance, have limited treatment options, and require DTG to construct a viable antiretroviral (ARV) regimen for therapy. Patients must not have been eligible for
another ongoing DTG clinical trial in order to participate in this EAP. DTG is being made available through this international EAP; it was estimated that no more than 1000 patients worldwide would be enrolled. Eligible patients received DTG 50 mg given orally twice daily.

No formal hypotheses testing were performed. Data from this EAP provide only descriptive information on safety and tolerability.

1.1.4.4. **ING115502 (Named Patient Program)**

DTG is being made available on a compassionate use, open-label, patient-by-patient basis to facilitate its availability for the treatment of HIV-1 infection in patients with INI resistance who have no available alternatives and/or limited treatment options (e.g., who are unable to participate in the Phase III clinical studies or do not qualify), and are in need of new drugs to construct an effective antiviral regimen. Currently, DTG is not approved for use in any country.

The objective of this study is to provide a mechanism to supply DTG patients with integrase resistance who had no available alternatives and/or limited treatment options.

Minimal data were formally collected.

1.1.5. **Description of Safety Population**

1.1.5.1. **Pivotal and Supportive Clinical Trials in Adults**

The Intent-to-Treat Exposed (ITT-E) population consists of all randomized subjects who received at least one dose of investigational product. The ITT-E population will be the primary population used for Baseline demographic and study population analyses. In randomised studies, subjects were analyzed according to their randomized treatment, regardless of the treatment they actually received. In study ING111762, the modified ITT-E population (mITT-E) was used due to a Good Clinical Practice (GCP) non-compliance issue (exclusion of 4 subjects from ITT-E population).

The Safety population consists of all subjects who received at least one dose of investigational product. This is the primary population used for safety analyses. In randomized studies, subjects were analysed according to the treatment they actually received, regardless of randomization. In study ING111762, the safety population included the 4 subjects excluded from the mITT-E population.

In total, 2813 subjects from pivotal and supportive Phase IIb and III studies are included in m2.7.4: 1364 subjects received DTG once daily, 207 subjects received DTG BID and 1242 subjects received comparator (Table 4).
Table 4  Summary of Safety Population by Study for Pivotal and Supportive Phase IIb and Phase III Studies

<table>
<thead>
<tr>
<th>Study Description</th>
<th>DTG</th>
<th>Comparator</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Safety population, n</strong></td>
<td>1571</td>
<td>1242</td>
<td>2813</td>
</tr>
<tr>
<td><strong>ART-Naïve population, n</strong></td>
<td>980</td>
<td>880</td>
<td>1860</td>
</tr>
<tr>
<td>ING112276</td>
<td>155</td>
<td>50</td>
<td>205</td>
</tr>
<tr>
<td>ING113086</td>
<td>411</td>
<td>411</td>
<td>822</td>
</tr>
<tr>
<td>ING114467</td>
<td>414</td>
<td>419</td>
<td>833</td>
</tr>
<tr>
<td><strong>ART-Experienced (INI-Naïve) population, n</strong></td>
<td>357</td>
<td>362</td>
<td>719</td>
</tr>
<tr>
<td>ING111762</td>
<td>357</td>
<td>362</td>
<td>719</td>
</tr>
<tr>
<td><strong>ART-Experienced (INI-Resistant) population, n</strong></td>
<td>234</td>
<td>-</td>
<td>234</td>
</tr>
<tr>
<td>ING112961 Cohort I 50 mg once daily</td>
<td>27</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>ING112961 Cohort II 50 mg BID</td>
<td>24</td>
<td>-</td>
<td>24</td>
</tr>
<tr>
<td>ING112574 50 mg BID</td>
<td>183</td>
<td>-</td>
<td>183</td>
</tr>
</tbody>
</table>

Data Sources:
ING112276 Week 96 CSR Table 6.1
ING113086 Week 48 CSR Table 6.1
ING114467 Week 48 CSR Table 6.1
ING111762 Week 24 CSR Table 6.1
ING112961 Cohort I Week 96/Cohort II Week 48 CSR Table 6.1
ING112574 Week 24 CSR Table 6.1

1.1.5.2. Integrated Clinical Pharmacology Studies in Adults

In total, 559 subjects from 26 integrated clinical pharmacology studies are included in the pooled safety analysis. Due to the cross over design of many of the Phase I studies, some subjects received DTG and/or placebo (PBO) and/or at least one other protocol-defined medicinal product, either sequentially and/or in combination. Thus, the Total Safety Population does not necessarily equal the sum of the All DTG and All PBO treatment populations.

A total of 526 subjects received single or repeat doses of DTG; of these, 28 were HIV-infected subjects and 498 were healthy subjects. Of these 498 healthy subjects, 445 took DTG alone. A total of 72 subjects received PBO; 33 subjects only received PBO or comparator instead of DTG, of whom 7 were HIV-infected and 26 were healthy volunteers [Data Source: Clinical Pharmacology Metaanalysis (CPM) Table 1].

1.1.6. Statistical Methods

For complete details of data handling and analysis for the integrated Phase I and separate Phase IIb and III analyses, please refer to the Summary Document Analysis Plan (SDAP; m5.3.5.3).
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Module 2.7.4 Summary of Clinical Safety

1.1.6.1. Pivotal and Supportive Clinical Trials in Adults

In this module, studies in ART-naïve adults (ING112276, ING113086, and ING114467), ART-experienced (INI-naïve) adults (ING111762), and ART-experienced (INI-resistant) adults (ING112961 and ING112574) are considered separately due to the different treatment populations and the different doses of DTG being administered (i.e., DTG 50 mg once daily versus DTG 50 mg BID). Outputs are summarized by study and treatment arm. A total is displayed for DTG once daily for the ART-naïve population, and DTG BID for the ART-Experienced (INI-resistant) population only. All other ongoing studies are considered separately.

All demography and study population tables are presented on the ITT-E Population, except for ING111762 where the Modified ITT_E Population is used. All safety analyses are performed on the Safety Population.

By default, for randomised, controlled studies, data is summarized for the randomized phases of the studies. ING112961 is an open-label study and subjects in Cohort I were able to switch from once daily to BID dosing after Week 96. In the analysis tables, data from the open-label period prior to switch is the default data presentation.

Safety analyses include summaries of extent of exposure, adverse event, laboratory tests, vital signs and electrocardiograms (ECGs). Special interest categories for Adverse Events (AEs) and laboratory tests specific to this module were defined. These may not match special interest categories in individual CSRs.

This module output uses the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and GSKDrug dictionaries for AEs and concomitant medications at the time of running the integrated analysis. ING111762 was analysed at a later date, and therefore results for that study utilise a later dictionary version than this module, which may be different.

1.1.6.2. Integrated Clinical Pharmacology Studies in Adults

An overview of the completed Phase Ila study and 25 Phase I studies were included in the integrated Clinical Pharmacology safety dataset. Data from 5 completed studies (ING113125, ING115697, ING115465, ING116915, and ING114580) was not included in this integrated analysis of safety.

For cross-over and multiple-period clinical pharmacology studies (i.e., studies where a subject received more than one treatment during the study), the period treatment is used for safety summaries. For studies with parallel design, the treatment received during the study was used for safety summaries. DTG doses ranged from 2 mg to 250 mg and dosing days ranged from single dose and up to 19 days in Phase I and Ila studies.

AEs were summarized by population and combined treatment group (healthy subject versus HIV-infected, DTG alone or DTG + combination drug). Selected labs were summarized by combined treatments (placebo, DTG alone, DTG with at least one other protocol-defined medicinal product).
Safety analyses include summaries of extent of exposure, adverse event and laboratory tests and are presented in Section 5.6.

In text tables present data in this safety summary using three “dosing periods”, in which treatment is combined regardless of dose and duration as placebo, DTG alone, and DTG with at least one other protocol-defined medicinal product. As such, subjects who may have been exposed to both PBO and DTG could have AEs in both dosing periods. AEs or lab findings were summarized within the dosing period in which the AEs or lab findings were reported.

1.1.6.3. Other Completed and Ongoing Studies in Adults

ING114915 had a limited number of safety outputs produced in order to describe the safety data up to the cut-off date for this module. Safety analyses include summaries of demography, disposition, SAEs, AEs leading to withdrawal, and post Baseline-emergent clinical chemistry and haematology toxicities. As the study is ongoing and not all exposure data has been entered, the analysis includes the assumption that all randomized subjects received study drug.

ING116070 had a completed, planned Week 2 interim analysis, and safety data from it are included.

1.1.6.4. Clinical Development Program in Paediatric Subjects

ING112578 (P1093) had an interim analysis conducted when the 10 subjects in Cohort I, Stage 1 were through Week 24. Safety data from this analysis are included in Section 5.5.2.

All subjects were on DTG, therefore the All-Treated population was the primary safety population, and was defined as all randomized subjects who received at least one dose of DTG. For Cohort I, doses ranged from 35 mg (~1 mg/kg dosing) to 50 mg once daily.

Safety analyses include summaries of extent of exposure, adverse event and laboratory tests, and vital signs and are presented in Section 5.5.2.

1.1.7. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) was initially formed to ensure that subjects recruited with high Baseline HIV-1 RNA were not being sub-optimally treated in study ING114467, which was a double blind placebo controlled randomized clinical trial comparing DTG plus the ABC/3TC fixed dose combination tablet once daily 1:1 with the once daily single regimen tablet Atripla. As an additional remit, the IDMC also reviewed the overall safety of subjects enrolled in study ING114467 as well as the other Phase III studies, ING113086, ING112574 and ING111762.

In addition to overall safety, specific safety data that was reviewed included renal AEs and graded renal laboratory abnormalities, liver AEs and liver chemistry abnormalities, and AEs or constellations of AEs consistent with hypersensitivity reactions for subjects exposed to DTG in these studies. The overall responsibility of the IDMC was to protect
the safety interests of subjects recruited into the ING113086, ING111762, ING112574 and ING114467 studies, while protecting as far as possible the scientific validity of the data. The IDMC met at predefined times to evaluate the clinical response in the high viral load sub-population in ING114467 and to monitor general safety in subjects receiving DTG.

Six planned interim reviews of unblinded safety data have been conducted by the IDMC, the most recent completed on [redacted], which did not identify any safety concerns that precluded continuation of the clinical trials.

Following their third planned interim review of safety data on [redacted], the IDMC raised the importance of immune reconstitution inflammatory syndrome (IRIS) in the setting of a rapid decrease of viremia and increase of CD4 counts brought about by INI-containing ART. The IDMC recommended an evaluation of cases with either: an over all diagnosis of IRIS, or opportunistic infections (OI), reported as a HIV-related condition within the first 2-3 months of starting antiretroviral therapy, to determine whether they were indicative of IRIS, and coded accordingly. For ING113086, the IDMC suggested evaluating subjects with HIV/IRIS-related medical conditions occurring within the first 100 days. Subsequently, based on a review of the recent literature on IRIS, for ING114467, ING111762, and ING112574, the IDMC agreed to evaluate subjects with HIV/IRIS-related medical conditions and flares of hepatitis in subjects coinfected with hepatitis viruses occurring within the first 180 days.

### Subject Disposition

- A total of 980 subjects in the ART-naïve population (ING112276, ING113086, and ING114467) received a DTG-containing regimen (DTG 50 mg once daily). The majority of these subjects were still ongoing at the time of this analysis (87%).
- A total of 357 subjects in the adult ART-experienced (INI-naïve) population (ING111762) received a DTG-containing regimen (DTG 50 mg once daily). The majority of these subjects were still ongoing at the time of this analysis (86%). Note that the safety population for this study (n=357) differs from the mITT-E (n=354) population.
- A total of 234 ART-experienced (INI-resistant) subjects from ING112961 and ING112574 received a DTG-containing regimen [DTG 50 mg once daily (n=27) or DTG 50 mg BID (n=207)]. Eighty-three percent of BID subjects were still ongoing at the time of this analysis.
- In the paediatric population (ING112578, P1093), nine subjects received a DTG-containing regimen of DTG 50 mg once daily. One subject received DTG 35 mg once daily (~1 mg/kg dosing). Enrolment is ongoing in this study.

### Studies in ART-Naïve Adults

Overall, in the three randomized, controlled trials in the ART-naïve population, the percentage of subjects from the DTG treatment arms who prematurely withdrew for any reason was 13%. Few subjects (≤3% of total DTG) withdrew for each of the specific
primary reasons for discontinuation (e.g., due to either an adverse event, lack of efficacy, protocol deviation, etc.) (Table 5).
## Table 5  Summary of Subject Disposition by ART-Naïve Population

<table>
<thead>
<tr>
<th>Completion status</th>
<th>ART-Naïve Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ING112276</td>
</tr>
<tr>
<td></td>
<td>DTG Once Daily + 2 NRTI N=155 n (%)</td>
</tr>
<tr>
<td></td>
<td>EFV 600 mg Once Daily + 2 NRTI N=50 n (%)</td>
</tr>
<tr>
<td></td>
<td>ING113086</td>
</tr>
<tr>
<td></td>
<td>DTG 50 mg Once Daily + 2 NRTI N=411 n (%)</td>
</tr>
<tr>
<td></td>
<td>RAL 400 mg BID + 2 NRTI N=411 n (%)</td>
</tr>
<tr>
<td></td>
<td>ING114467</td>
</tr>
<tr>
<td></td>
<td>DTG 50 mg + ABC/3TC Once Daily N=414 n (%)</td>
</tr>
<tr>
<td></td>
<td>EFV/TDF/FTC Once Daily N=980 n (%)</td>
</tr>
<tr>
<td><strong>Primary/subreason</strong></td>
<td><strong>discontinuation</strong></td>
</tr>
<tr>
<td>Adverse event</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Suspected hypersensitivity to</td>
<td>0</td>
</tr>
<tr>
<td>investigational product</td>
<td>0</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Insufficient viral load response</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>0</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Prohibited medication use</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance with IP treatment</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Non-compliance with protocol procedures</td>
<td>0</td>
</tr>
<tr>
<td>Subject reached protocol-defined</td>
<td>0</td>
</tr>
<tr>
<td>stopping criteria</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Subject met the GSK-defined</td>
<td>0</td>
</tr>
<tr>
<td>liver chemistry stopping criteria</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Study closed/terminated</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Subject was incarcerated</td>
<td>0</td>
</tr>
<tr>
<td>Investigator discretion</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

| **Completion status**                  | **n (%)**                                                                       |
| Completed                              | 0                                                                               |
| prematurely discontinued               | 28 (18)                                                                        |
| ongoing at time of analysis            | 127 (82)                                                                       |
| adverse event                          | 5 (3)                                                                           |
| suspected hypersensitivity to          | 0                                                                               |
| investigational product                | 0                                                                               |
| lack of efficacy                       | 3 (2)                                                                           |
| insufficient viral load response       | 3 (2)                                                                           |
| virologic failure                      | 0                                                                               |
| protocol deviation                     | 3 (2)                                                                           |
| pregnancy                              | 1 (<1)                                                                          |
| prohibited medication use              | 0                                                                               |
| non-compliance with ip treatment       | 1 (<1)                                                                          |
| non-compliance with protocol procedures| 0                                                                               |
| subject reached protocol-defined       | 0                                                                               |
| stopping criteria                      | 1 (2)                                                                           |
| subject met the gsk-defined            | 0                                                                               |
| liver chemistry stopping criteria      | 1 (2)                                                                           |
| study closed/terminated                | 0                                                                               |
| lost to follow                         | 6 (4)                                                                           |
| subject was incarcerated               | 0                                                                               |
| investigator discretion                | 2 (1)                                                                           |
## Module 2.7.4 Summary of Clinical Safety

<table>
<thead>
<tr>
<th>ART-Naive Adults</th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>TOTAL DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG Once Daily</td>
<td>EFV 600 mg Once</td>
<td>DTG 50 mg Once</td>
<td>DTG 50 mg + ABC/3TC Once Daily</td>
</tr>
<tr>
<td></td>
<td>+ 2 NRTI N=155 n</td>
<td>Daily + 2 NRTI N=411</td>
<td>50 mg Once Daily + 2 NRTI N=411</td>
<td>EFV/TDF/FTC Once Daily N=419 n (%)</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(6)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>Withdraw consent</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Subject relocated</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Burden of travel</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: Integrated Safety Output (ISO) Table 1.4

EFV/TDF/FTC = efavirenz (EFV) 600 mg TDF 300 mg, FTC 200 mg in the form of Atripla; IP = investigational product

a. Subjects can only have one reason for withdrawal.
b. Percentages for subreasons may have summed to more or less than 100%. Subjects may have had more than one subreason underneath a single primary reason. Subjects were not required to indicate subreasons.
c. Site 083505 closed due to GCP non-compliance issues.
1.1.8.2. Studies in ART-Experienced (INI-Naïve) Adults

The majority of subjects (86%) from the DTG treatment arm were ongoing at the time of the analysis, whilst in the RAL arm, approximately one third (31%) of subjects had completed the study; this is due to the study design, which allowed DTG subjects to continue to receive DTG in an open label fashion until it is approved and available. In the DTG treatment arm, the percentage of subjects that withdrew for any reason was 14%. The primary reason for withdrawal was lack of efficacy due to virologic failure, which occurred in 4% of subjects. All other reasons for withdrawal occurred in ≤3% of subjects (Table 6).

Table 6 Summary of Subject Disposition – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Completion status</th>
<th>ING111762</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Prematurely discontinued</td>
<td>48 (14)</td>
</tr>
<tr>
<td>Ongoing at time of analysis</td>
<td>305 (86)</td>
</tr>
<tr>
<td>Total N=354</td>
<td>111 (31)</td>
</tr>
<tr>
<td>Percent</td>
<td>112 (16)</td>
</tr>
<tr>
<td>Total N=361</td>
<td>61 (17)</td>
</tr>
<tr>
<td>Percent</td>
<td>109 (15)</td>
</tr>
<tr>
<td>Total N=715</td>
<td>189 (52)</td>
</tr>
<tr>
<td>Percent</td>
<td>494 (69)</td>
</tr>
</tbody>
</table>

Primary/subreason\(^{a}\) for discontinuation

<table>
<thead>
<tr>
<th>Reason</th>
<th>ING111762</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Prohibited ART</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Prohibited medication use</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Non-compliance with IP treatment</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Non-compliance with protocol procedures</td>
<td>0</td>
</tr>
<tr>
<td>Subject reached protocol-defined stopping criteria</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Subject met the GSK-defined liver chemistry stopping criteria</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Subject incarcerated</td>
<td>0</td>
</tr>
<tr>
<td>Investigator discretion</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Subject relocated</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Burden of travel or lack of access to travel</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

BR = background regimen

Data Source: ING111762 Week 24 CSR Table 6.3

Notes:

a. Subjects can only have one reason for withdrawal.
b. Percentages for subreasons may have summed to more or less than 100%. Subjects may have had more than one subreason underneath a single primary reason. Subjects were not required to indicate subreasons.
1.1.8.3. Studies in ART-Experienced (INI-Resistant) Adults

In the studies with ART-experienced (INI-resistant) subjects (ING112961 and ING112574), the percentage of subjects who prematurely withdrew for any reason was 17% for the DTG 50 mg BID treatment arms (i.e., the selected dose for those with INI resistance), and 21% across all arms (i.e., when the DTG 50 mg once daily group from ING112961 Cohort I is combined with the Total DTG 50 mg BID group). For the combined DTG 50 mg BID group, the primary reason for withdrawal across studies was lack of efficacy (11%), followed by virologic failure (9%), and few subjects withdrew due to an AE (6/207, 3%).

Table 7 Summary of Subject Disposition - ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th></th>
<th>ING112961 Cohort I DTG 50 mg Once Daily + BR N=27</th>
<th>ING112574 Cohort II DTG 50 mg BID + BR N=24</th>
<th>Total DTG 50 mg BID N=183</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>0</td>
<td>15 (56)</td>
<td>0</td>
</tr>
<tr>
<td>Prematurely discontinued</td>
<td>15 (56)</td>
<td>7 (29)</td>
<td>28 (15)</td>
</tr>
<tr>
<td>Ongoing at time of analysis</td>
<td>12 (44)</td>
<td>17 (71)</td>
<td>155 (85)</td>
</tr>
<tr>
<td>Primary subreasons for discontinuation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>2 (7)</td>
<td>2 (8)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>12 (44)</td>
<td>3 (13)</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Disease progressed/progression</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Insufficient viral load response</td>
<td>12 (44)</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Insufficient CD4 response</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>0</td>
<td>0</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Non-compliance with IP treatment</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Subject reached protocol-defined stopping criteria</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Subject met the GSK defined liver chemistry stopping criteria</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>1 (4)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 1.5
a. Subjects can only have one reason for withdrawal.
b. Percentages for subreasons may sum to more or less than 100%. Subjects may have had more than one subreason underneath a single primary reason. Subjects were not required to indicate subreasons.
c. Does not include the one subject withdrawn due to meeting protocol defined liver stopping criteria [alanine aminotransferase (ALT) >5x upper limit of normal (ULN) but <10x ULN], as this was not captured as an AE.
1.1.8.4. Integrated Clinical Pharmacology Studies in Adults

In the Integrated Clinical Pharmacology Studies Analysis, 518 (93%) subjects completed the studies, and 41 (7%) of subjects withdrew early. A total of 12 (2%) subjects withdrew due to an AE (Data Source: CPM Table 1).

1.1.8.5. Other Completed and Ongoing Studies in Adults

For ongoing studies ING114916 and ING115502, no statistical analysis has been conducted and enrolment continues globally. Therefore, subject disposition data has not been summarized.

In Study ING116070, 13 subjects have enrolled and 12 were ongoing. One subject discontinued for an AE (Data Source: m5.3.4.2 ING116070 Week 2 Synoptic CSR Table 6.3).

In study ING114915, 236 (99%) of subjects are currently ongoing. Three (1%) subjects discontinued (Data Source: ING114915 Table 2).

As of [redacted], in Study ING116529, 30 subjects have enrolled and 28 subjects are ongoing. One subject withdrew at Day 8 for protocol deviation (inclusion criterion 5 not met), and another subject had a fatal event (suspected cardiovascular death) unrelated to investigational product (IP). [NOTE: The study summary in m5.3.5.4 was created at an earlier timepoint and thus reflects lower enrolment.]

The following summarizes the subject disposition for ongoing clinical pharmacology studies:

- Study ING113125: All 16 subjects who enrolled completed the study as planned (Data Source: ING113125 CPSR Table 9.1).
- Study ING115697: 32 subjects enrolled into this study, 28 completed and 4 subjects withdrew due to an adverse event (Data Source: ING115697 CPSR Table 1.1).
- Study ING115465: 11 subjects enrolled into this study, and 3 subjects withdrew from the study because of the inability to obtain 80% of cervicovaginal fluid (CVF) samples as required by protocol (Data Source: ING115465 CPSR Table 4).
- ING116195: A total of 14 were enrolled, and 12 completed the study as planned; there was 1 withdrawal due to an unrelated adverse event (panic reaction) and 1 withdrawal due to inability to place an intravenous line (Data Source: ING116195 CPSR Table 9.1).
- Study ING114580: no statistical analysis has been conducted; therefore, subject disposition data has not been summarized.

1.1.8.6. Clinical Development Program in Paediatric Subjects

In the paediatric population, a total of 10 subjects were enrolled in Cohort I, Stage 1 and received at least one dose of DTG once daily (Data Source: ING112578 (P1093) Week 24 CSR Table 3). At the time of data cut-off for this analysis, enrolment of paediatric ART-experienced subjects into ING112578 (P1093) Cohort I, Stage 2 was
complete (n=12). However, not all of these subjects had reached Week 24 and therefore, were not included in this analysis. All 10 subjects in Cohort I, Stage 1 are through Week 24 and continuing on study; 4 of the 10 subjects have reached Week 48.

1.2. Overall Extent of Exposure

As of the analysis cut-off date, a total of 2663 subjects (2026 HIV-infected and 637 healthy) have been exposed to at least one dose of DTG in the entire clinical development programme for this product. This total comprises:

- 526 healthy subjects and HIV-infected subjects from the Integrated Clinical Pharmacology Studies Analysis (Data Source: CPM Table 1)
- 1,571 HIV-infected subjects from the Phase IIb and Phase III studies (Data Source: ISO Table 2.501, Table 2.502, and Table 2.503)
- 139 adult healthy subjects from the five additional Phase I studies that were ongoing at data cut-off date for the Integrated Clinical Pharmacology Studies Analysis (i.e., ING113125, ING115697, ING115465, ING116915, and ING114580)
- 284 HIV-infected subjects who received at least one dose of DTG as part of ongoing Phase IIIb clinical trials (ING114915, ING116070 and ING116529), which were all fully enrolled by
- 110 HIV-infected adult subjects received DTG up to through the ongoing compassionate use programme (ING115502 and ING114916), which is still enrolling patients
- 33 adolescents and children in the ongoing paediatric study ING112578 (P1093) have been exposed to DTG to the same data lock point; this study is also still enrolling patients. Further data from ING112578 is provided in Section 5.5.2.

1.2.1. Overall Exposure in Phase IIb and Phase III Pivotal and Supportive Clinical Trials

In the combined Phase IIb and Phase III clinical studies, subjects received DTG for up to 134 weeks, whereas the majority of subjects in the comparator groups had between 60 to 100 weeks of exposure.

The extent of exposure of DTG in the combined key Phase IIb and Phase III clinical studies was equal to approximately 1595.9 subject-years; the extent of exposure to the comparator arms of RAL, EFV, or Atripla was lower and varied (82.0 to 497.0 subject-years), dependent upon the length of the randomized phase of the study (Data Source: ISO Table 2.501, Table 2.502 and Table 2.503; summarized in Appendix Table 2). The mean duration of exposure was 340 days for DTG, with a range of 1 to 943 days.

1.2.1.1. Studies in ART-Naïve Adults

One hundred and fifty five ART-naïve subjects randomized to one of three DTG doses (10 mg, 25 mg, or 50 mg group) have been treated with DTG once daily in the Phase IIb
study ING112276; these subjects were followed for 96 weeks on the randomized dose, after which all remaining subjects were switched to the selected 50 mg DTG dose.

Approximately 825 ART-naïve subjects in the Phase III studies ING113086 and ING114467, have been treated with DTG 50 mg once daily for at least 48 weeks.

The extent of exposure to DTG in the Phase IIb and Phase III controlled trials in ART-naïve adult subjects was equal to approximately 1185.4 subject years. The majority of subjects in the DTG treatment groups and in each comparator group had between 48 and 96 weeks of exposure to study drug. The median total exposure to DTG was 422 days, with a range of 1 to 716 days (Appendix Table 2). The mean total exposure of DTG 50 mg in the Phase IIb study ING112276 was higher than the DTG mean total exposure in both Phase III studies ING113086 and ING114467, due to the majority of subjects in ING112276 having ≥96 weeks exposure to DTG (Appendix Table 3).

1.2.1.2. Studies in ART-Experienced (INI-Naïve) Adults

Approximately 357 ART-experienced (INI-naïve) subjects have received DTG 50 mg once daily (Appendix Table 2). The extent of exposure was 250.3 subject years. Median duration of exposure was 281 days (range 10 to 370 days).

1.2.1.3. Studies in ART-Experienced (INI-Resistant) Adults

Approximately 234 ART-experienced (INI-resistant) subjects have been treated with DTG 50 mg (once daily or BID). The extent of exposure to DTG 50 mg BID in ING112961, Cohort II and ING112574 was 122.4 subject years (Appendix Table 2). The extent of exposure to DTG once daily in ING112961, Cohort I was equal to approximately 37.9 subject years (Appendix Table 2).

1.2.2. Overall Exposure in Clinical Pharmacology Studies

From the Integrated Clinical Pharmacology Studies Analysis, a total of 526 subjects received at least one dose of DTG; 220 healthy subjects received single doses of DTG from 2 mg to 250 mg; and 306 healthy subjects and HIV-infected subjects have received repeat, once daily (10 mg to 50 mg) or BID (50 mg) doses of DTG for up to 19 and 14 days, respectively (Data Source: CPM Table 1).

Clinical Pharmacology Studies ING113125, ING115697, ING115465, ING116915, and ING114580: These five studies were ongoing at the time of the data cut-off date for the Integrated Clinical Pharmacology Studies Analysis, and thus were not included in that integrated safety analysis. Subsequently, these five studies enrolled an additional 82 subjects who received single-dose DTG and 57 subjects who received repeat-dose DTG. Final study reports are available, and details on these studies can be found in m2.7.2 and m5.3.3.1, m5.3.3.3 and m5.3.3.4.

Additional data on Clinical Pharmacology studies are summarized in Section 5.6.
1.2.3. **Overall Exposure in Other Completed and Ongoing Studies in Adults**

**ING116070:** The median time of exposure to DTG 50 mg once daily was 57 days, and 92% of subjects (N=13) received therapy for at least 4 weeks. Almost half of the subjects (6/13, 47%) had received at least 12 weeks of therapy as of the data cut-off (Data Source: ING116070 Week 2 Synoptic CSR Table 8.1).

**ING114915:** This study was ongoing at the time of the data cut-off date, with 239 subjects randomized to receive DTG. The first subject was enrolled in this study on with the last subject enrolled on (Data Source: m5.3.5.4. ING114915 Study Summary).

1.3. **Demographic and Other Characteristics of Study Population**

Demographic and Baseline characteristics were collected for the ITT-E population in all of the following studies, with the exception of ING111762, which used the Modified ITT-E population.

1.3.1. **Demographic Characteristics**

1.3.1.1. **Studies in ART-Naïve Adults**

In each of the three randomized, controlled trials in ART-naïve adult subjects, there were no meaningful differences among treatment groups with respect to age or height (Table 8). The median age across treatment groups and studies ranged from 35 to 40 years. The majority of subjects across all three studies were male and White/Caucasian. Study ING114467 included a greater percentage of African American/African Heritage (AA/AH) subjects (24%).
### Table 8  Summary of Demographic Characteristics for Integrated Safety Analysis – ART-Naïve Population

<table>
<thead>
<tr>
<th></th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG Once Daily + 2 NRTI N=155</td>
<td>EFV 600 mg Once Daily + 2 NRTI N=50</td>
<td>DTG 50 mg Once Daily + 2 NRTI N=411</td>
<td>RAL 400 mg BID + 2 NRTI N=411</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>36 (20-64)</td>
<td>40 (20-79)</td>
<td>37 (18-68)</td>
<td>35 (18-75)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (14)</td>
<td>6 (12)</td>
<td>63 (15)</td>
<td>56 (14)</td>
</tr>
<tr>
<td>Male</td>
<td>133 (86)</td>
<td>44 (88)</td>
<td>348 (85)</td>
<td>355 (86)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>25 (16)</td>
<td>7 (14)</td>
<td>43 (10)</td>
<td>52 (13)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>130 (84)</td>
<td>43 (86)</td>
<td>368 (90)</td>
<td>359 (87)</td>
</tr>
<tr>
<td><strong>Height, centimetres (cm)</strong></td>
<td>176 (150-197)</td>
<td>175.5 (150-192)</td>
<td>175 (149-207)</td>
<td>175 (146-207)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White - White/Caucasian/European heritage</td>
<td>120 (77)</td>
<td>42 (84)</td>
<td>342 (83)</td>
<td>342 (83)</td>
</tr>
<tr>
<td>African American/African heritage</td>
<td>21 (14)</td>
<td>4 (8)</td>
<td>49 (12)</td>
<td>39 (9)</td>
</tr>
<tr>
<td>American Indian or Alaska native</td>
<td>8 (5)</td>
<td>2 (4)</td>
<td>7 (2)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>White - Arabic/North African heritage</td>
<td>1 (&lt;1)</td>
<td>1 (2)</td>
<td>4 (&lt;1)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Mixed race</td>
<td>2 (1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Asian - Central/South Asian heritage</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Asian - East Asian heritage</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Asian - Japanese heritage</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Asian - South East Asian heritage</td>
<td>0</td>
<td>1 (2)</td>
<td>2 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Native Hawaiian or other pacific islander</td>
<td>3 (2)</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>White - mixed race</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 1.10 and Table 1.14

### 1.3.1.2. Studies in ART-Experienced (INI-Naïve) Adults

The median age of subjects enrolled in study ING111762 was 43 years (Table 9). In contrast to the studies in ART-naïve subjects, a higher percentage of women (230/715, 32%) and AA/AH subjects (303/715, 42%) were enrolled into ING111762, which may be
due in part to the country distribution that included South America and South Africa (ING111762 Table 6.10 and Table 6.12).

**Table 9** Summary of Demographic Characteristics for Integrated Safety Analysis – ART-Experienced (INI-Naive) Population

<table>
<thead>
<tr>
<th></th>
<th>Study ING111762</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG 50 mg Once Daily + BR N=354</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>42 (21-69)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>107 (30)</td>
</tr>
<tr>
<td>Male</td>
<td>247 (70)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>135 (38)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>219 (62)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White-White/Caucasian/European Heritage</td>
<td>175 (50)</td>
</tr>
<tr>
<td>African American/African Heritage</td>
<td>143 (41)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Mixed Race</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Asian-East Asian Heritage</td>
<td>6 (2)</td>
</tr>
<tr>
<td>White-Arabic/North African Heritage</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Asian-Central/South Asian Heritage</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Asian-South East Asian Heritage</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 6.10 and Table 6.12

### 1.3.1.3. Studies in ART-Experienced (INI-Resistant) Adults

In the two clinical trials in ART-experienced (INI-resistant) adult subjects, there was no difference among treatment groups with respect to age (Table 10). The median age across study groups was 47 to 48 years. The majority of subjects were male and White/Caucasian. A similar percentage of AA/AH subjects received DTG BID in ING112961 and ING112574 (21 and 27%, respectively), whilst a lower percentage of AA/AH (11%) received DTG once daily in ING112961.
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Module 2.7.4 Summary of Clinical Safety

Table 10 Summary of Demographic Characteristics for Integrated Safety Analysis – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>ING112961</th>
<th>ING112574</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort I DTG 50 mg Once Daily + BR N=27</td>
<td>Cohort II DTG 50 mg BID + BR N=24</td>
<td>DTG 50 mg BID + BR N=183</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Median (range)</th>
<th>48 (19-61)</th>
<th>47 (33-68)</th>
<th>48 (19-67)</th>
<th>47 (19-68)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sex, n (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2 (7)</td>
<td>6 (25)</td>
<td>42 (23)</td>
<td>48 (23)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (93)</td>
<td>18 (75)</td>
<td>141 (77)</td>
<td>159 (77)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity, n (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic/Latino</td>
<td>3 (11)</td>
<td>5 (21)</td>
<td>20 (11)</td>
<td>25 (12)</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>24 (89)</td>
<td>19 (79)</td>
<td>163 (89)</td>
<td>182 (88)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race, n (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White/Caucasian/European heritage</td>
<td>23 (85)</td>
<td>18 (75)</td>
<td>125 (68)</td>
<td>143 (69)</td>
<td></td>
</tr>
<tr>
<td>African American/African heritage</td>
<td>3 (11)</td>
<td>5 (21)</td>
<td>49 (27)</td>
<td>54 (26)</td>
<td></td>
</tr>
<tr>
<td>White - Arabic/North African heritage</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>5 (3)</td>
<td>6 (3)</td>
<td></td>
</tr>
<tr>
<td>Mixed race</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>Asian - central/south Asian heritage</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
</tbody>
</table>

Data Source: ISO Table 1.11 and Table 1.15

1.3.1.4. Other Completed and Ongoing Studies in Adults

Two other ongoing studies, ING114915 and ING116070, are being conducted in ART-naïve adults. For ING114915, the median age was 34, and 85% of subjects were male (CSR ING114915 Table 1). For ING116070, the median age was 42, and 100% of subjects were White males (ING116070 Week 2 Synoptic CSR Table 6.7 and Table 6.8).

1.3.2. Baseline Characteristics

1.3.2.1. HBV and/or HCV Co-Infection Status and CDC Classification

1.3.2.1.1. Studies in ART-Naïve Adults

As detailed in Table 11, in the three pivotal studies in ART-naïve adults, Baseline characteristics were comparable across the studies and treatment arms with regard to hepatitis C virus (HCV) status and Centers for Disease Control and Prevention (CDC) category, using the CDC Classification System of HIV Infection [CDC, 1992]. Hepatitis B surface antigen positivity was an exclusion criterion for ING112276 (due to the earlier nature of the safety data for DTG) and ING114467 (due to blinded use of abacavir/lamivudine and thus possible receipt of lamivudine monotherapy).
1.3.2.1.2. Studies in ART-Experienced (INI-Naïve) Adults

In ART-experienced (INI-naïve) adults, 19-25% of subjects were co-infected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV). Over 40% of subjects were classified as CDC category C or AIDS in both treatment groups (Table 11).
## Table 11 Summary of HBV and/or HCV Co-Infection Status and CDC Classification in ART-Naïve and ART-Experienced (INI-Naïve) Adult Subjects

<table>
<thead>
<tr>
<th>ART-Naïve Adults</th>
<th>ART-Exp Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ING112276 DTG Once Daily + 2 NRTI N=155</td>
</tr>
<tr>
<td>Hepatitis B test results</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>155</td>
</tr>
<tr>
<td>Reactive, n (%)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Negative</td>
<td>154 (&gt;99)</td>
</tr>
<tr>
<td>Hepatitis C test results</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>154</td>
</tr>
<tr>
<td>Reactive</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Negative</td>
<td>142 (92)</td>
</tr>
<tr>
<td>Hepatitis B &amp; C reactive test results</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>154</td>
</tr>
<tr>
<td>B only</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>C only</td>
<td>12 (8)</td>
</tr>
<tr>
<td>B and C</td>
<td>0</td>
</tr>
<tr>
<td>Neither</td>
<td>141 (91)</td>
</tr>
<tr>
<td>CDC category</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>155</td>
</tr>
<tr>
<td>A: asymptomatic or lymphadenopathy or acute HIV</td>
<td>133 (86)</td>
</tr>
<tr>
<td>B: symptomatic, not AIDS</td>
<td>21 (14)</td>
</tr>
<tr>
<td>C: AIDS</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 1.16, ISO Table 1.18, and ING111762 Week 24 CSR Table 6.13 and Table 6.14

BR, background regimen
1.3.2.1.3. Studies in ART-Experienced (INI-Resistant) Adults

In the two pivotal studies in ART-experienced (INI-resistant) adults, 24% of subjects were HBV and/or HCV co-infected. The percentage of subjects who were positive for HCV was greater in the subjects that received DTG BID compared to the subjects that received DTG once daily. A large proportion of subjects were classified as CDC category C/AIDS at Baseline, reflective of their advanced treatment status.

Table 12 Summary of HBV and/or HCV Co-Infection Status and CDC Classification – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th></th>
<th>ING112961 Cohort I DTG 50 mg Once Daily + BR N=27</th>
<th>ING112574 Cohort II DTG 50 mg BID + BR N=24</th>
<th>TOTAL DTG 50 mg BID N=207 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B &amp; C reactive test results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>23</td>
<td>21</td>
<td>182</td>
</tr>
<tr>
<td>B only, n (%)</td>
<td>0</td>
<td>2 (8)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>C only</td>
<td>2 (7)</td>
<td>6 (25)</td>
<td>26 (14)</td>
</tr>
<tr>
<td>B and C</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Neither</td>
<td>21 (78)</td>
<td>13 (54)</td>
<td>144 (79)</td>
</tr>
<tr>
<td>CDC category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>27</td>
<td>24</td>
<td>183</td>
</tr>
<tr>
<td>A: asymptomatic or lymphadenopathy or acute HIV</td>
<td>4 (15)</td>
<td>10 (42)</td>
<td>44 (24)</td>
</tr>
<tr>
<td>B: symptomatic, not AIDS</td>
<td>7 (26)</td>
<td>6 (25)</td>
<td>37 (20)</td>
</tr>
<tr>
<td>C: AIDS</td>
<td>16 (59)</td>
<td>8 (33)</td>
<td>102 (56)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 1.17 and Table 1.19
BR, background regimen

1.3.2.1.4. Other Completed and Ongoing Studies in Adults

In the ongoing study ING116070, all subjects were negative for HBV or HCV, with approximately half (54%) of the subjects classified as CDC category A at Baseline (ING116070 Week 2 Synoptic CSR Table 6.10 and Table 6.11).

1.3.2.2. Plasma HIV-1 RNA Values and CD4+ Cell Counts at Baseline

1.3.2.2.1. Studies in ART-Naïve Adults

Median Baseline HIV-1 RNA ranged from 4.46 to 4.69 \( \log_{10} \) copies per millilitre (c/mL), and median Baseline CD4+ cell count ranged from 305 to 362 cells/cubic millimetre (mm\(^3\)) (Data Source: ISO Table 1.30 and Table 1.32).

1.3.2.2.2. Studies in ART-Experienced (INI-Naïve) Adults

In ART-experienced (INI-naïve) subjects, median Baseline HIV-1 RNA ranged from 4.171 to 4.209 \( \log_{10} \) c/mL, and median Baseline CD4+ cell count ranged from 204.5 to 193 cells/mm\(^3\) (Data Source: ING111762 Week 24 CSR Table 6.21 and Table 6.22).
1.3.2.2.3. **Studies in ART-Experienced (INI-Resistant) Adults**

Median Baseline HIV-1 RNA ranged from 4.26 to 4.48 log_{10} c/mL, median Baseline CD4+ cell count ranged from 114 to 202 cells/mm^3 (Data Source: ISO Table 1.31 and Table 1.33).

1.3.2.2.4. **Other Completed and Ongoing Studies in Adults**

In ING116070, median Baseline HIV-1 RNA was 4.726 log_{10} c/mL, and median Baseline CD4+ cell count was 360 cells/mm^3 (Data Source: ING116070 Week 2 Synoptic CSR Table 6.17 and Table 6.18).

1.3.2.3. **Concomitant ART**

1.3.2.3.1. **Studies in ART-Naïve Adults**

The NRTI backbone was investigator-selected in studies ING112276 and ING113086, and was a choice of either TDF/FTC or ABC/3TC. Table 13 summarizes the numbers of subjects on TDF/FTC versus ABC/3TC for these two studies.

<table>
<thead>
<tr>
<th>NRTI Backbone</th>
<th>ING112276</th>
<th>ING113086</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG Once Daily + 2 NRTI</td>
<td>EFV 600 mg Once Daily + 2 NRTI</td>
</tr>
<tr>
<td>N=155</td>
<td>N=50</td>
<td>N=411</td>
</tr>
<tr>
<td>TDF/FTC, n (%)</td>
<td>104 (67)</td>
<td>34 (68)</td>
</tr>
<tr>
<td>ABC/3TC, n (%)</td>
<td>51 (33)</td>
<td>16 (32)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 1.41

In study ING114467, subjects were randomized to receive either DTG 50 mg plus ABC/3TC once daily or TDF/FTC/EFV once daily; thus by design, approximately 50% of subjects received each NRTI backbone.

1.3.2.3.2. **Studies in ART-Experienced (INI-Naïve) Adults**

The background regimen for subjects in ING111762 was investigator-selected and was limited to two agents, one of which must have been fully active based on Screening resistance testing. The majority of subjects on either arm received a protease inhibitor, with DRV plus RTV used most commonly, followed by lopinavir (LPV)/RTV, and atazanavir (ATV) plus RTV. The NRTI tenofovir and non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine were also commonly used in OBR (Table 14).
Table 14  Summary of Background Antiretroviral Regimen (≥5% in Any Treatment Arm) – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Background Regimen</th>
<th>DTG 50 mg Once Daily + BR</th>
<th>RAL 400 mg BID + BR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=354 n (%)</td>
<td>N=361 n (%)</td>
<td>N=715 n (%)</td>
<td></td>
</tr>
<tr>
<td>darunavir/ritonavir, tenofovir</td>
<td>62 (18)</td>
<td>73 (20)</td>
<td>135 (19)</td>
</tr>
<tr>
<td>lopinavir/ritonavir, tenofovir</td>
<td>40 (11)</td>
<td>40 (11)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>darunavir/ritonavir, etravirine</td>
<td>33 (9)</td>
<td>40 (11)</td>
<td>73 (10)</td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>36 (10)</td>
<td>35 (10)</td>
<td>71 (10)</td>
</tr>
<tr>
<td>atazanavir/ritonavir, tenofovir</td>
<td>36 (10)</td>
<td>33 (9)</td>
<td>69 (10)</td>
</tr>
<tr>
<td>darunavir/ritonavir, maraviroc</td>
<td>23 (6)</td>
<td>19 (5)</td>
<td>42 (6)</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 6.35
BR, background regimen

1.3.2.3.3. Studies in ART-Experienced (INI-Resistant) Adults

A wide variety of antiretrovirals were used as OBR, when optimization of background regimen was allowed and encouraged by protocol [at Day 11 (ING112961) or Day 8 (ING112754)] in the ART-experienced (INI-resistant) subjects, as summarized in Table 15. The most commonly co-administered antiretrovirals in both studies were DRV-RTV, FTC+TDF, and ETR.
### Table 15  Summary of Background ART Received at Day 11 and Day 8 (≥5% in Any Treatment Arm) - ART-Experienced (INI-Resistant) Adults

<table>
<thead>
<tr>
<th></th>
<th>ING112961 at Day 11</th>
<th>Cohort I DTG 50 mg Once Daily + BR N=27</th>
<th>Cohort II DTG 50 mg BID + BR N=24</th>
<th>ING112574 at Day 8 DTG 50 mg BID + BR N=183</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any medication, n (%)</td>
<td>27 (100)</td>
<td>24 (100)</td>
<td>183 (100)</td>
<td></td>
</tr>
<tr>
<td>Darunavir-ritonavir</td>
<td>22 (81)</td>
<td>20 (83)</td>
<td>120 (66)</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>13 (48)</td>
<td>13 (54)</td>
<td>66 (36)</td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>4 (15)</td>
<td>4 (17)</td>
<td>57 (31)</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>12 (44)</td>
<td>8 (33)</td>
<td>47 (26)</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1 (4)</td>
<td>4 (17)</td>
<td>27 (15)</td>
<td></td>
</tr>
<tr>
<td>Tipranavir-ritonavir</td>
<td>0</td>
<td>0</td>
<td>14 (8)</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>2 (7)</td>
<td>0</td>
<td>9 (5)</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>3 (11)</td>
<td>1 (4)</td>
<td>8 (4)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine+abacavir</td>
<td>4 (15)</td>
<td>1 (4)</td>
<td>6 (3)</td>
<td></td>
</tr>
<tr>
<td>Atazanavir-ritonavir</td>
<td>3 (11)</td>
<td>2 (8)</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>4 (15)</td>
<td>4 (17)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Lopinavir-ritonavir</td>
<td>3 (11)</td>
<td>1 (4)</td>
<td>6 (3)</td>
<td></td>
</tr>
<tr>
<td>Saquinavir-ritonavir</td>
<td>0</td>
<td>2 (8)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Zidovudine+lamivudine</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Etravirine-ritonavir</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Zidovudine+lamivudine+abacavir</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Efavirenz+emtricitabine+tenofovir</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
</tbody>
</table>

Data Source: ING112961 Week 96 CSR Table 6.36 and ING112574 Week 24 CSR Table 6.42
BR, background regimen

### 1.3.2.3.4. Other Completed and Ongoing Studies in Adults

Background ART for ING116070 was ABC/3TC and therefore all 13 subjects were receiving ABC/3TC at the start of the study (Data Source: ING116070 Week 2 Synoptic CSR Table 6.22).
2. ADVERSE EVENTS

2.1. Analysis of Adverse Events

The definition of an Adverse Event (AE) is provided in APPENDIX 3.

2.1.1. Common Adverse Events

For ART-naïve and ART-experienced (INI-naïve) patients, the safety profile for DTG 50 mg once daily was comparable to RAL and generally favourable to Atripla and EFV. The most frequently observed AEs across patient populations were diarrhoea, nausea, and headache, which were typically Grade 1 or 2 in severity, and typically did not lead to discontinuation from studies. Gastrointestinal (GI) tolerability was comparable to RAL- and EFV-containing regimens. Few cases of hypersensitivity reaction and/or severe rash were seen, and the rates of these events were comparable to or lower than RAL- and EFV-containing regimens, respectively. No subjects were reported to have the most serious forms of rash, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or erythema multiforme (EM). The incidence of mild to moderate skin reactions with DTG were comparable to or lower than observed with RAL- or EFV-containing regimens, respectively. Finally, psychiatric and nervous system disorders with DTG were comparable to RAL and favourable to both Atripla and EFV, in terms of reporting rates, nature and severity. Overall, the AE profile was generally similar to RAL and improved when compared with an EFV-containing regimen.

In addition, the safety profile for DTG at the 50 mg twice daily dose recommended for ART-experienced, INI-resistant patients is generally comparable to the safety profile for the 50 mg once daily dose.

2.1.1.1. Frequently Reported Adverse Events

A summary of AEs by System Organ Class (SOC) and maximum toxicity per study and overall is provided in ISO Table 2.508. The most commonly reported AEs in the total DTG population were diarrhoea, nausea, and headache (Table 16).
Table 16  Summary of Common Adverse Events by Frequency (≥5% of Subjects) – Total Phase IIb/III DTG Treatment Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Total DTG N=1571 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>1315 (84)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>257 (16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>189 (12)</td>
</tr>
<tr>
<td>Headache</td>
<td>183 (12)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>171 (11)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>126 (8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>124 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>113 (7)</td>
</tr>
<tr>
<td>Cough</td>
<td>108 (7)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>84 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>85 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>71 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>82 (5)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.508

2.1.1.1.  Studies in ART-Naïve Adults

Diarrhoea, nasopharyngitis, nausea, headache, and fatigue were the most commonly reported clinical AEs and occurred at similar rates across the treatment groups (see ISO Table 2.17 for a full listing of AEs). Insomnia was observed at a significantly higher frequency with DTG in ING114467. However, the incidence was lower than EFV in ING112276 and similar to RAL in ING113086. In ING114467, insomnia events were generally mild in intensity, with only one subject discontinuing on the DTG+ABC/3TC arm (vs. two subjects discontinuing on the EFV/TDF/FTC arm). Data on insomnia are further described in Section 2.1.5.8.2. AE rates between DTG and RAL were generally similar, and AEs such as dizziness, rash, and abnormal dreams occurred at higher frequencies in the EFV and/or Atripla treatment groups. The majority of events reported in DTG and comparator groups were considered Grade 1 or Grade 2 in intensity, with few Grade 3 or Grade 4 AEs reported. In the DTG total, 8% (75/980) and 2% (24/980) of subjects had Grade 3 or 4 AEs, respectively. From the Phase 3 studies, in the EFV/TDF/FTC group in ING114467, 14% (58/419) and 2% (10/419) of subjects had Grade 3 or 4 AEs, respectively, and in the RAL group in ING113086, 8% (32/411) and 1% (5/411) of subjects had Grade 3 or 4 AEs, respectively (Data Source: ISO Table 2.20).
Table 17  Summary of Common Adverse Events by Frequency (≥5% of Subjects in the Combined DTG Group) – ART-Naïve Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ING112276 DTG once daily + 2 NRTI N=155</th>
<th>EFV 600 mg once daily + 2 NRTI N=50</th>
<th>ING113086 DTG 50 mg once daily + 2 NRTI N=411</th>
<th>RAL 400 mg BID + 2 NRTI N=411</th>
<th>ING114467 DTG 50 mg + ABC/3TC once daily N=414</th>
<th>EFV/TDF/FTC once daily N=419</th>
<th>TOTAL DTG once daily N=980</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)(a)</td>
<td>n (%)(a)</td>
<td>n (%)(a)</td>
<td>n (%)(a)</td>
<td>n (%)(a)</td>
<td>n (%)(a)</td>
<td>n (%)(a)</td>
<td>n (%)(a)</td>
</tr>
<tr>
<td>Any event</td>
<td>142 (92)</td>
<td>46 (92)</td>
<td>343 (83)</td>
<td>346 (84)</td>
<td>369 (89)</td>
<td>387 (92)</td>
<td>854 (87)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>25 (16)</td>
<td>7 (14)</td>
<td>49 (12)</td>
<td>51 (12)</td>
<td>72 (17)</td>
<td>75 (18)</td>
<td>146 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (15)</td>
<td>7 (14)</td>
<td>60 (15)</td>
<td>54 (13)</td>
<td>59 (14)</td>
<td>57 (14)</td>
<td>142 (14)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>22 (14)</td>
<td>5 (10)</td>
<td>53 (13)</td>
<td>54 (13)</td>
<td>62 (15)</td>
<td>60 (14)</td>
<td>137 (14)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (14)</td>
<td>3 (6)</td>
<td>53 (13)</td>
<td>49 (12)</td>
<td>55 (13)</td>
<td>56 (13)</td>
<td>130 (13)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (8)</td>
<td>6 (12)</td>
<td>22 (5)</td>
<td>18 (4)</td>
<td>64 (15)</td>
<td>43 (10)</td>
<td>99 (10)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (5)</td>
<td>6 (12)</td>
<td>20 (5)</td>
<td>19 (5)</td>
<td>54 (13)</td>
<td>50 (12)</td>
<td>81 (8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11 (7)</td>
<td>1 (2)</td>
<td>29 (7)</td>
<td>26 (6)</td>
<td>36 (9)</td>
<td>43 (10)</td>
<td>76 (8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (5)</td>
<td>11 (22)</td>
<td>23 (6)</td>
<td>24 (6)</td>
<td>37 (9)</td>
<td>148 (35)</td>
<td>68 (7)</td>
</tr>
<tr>
<td>Cough</td>
<td>15 (10)</td>
<td>2 (4)</td>
<td>20 (5)</td>
<td>18 (4)</td>
<td>24 (6)</td>
<td>29 (7)</td>
<td>59 (6)</td>
</tr>
<tr>
<td>Depression</td>
<td>11 (7)</td>
<td>6 (12)</td>
<td>21 (5)</td>
<td>18 (4)</td>
<td>23 (6)</td>
<td>26 (6)</td>
<td>55 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (7)</td>
<td>4 (8)</td>
<td>21 (5)</td>
<td>22 (5)</td>
<td>23 (6)</td>
<td>22 (5)</td>
<td>55 (6)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>3 (2)</td>
<td>4 (8)</td>
<td>12 (3)</td>
<td>8 (2)</td>
<td>30 (7)</td>
<td>72 (17)</td>
<td>45 (5)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>9 (6)</td>
<td>5 (10)</td>
<td>22 (5)</td>
<td>18 (4)</td>
<td>20 (5)</td>
<td>15 (4)</td>
<td>51 (5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (5)</td>
<td>4 (8)</td>
<td>16 (4)</td>
<td>20 (5)</td>
<td>23 (6)</td>
<td>17 (4)</td>
<td>46 (5)</td>
</tr>
</tbody>
</table>

2.1.1.1.2. Studies in ART-Experienced (INI-Naïve) Adult Subjects

The most commonly reported individual AEs among subjects receiving DTG were diarrhoea, upper respiratory tract infection, headache, nausea, and cough, with no appreciable difference between treatment groups (Table 18). Overall, individual AE rates between DTG and RAL were generally similar. The majority of AEs for DTG and RAL were Grade 1 or 2 in intensity. In the DTG treatment group, 7% (25/357) and 2% (8/357) of subjects had Grade 3 or 4 AEs, respectively, and in the RAL treatment group, 11% (40/362) and 3% (11/362) of subjects had Grade 3 or 4 AEs (Data Source: ING111762 Week 24 CSR Table 8.4).
Table 18  Summary of Common Adverse Events by Frequency (≥5% of Subjects in any Treatment Group) – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>DTG 50 mg once daily + BR N=357 n (%)a</th>
<th>RAL 400 mg BID + BR N=362 n (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>265 (74)</td>
<td>281 (78)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>72 (20)</td>
<td>62 (17)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>38 (11)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (9)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (7)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (8)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>26 (7)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Influenza</td>
<td>21 (6)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (6)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (4)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (5)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Rash</td>
<td>18 (5)</td>
<td>17 (5)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.524
a. Number and percent of subjects with adverse event.

2.1.1.1.3. Studies in ART-Experienced (INI-Resistant) Adults

The most commonly reported individual AEs were diarrhoea, bronchitis, nausea, headache, and pyrexia (Table 19). Diarrhoea, nausea, and headache for this study population are further described under Section 2.1.5.5.3 and Section 2.1.5.7.3. The majority of events reported were considered Grade 1 or Grade 2 in intensity, with few Grade 3 or Grade 4 AEs. In the group of subjects receiving DTG 50 mg BID, 18% (37/207) and 5% (11/207) of subjects had Grade 3 or 4 AEs, respectively (Data Source: ISO Table 2.21).
Table 19 Summary of Common Adverse Events by Frequency (in at least 5% of Subjects in the Combined DTG Group) – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ING112961</th>
<th>ING112574</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort I</td>
<td>Cohort II</td>
<td>DTG 50 mg</td>
</tr>
<tr>
<td></td>
<td>DTG 50 mg once daily</td>
<td>BID</td>
<td>N=27 a</td>
</tr>
<tr>
<td>Any event</td>
<td>26 (96)</td>
<td>23 (96)</td>
<td>147 (80)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (19)</td>
<td>9 (38)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 (15)</td>
<td>6 (25)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (15)</td>
<td>2 (8)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (15)</td>
<td>5 (21)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (7)</td>
<td>2 (8)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (11)</td>
<td>4 (17)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (4)</td>
<td>4 (17)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (19)</td>
<td>1 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (19)</td>
<td>2 (8)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (4)</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

a. Number and percent of subjects with adverse event.
Data Source: ISO Table 2.18

2.1.1.2. Adverse Events by Maximum Intensity

The majority of adverse events reported in the clinical studies were Grade 1 or 2 (mild or moderate). In the ART-experienced (INI-resistant) studies, more Grade 3 events were reported, but this patient population had more advanced HIV (Section 1.3.2.2.3) and more concomitant antiretrovirals (Table 15), which likely contributed to this finding.

Table 20 Summary of All Adverse Events by Maximum Toxicity – Total Phase IIb/III DTG Treatment Population

<table>
<thead>
<tr>
<th>Maximum Toxicity</th>
<th>Total DTG N=1571 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>562 (36)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>561 (36)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>142 (9)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>49 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>1315 (84)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.508

2.1.1.3. Investigator-Assessed Drug-Related Adverse Events

A summary of treatment-related adverse events by study and overall is provided in ISO Table 2.511. Adverse events judged by the investigator to be reasonably attributable to DTG, with a frequency of at least 1% in the combined database of all DTG subjects
(n=1571), are presented in Table 21. Nausea and diarrhoea were the most commonly reported AEs in the total DTG population.

Table 21  Summary of Treatment-Related Adverse Events in at least 1% of Subjects – Total Phase IIb/III DTG Treatment Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Total DTG N=1571 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>508 (32)</td>
</tr>
<tr>
<td>Nausea</td>
<td>124 (8)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>93 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>68 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>48 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>54 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43 (3)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>37 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32 (2)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>22 (1)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>18 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>22 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19 (1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.511

2.1.1.4. Labelling and Adverse Drug Reactions

Adverse reactions listed in the Company Reference Safety Information (RSI) and Local Country Labelling are events that have been assessed as being at least possibly causally related to DTG.

Sponsor causality was by evaluation of the frequency and severity of AEs that were considered by investigators to be related to DTG treatment. Study investigators were obligated to assess the relationship between investigational product (IP) and the occurrence of each AE/SAE. A ‘reasonable possibility’ of relatedness to IP is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigators were instructed to use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP were to be considered and investigated. Investigators were also instructed to consult the Investigator Brochure (IB) and/or Product Information (for marketed products, which may be comparators or included in a treatment regimen) in the determination of their assessments.

For the company RSI, and where it is required in Local Country Labelling that adverse events are presented from integrated data by SOC and frequency, adverse events judged by the investigator to be reasonably attributable to DTG, with a frequency of at least 1% in the combined database of all Phase IIb and III DTG subjects (n=1571), were selected for inclusion in the label and are those presented above in Table 21. Nausea and diarrhoea were the most commonly reported AEs in the total DTG population.
Events that occurred below the 1% threshold, but where there was a reasonable possibility of causal relationship to DTG treatment, including events that were indicative of typical severe drug-induced adverse reactions (e.g., hypersensitivity, hepatitis) were considered for inclusion, independent of the incidence. Hypersensitivity and hepatitis were considered possibly related and added to the Company RSI/Local Country Labelling. Those events (e.g., abdominal pain and discomfort) clearly related to an event of higher frequency (e.g., upper abdominal pain) were also selected for inclusion.

Class label statements such as immune reconstitution syndrome were also included.

The frequency categories of events for the label were derived from the frequency of all adverse events in the total Phase IIb and III DTG population, regardless of causality (Data Source: ISO Table 2.508), not just the frequency of events considered to be at least possibly related by the investigator (Table 21). These categories are defined according to MedDRA convention, as follows:

- **Very common:** ≥1/10
- **Common:** ≥1/100 to <1/10
- **Uncommon:** ≥1/1000 to <1/100

Where adverse events are to be presented in Local Country Labelling as a subset of data from individual clinical trials, events for inclusion were assessed by evaluation of the frequency and severity of each AE considered by investigators to be related to DTG in the four pivotal Phase III clinical trials. A cut-off was applied to Grade 2-4 events with a frequency of ≥2% of subjects in any treatment arm within these four studies.

Laboratory abnormalities with a worsening grade from Baseline in ≥2% (for Grades 3 to 4 combined) were provided where required.

### 2.1.1.5. Three-Tier System for the Analysis of Adverse Events

The DTG program has utilized a three-tier system in testing for differences in adverse event rates between treatment arms. Please see the SDAP in m5.3.5.3 for details.

Due to the different populations studied, the analysis was carried out separately on the two pivotal Phase III studies comparing DTG to RAL (ING113086 and ING111762). A different approach was taken for ING114467 with pre-specified analyses based on the AE profile of Atripla.

Tier 1 events for the DTG program are nausea, diarrhoea, and headache. Tier 2 events are any events occurring in at least 4 subjects in any treatment arm within each study. Tier 3 events are all the other events reported in the studies, and were reviewed as part of the overall AE tables.

**ING113086**

For the three Tier 1 events, the reported incidence rates were very similar for DTG and RAL, and the differences were not statistically significant. Nausea was reported in 15% and 13% of subjects on DTG and RAL, respectively; diarrhoea was reported in 12% of
subjects in both arms; headache was reported in 13% and 12% of subjects on DTG and RAL, respectively.

Table 22  Summary of Tier 1 Adverse Events in ING113086

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Treatment</th>
<th>Number with event</th>
<th>Treatment diff (SE)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>DTG</td>
<td>60 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>54 (13%)</td>
<td>1.46% (0.024)</td>
<td>0.5448</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>DTG</td>
<td>49 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>51 (12%)</td>
<td>-0.49% (0.023)</td>
<td>0.8310</td>
</tr>
<tr>
<td>Headache</td>
<td>DTG</td>
<td>53 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>49 (12%)</td>
<td>0.97% (0.023)</td>
<td>0.6722</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.121
Based on Chi-squared test.

For the common Tier 2 events, the adjusted p-values using a Double False Discovery Rate multiplicity method applied at the SOC level, and then preferred term level, did not result in any statistically significant p-values. Therefore no common adverse events were identified as having a potential safety signal for DTG versus RAL in this study.

The review of all other adverse events that occurred at a low frequency and contribute to Tier 3 of this analysis showed no clinically significant findings.

ING111762

For the three Tier 1 events, the reported incidence rates were very similar for DTG and RAL, and the differences were not statistically significant. Nausea was reported in 7% and 8% of subjects on DTG and RAL, respectively; diarrhoea was reported in 20% and 17% of subjects on DTG and RAL, respectively; headache was reported in 9% and 8% of subjects on DTG and RAL, respectively.

Table 23  Summary of Tier 1 Adverse Events in ING111762

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Treatment</th>
<th>Number with event</th>
<th>Treatment diff (SE)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>DTG</td>
<td>26 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>28 (8%)</td>
<td>-0.45% (0.020)</td>
<td>0.8182</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>DTG</td>
<td>72 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>62 (17%)</td>
<td>3.04% (0.029)</td>
<td>0.2951</td>
</tr>
<tr>
<td>Headache</td>
<td>DTG</td>
<td>31 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>29 (8%)</td>
<td>0.67% (0.021)</td>
<td>0.7444</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.556
Based on Chi-squared test.
For the common Tier 2 events, the adjusted p-values using a Double False Discovery Rate multiplicity method applied at the System Organ Class level, and then preferred term level, did not result in any statistically significant p-values. Therefore no common adverse events were identified as having a potential safety signal for DTG versus RAL in this study.

The review of all other adverse events which occurred at a low frequency and contribute to Tier 3 of this analysis showed no clinically significant findings.

2.1.1.6. Pharmacokinetic/Pharmacodynamic Analyses

There was no statistically significant (p>0.05) correlation between DTG exposure and occurrence of the most common AEs including diarrhoea, headache, nausea, and abdominal pain in all study populations evaluated based on PK/PD analyses in each Phase IIb/III study, suggesting the presence of these most common AEs were not driven by systemic DTG exposure (m2.7.2, Section 3.2).

Full details of the pharmacokinetics and PK/PD analyses can be found in m2.7.2, Section 2.3 and m2.7.2 Section 3.2.

2.1.2. Deaths

As of the submission cut-off date, there were 16 deaths reported across the DTG clinical studies and compassionate use program:

- Six deaths were reported in the ART-naïve population (ING112276, ING113086, and ING114467); 3 on DTG 50 mg once daily, 1 on RAL, and 2 on Atripla. A tabular listing of these deaths is provided in Appendix Table 4.

- Two deaths were reported in the ART-experienced (INI-naïve) population (ING111762), both on RAL. A tabular listing of these deaths is provided in Appendix Table 5.

- Four deaths were reported in the ART-experienced (INI-resistant) population (ING112961 and ING112574), all receiving DTG at doses of either 50 mg once daily (n=2) or 50 mg BID (n=2). A tabular listing of these deaths is provided in Appendix Table 6.

- Four deaths were reported in other ongoing studies and the compassionate use program, all with DTG dosed at 50 mg BID; a tabular listing of these deaths is provided in Appendix Table 7.

None of the 16 deaths were considered by the investigator to be related to study drug. Deaths were generally due to comorbidities seen in HIV-infected patients.

All 12 cases from the completed clinical studies were included in the Integrated Safety Output (ISO); however it is important to note that the listings of deaths presented in Section 9.4 represents data retrieved from the Sponsor’s global safety database (i.e., OCEANS) on. Since OCEANS is maintained separately from the clinical trials database for these studies, the data presented here will likely be more up to date than that presented in the individual study CSRs. Additionally, discrepancies may
also arise between subject age presented from OCEANS data compared to age presented from the clinical trials database, since OCEANS reports the age of the subject at SAE onset whereas the clinical trials database records age of subject at screening.

Full case narratives for all fatalities are included in APPENDIX 5. Additionally, the deaths relating to adverse events of special interest (AESI) are briefly described below.

**Suicide AESI**

The AESI “Suicide Ideation and Behaviours” is discussed further in Section 2.1.5.8.3. Two subjects committed suicide. One subject was on DTG and the other on RAL:

**Subject 2463 (ING112961)** was a 1 year old White, male, with (Baseline HIV-1 RNA of 2525 c/mL and CD4+ cell count of 452 cells/µL), who started DTG 50 mg BID on 26 September and optimized background regimen at Day 11 with DRV/RTV and ETR. He responded well and his HIV-1 RNA viral load was fully suppressed to <50 c/mL by Day 11. He had a past history of depression, although he had no known history of suicidal ideation or attempts. There was no recorded use of drugs or alcohol. He did have psychosocial stressors of losing his job and apartment, but his suicide on Day 233 was unexpected.

**Subject 3528, (ING113086)** was a 1 year old White male (Baseline HIV-1 RNA viral load of 72,188 c/mL and CD4+ cell count of 746 cells/µL), who was randomized to RAL 400 mg BID with investigator selected backbone of TDF/FTC. His HIV-1 viral load was undetectable at Week 4 and Week 16. There was no reported past history of psychiatric disease or substance abuse and he was not taking any concomitant medication at the time of the event. The police reported that he committed suicide on Day 116.

**Cardiovascular AESI**

The AESI “Cardiovascular Disorders” is discussed in Section 2.1.5.11. Three subjects are summarized here due to a cardiovascular AESI:

**Subject 0055 (ING1112276)** was a 1 year old male, (Baseline HIV-1 RNA viral load of 1,789 c/mL and CD4+ cell count of 159 cells/µL who was randomized to DTG 50 mg once daily and investigator selected TDF/FTC. He was a smoker, with a family history of stroke before the age of 55 years and a Framingham score of 9.7%. He had hyperlipidemia controlled by diet and Grade 1 elevated Total cholesterol (5.9 mmol/L) and LDL cholesterol (4.06 mmol/L) at Baseline. During the study he had transient increases in transaminases associated with alcohol abuse. Throughout the study his lipid levels remained similar or lower than those recorded at baseline. On Study Day 655 he suffered a myocardial infarction without ST elevation. Coronary angiography revealed 100% occlusion of the Right Coronary Artery and 30% stenosis of the distal Left Main Coronary Artery. He was treated with angioplasty and stent placement and started on prasugrel, aspirin, metoprolol and pravastatin. On Day 830 the subject was hospitalized with chest pain and shortness of breath. Cardiac enzymes, ECG tracings, and CT pulmonary angiogram were all normal. The subject admitted use of alcohol and being under psychological stress. A possible anxiety attack was considered. On Day 935 the subject was found face down on the kitchen floor and was pronounced dead. No autopsy
was performed but a diagnosis of myocardial infarction was presumed. The police report stated that there was no foul play and no suspicion of suicide. The investigator considered that there was no reasonable possibility that the events were related to DTG.

**Subject 241 (ING116529)** was a year old male (Baseline HIV-1 RNA viral load of 3823 c/mL and CD4+ cell count of 230 cells/μL), who was randomized to blinded investigational product for seven days, followed by DTG 50 mg BID for 27 days with OBR of ETR and DRV/RTV. The subject's medical history included stroke, hypertension and left ventricular hypertrophy. On 01 August, 34 days after the start of investigational product and 27 days after the start of open-label DTG, the subject died at home due to suspected cardiovascular death. Exact cause of death was unknown. It was unknown whether an autopsy was performed at the time of writing. The investigator considered that there was no reasonable possibility that the suspected cardiovascular death may have been caused by investigational product and DTG.

**Subject FRA-022-001 (ING115502)** was a year male subject, who was taking DTG 50 mg BID with OBR of TDF/FTC and DRV/RTV. The patient’s medical history included encephalitis, Kaposi’s sarcoma, meningioma, and pancytopenia. On 25 August, approximately 7 to 10 days after starting DTG, the subject developed septicaemia and septic shock. He later died on 31 August due to septicaemia and septic shock associated with myocardial infarction and cardiorespiratory arrest. The investigator considered that there was no reasonable possibility that the septicaemia and septic shock may have been caused by DTG.

**Renal AESI**

For further information on the AESI “Renal Disorders” refer to Section 3.1.2 on renal function. Subject 5315 and 9012 are summarized here due to a renal AESI:

**Subject 5315 (ING114467)** was a year old AA/AH male (Baseline HIV-1 RNA viral load of 135,515 c/mL and CD4+ cell count of 219 cells/μL), who was randomized to Atripla, one tablet daily. On 18 December, 262 days after starting study therapy, the subject developed Grade 4 septic shock, renal failure and candidemia. Two days later he developed Grade 4 respiratory failure and then developed a Grade 4 pseudoaneurysm of the lung vessel branch. On 16 January the patient died from renal and respiratory failure. The investigator considered that there was no reasonable possibility that the septic shock, candidemia, pseudoaneurysm of lung vessel branch, and respiratory failure may have been caused by investigational product, but considered that there was a reasonable possibility that the renal failure may have been caused by investigational product.

**Subject 9012 (ING111762)** was a year old male who was randomized to RAL 400 mg BID. The subject had no history of hepatobiliary disorders or infections/infestations other than HIV. On 19 December, 104 days after starting study therapy, the subject developed a Grade 2 infection of unknown origin. On 31 December, he developed Grade 4 acute hepatic failure, renal failure, epistaxis and coagulation factor deficiency. The subject was hospitalized and was withdrawn from the study. The subject died on 01 January due to acute hepatic failure and acute
renal failure. The investigator considered that there was no reasonable possibility that the events were caused by investigational product.

### 2.1.3. Other Serious Adverse Events (SAEs)

The SAE definition in the DTG program was based on International Conference on Harmonisation (ICH) E2A guidance [ICH E2A, 1994]. Additional definitions for the purpose of the DTG clinical program included:

a. All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT ≥3xULN and bilirubin ≥2xULN (>35% direct).

b. All clinically suspected cases of hypersensitivity reaction (HSR) to ABC must have been reported as SAEs in subjects receiving ABC/3TC (or PBO) as IP (ING114467 and ING116070) or as an investigator-selected dual NRTI backbone (investigators could have selected either ABC/3TC or TDF/FTC in ING112276, ING113086, and ING114915), or in those whom may have received an ABC-containing product as OBR in combination with DTG (ING112961, ING112574, ING114916, ING115502 and ING116529). In addition to reporting the case as an SAE, the ABC HSR Case Report Form (CRF) should have been completed within one week of the onset of the hypersensitivity reaction.

No trends in SAEs were noted across the patient populations assessed in the clinical program. The only SAEs reported consistently across the clinical program were pneumonia and suicidal ideation or attempt, but these events were reported in both DTG and comparator treatments, and are more frequently observed in HIV-infected patients than in the general population.

#### 2.1.3.1. Studies in ART-Naïve Adults

The rate of subjects developing at least one SAE at the time of data cut-off for this analysis was low and similar between treatment groups (Table 24).

With the exception of suicide attempt, depression, and neurosyphilis in the EFV group (which were reported in 1 subject each in ING112276), all other individually-reported SAE preferred terms had a reporting rate of <1% across all treatment groups.
Table 24  Summary of Serious Adverse Events in at Least Two Subjects in the Combined DTG Group – ART-Naïve Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG once daily + 2 NRTI N=155</td>
<td>EFV 600 mg once daily + 2 NRTI N=50</td>
<td>DTG 50 mg once daily + 2 NRTI N=411</td>
<td>RAL 400 mg BID + 2 NRTI N=411</td>
</tr>
<tr>
<td>Any event</td>
<td>16 (10)</td>
<td>7 (14)</td>
<td>33 (8)</td>
<td>36 (9)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>0</td>
<td>1 (2)</td>
<td>2 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>0</td>
<td>0</td>
<td>3 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Syphilis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Foot fracture</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intentional overdose</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Humerus fracture</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Road traffic accident</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.39

Few SAEs were considered reasonably attributable to IP by reporting investigators across treatment groups, with no emerging trends apparent for DTG from these data (Table 25).
## Table 25  Summary of All Drug-Related Serious Adverse Events – ART-Naïve Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ING112276 DTG Once Daily + 2 NRTI N=155</th>
<th>ING113086 DTG 600 mg Once Daily + 2 NRTI N=50</th>
<th>ING114467 DTG 50 mg Once Daily + 2 NRTI N=411</th>
<th>RAL 400 mg BID + 2 NRTI N=411</th>
<th>TOTAL DTG 50 mg + ABC/3TC Once Daily N=414</th>
<th>EFV/TDF/FTC Once Daily N=419</th>
<th>TOTAL DTG Once Daily N=980</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>1 (&lt;1)</td>
<td>1 (2)</td>
<td>3 (&lt;1)</td>
<td>5 (1)</td>
<td>1 (&lt;1)</td>
<td>8 (2)</td>
<td>5 (&lt;1)</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hallucination, visual</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Homicidal ideation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paranoia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Convulsion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aphasia</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.41

### 2.1.3.2. Studies in ART-Experienced (INI-Naïve) Adults

No patterns were observed as all SAEs were reported in ≤ 1% of subjects in each treatment group (Table 26).
Table 26  Summary of Serious Adverse Events in at least Two Subjects in any treatment group – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>DTG 50 mg once daily + BR</th>
<th>RAL 400 mg BID + BR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=357 n (%)</td>
<td>N=362 n (%)</td>
</tr>
<tr>
<td>Any event</td>
<td>28 (8)</td>
<td>41 (11)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (&lt;1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Post operative wound infection</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Alcohol withdrawal syndrome</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 8.13

Six subjects experienced SAEs considered by the investigator to be related to IP; two in DTG and four in RAL arms (Table 27).

Table 27  Summary of All Drug-Related Serious Adverse Events – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ING111762</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG 50 mg Once Daily + BR</td>
</tr>
<tr>
<td></td>
<td>N=357 n (%)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Oral mucosal blistering</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Myositis</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure acute</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Rash pruritic</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 8.14

2.1.3.3. Studies in ART-Experienced (INI-Resistant) Adults

The reporting rate of subjects developing at least one SAE at the time of data cut-off for this analysis was low for this treatment population with advanced HIV disease (Table 28). The most frequent individually reported SAE is pneumonia, otherwise all other SAEs had a reporting rate of <1% across the two studies.
Table 28 Summary of Serious Adverse Events in at least Two Subjects in the Combined DTG Group – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ING112961</th>
<th>ING112574</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort I DTG 50 mg once daily N=27</td>
<td>Cohort II DTG 50 mg BID N=24</td>
<td>DTG 50 mg BID N=183</td>
</tr>
<tr>
<td>Any event</td>
<td>6 (22)</td>
<td>8 (33)</td>
<td>27 (15)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>2 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.40

Only two subjects (<1%) were considered to have developed drug-related SAEs (Table 29). Drug eruption, increased alanine aminotransferase, and hyperbilirubinaemia were reported for Subject 568 (see Section 3.1.1.3) and rash and pruritus were reported for Subject 1219, which was subsequently attributed to co-administered etravirine after a negative re-challenge to DTG.

Table 29 Summary of All Drug-Related Serious Adverse Events – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ING112961</th>
<th>ING112574</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort I DTG 50 mg Once Daily N=27</td>
<td>Cohort II DTG 50 mg BID + BR N=24</td>
<td>DTG 50 mg BID + BR N=183</td>
</tr>
<tr>
<td>Any event</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Drug eruption</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.42

2.1.3.4. Other Completed and Ongoing Studies in Adults

ING114915: As of the cut-off date, ten subjects developed SAEs, five from the DTG arm (appendicitis, pyelonephritis, congestive cardiomyopathy, haematemesis, and Hodgkin’s disease) and five from the DRV/RTV arm (acute sinusitis, bronchitis, herpes zoster, bacterial pneumonia, and drug hypersensitivity). All individually-reported SAE terms were isolated and occurred in only one subject (Data Source: ING114915 Table 2). Most SAEs were reported from the Infections and Infestations SOC: two (<1%) in the DTG arm and four (2%) in the DRV/RTV arm.
None of these SAEs were considered as related to study drug by the investigators (Data Source: ING114915 Safety Summary Table 3).

**ING116070:** As of the [redacted] cut-off date for the Week 2 analysis, one SAE of non-drug-related pharyngitis was reported (Data Source: ING116070 Week 2 Synoptic CSR Table 8.10 and Table 8.11).

**ING115502:** As of the [redacted] cut-off date, five subjects developed seven SAEs: angina pectoris; lung infection pseudomonal, and recurrent lung infection pseudomonal; a Grade 4 pulmonary haemorrhage resulting in death; a Grade 4 ALT/aspartate aminotransferase (AST) increase; and a Grade 3 or severe compression of the L1 vertebra. One event of cytomegalovirus retinitis was reported and was considered possibly related to CD4+ cell counts and IRIS. This subject later died (unknown date); the event was considered related to IRIS. All SAE events reported were not considered reasonably attributable to DTG by the reporting investigators (see Brief Written Summary).

### 2.1.3.5. Additional SAEs (from date of last analysis to [redacted])

In addition to the cumulative SAEs reported through to the data cut-off dates applied to individual studies for this integrated summary of safety (refer to Table 3), the Sponsor’s global safety database (i.e., OCEANS) was searched in order to identify any SAE and pregnancy cases that were initially received by the Global Safety and Pharmacovigilance department for each individual study from the date of last analysis (as defined in Table 3) up to [redacted]. For compassionate use program ING114916 and clinical trial ING116529, this was a cumulative search to [redacted]. It is important to reiterate that no reconciliation was performed between OCEANS and the clinical trials’ databases in preparation for this analysis. Also, as these studies are still ongoing, these cases are still subject to change.

Seventy six subjects reported additional SAEs through [redacted]. Fifty of these subjects were receiving DTG and 26 were receiving comparator; additional breakdown by study is provided in Table 30.
### Table 30  SAEs Reported From Date of Last Analyses to

<table>
<thead>
<tr>
<th>Clinical Trial/Compassionate Use Programme</th>
<th>Indication</th>
<th>Dolutegravir</th>
<th>Comparator</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal and Supportive Clinical Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING112276 ART-Naïve</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ING113086 ART-Naïve</td>
<td>7</td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>ING114467 ART-Naïve</td>
<td>5</td>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>ING111762 ART-Experienced (INI-Naïve)</td>
<td>4</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>ING112961 ART-Experienced (INI-Resistant)</td>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ING112574 ART-Experienced (INI-Resistant)</td>
<td>5</td>
<td>NA</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Other Completed and Ongoing Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING114915 ART-Naïve</td>
<td>11</td>
<td>6</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>ING116070 ART-Naïve</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ING114916 ART-Experienced (INI-Resistant)</td>
<td>3</td>
<td>NA</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ING115502 ART-Experienced (INI-Resistant)</td>
<td>10</td>
<td>NA</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>ING116529 ART-Experienced (INI-Resistant)</td>
<td>4</td>
<td>NA</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ING112578 Paediatrics</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ING113125</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ING115697</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING115465</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING116195</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING114580</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>50</strong></td>
<td><strong>26</strong></td>
<td><strong>76</strong></td>
<td></td>
</tr>
</tbody>
</table>

Data Source: OCEANS (see Section 1.1.3)

a. Raltegravir 400 mg twice daily  
b. Atripla  
c. DTG 50 mg once daily

Narratives for the SAEs reported for these 76 subjects are provided in APPENDIX 6. Review of these data did not highlight any new signals for DTG. The most commonly reported SAEs in this data set, reported for 20 subjects, were infections and infestations, including respiratory tract infections, pneumonia, opportunistic infections, urinary tract infection, cellulitis, abscesses, and sepsis (DTG n=13; Atripla n=3; DRV+RTV n=3; RAL n=1). SAEs meeting definitions for AESI (described in Section 2.1.5), or falling in the same SOCs as AESI, are summarized below. Fractures were the only other SAEs observed in more than one subject (DTG n=2; Atripla n=2). The remainder of the SAEs were isolated events that were not AESI for the program and were not deemed related to DTG or comparator agent.

Two subjects in this data set reported SAEs that were considered reasonably attributable to IP by the reporting investigators. Both were episodes of syncope: one considered
related to DTG 50 mg BID (ING112574 Subject 521), and one considered related to Atripla (ING114467 Subject 5332).

**Hepatobiliary Disorders:** Two ART-naïve subjects developed hepatobiliary events; ING113086 Subject 4337 receiving RAL developed ‘hepatotoxicity’, and ING114915 Subject 476006 receiving DTG developed a gallstone.

**Renal Disorders:** ART-naïve Subject 476720 receiving DTG in ING114915 was noted to have acute renal failure during hospitalization for gastroenteritis.

**Gastrointestinal Events:** Nine subjects reported serious GI events in this dataset: seven on DTG, one on DRV/RTV, and one on RAL.

SAEs for DTG included the following GI AESI: abdominal pain (ING115502 Subject FRA-007-001), diarrhoea (ING116529 Subject 82), and acute pancreatitis (ING114915 469103). Additional serious GI events for DTG included haematochezia and rectal haemorrhage (ING112574 Subject 561 with history of angiodysplasia of the colon), gastroenteritis (ING113086 Subject 4700), small intestinal obstruction and abdominal adhesions (ING114915 Subject 468803 with history of partial colectomy) and ruptured haemorrhoids (ING114915 Subject 476016).

SAEs for comparators included: appendicitis (ING113086 Subject 3910 receiving RAL) and constipation (ING114915 485206 receiving DRV plus RTV).

**Nervous System Disorders:** Nine ART-naïve subjects and one ART-experienced (INI-resistant) subject developed neurological SAEs: six subjects on DTG and four on Atripla.

Events reported for DTG included: cerebrovascular accident (verbatim term suspected apoplexy) and cognitive disorder (MRI findings were consistent with the subject’s long history of intravenous amphetamine use) (ING113086 Subjects 3835 and 4556, respectively); epilepsy and Grand mal convulsion (ING114915 Subjects 486008 and 476915, both with relevant medical history); and syncope (ING114915 Subject 468803 and ING112574 Subject 521). Subject 521 in Study ING112574 developed syncope in the setting of dehydration and food poisoning, though the investigator considered that there was a reasonable possibility that the syncope may have been caused by DTG (APPENDIX 6).

Events reported for Atripla in ING114467 included VIIth nerve paralysis (Subjects 5764), sciatica (Subject 6068) and syncope (Subjects 6743 and 5332).

Currently, headache is the only nervous system disorder considered to be an AESI for the DTG development programme.

**Psychiatric disorders:** Twelve subjects in total developed SAE indicative of psychiatric disorders in this data set, comprising four subjects receiving DTG and eight subjects on comparator agents.
Cardiovascular disorders: Eight subjects reported cardiac events: five on DTG, one on blinded IP (DTG versus PBO in ING116529), and two on comparator agents. Events included chest pain, congestive cardiac failure, myocardial infarction, cardiac death (see Section 2.1.2), coronary artery occlusion or coronary artery disease, and atrial flutter.

Neoplasms: Five subjects developed neoplasms: four on DTG (non-Hodgkin’s lymphoma (NHL), squamous cell carcinoma, benign adenoma, metastatic neoplasm), and one on RAL (papilloma). Subject USA-005-001 in ING115502 with NHL died.

2.1.4. Other Significant Adverse Events

2.1.4.1. Adverse Events Leading to Withdrawal

Few subjects receiving DTG developed AEs resulting in the permanent discontinuation of IP and withdrawal from the study. There were no discernible trends for AEs leading to withdrawal for the DTG or comparator treatment groups, as most of these events were isolated cases in individual studies. However, withdrawals due to liver stopping criteria were noted on DTG and comparator arms across the Phase IIb and III studies (See Section 3.1.1). As noted throughout Section 3.1.1 for the various study treatment populations, these events were frequently confounded by concomitant medications or co-infection with hepatitis B or C virus.

2.1.4.1.1. Studies in ART-Naïve Adults

AEs leading to permanent discontinuation of IP and withdrawal from the study were more commonly reported for the Atripla and EFV treatment groups, compared to DTG, and similar between the DTG and RAL treatment groups.

Subjects in Atripla and EFV treatment groups more frequently developed psychiatric disorders resulting in withdrawal, and subjects receiving Atripla more frequently developed nervous system disorders resulting in withdrawal, compared to other treatment groups.
### Table 31  
**Summary of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product by System Organ Class – ART-Naïve Population**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred term</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>4 (3)</td>
<td>5 (10)</td>
<td>10 (2)</td>
<td>42 (10)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>0</td>
<td>3 (6)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Investigations</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>0</td>
<td>2 (4)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Social circumstances</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.43

With the exception of suicide attempt, neurosyphilis, and depression in the ING112276 EFV group, all other individually-reported AE preferred terms resulting in withdrawal had a reporting rate of <1% across all treatment groups.

#### 2.1.4.1.2. Studies in ART-Experienced (INI-Naïve) Adults

There were few AEs leading to discontinuation of investigational product in either group and there were no discernible patterns of events (Table 32).
Table 32  Summary of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product by System Organ Class – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>System organ class</th>
<th>DTG 50 mg Once Daily + BR N=357</th>
<th>RAL 400 mg BID + BR N=362</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>6 (2)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>2 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>1 (&lt;1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>0</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>0</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Investigations</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 8.15

2.1.4.1.3.  Studies in ART-Experienced (INI-Resistant) Adults

Few subjects developed AEs resulting in the permanent discontinuation of IP and withdrawal from the study. All individually reported AEs resulting in the permanent discontinuation of IP and withdrawal from the study had a rate of <1%.

Table 33  Summary of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product by System Organ Class – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>System organ class</th>
<th>ING112961</th>
<th>ING112574</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred term</td>
<td>Cohort I</td>
<td>Cohort II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DTG 50 mg</td>
<td>DTG 50 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Once Daily</td>
<td>BID + BR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=27</td>
<td>N=24</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>2 (7)</td>
<td>2 (8)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Investigations</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.44
2.1.5. Analysis of Adverse Events by Organ System or Syndrome

The AEs of Special Interest (AESI) have been determined for DTG based on: pre-clinical and/or clinical safety data for DTG; labelling and/or regulatory authority interest for approved integrase inhibitors and/or the INI class; and/or regulatory authority requirements. The AESIs for DTG are described in Table 34.
Table 34  Adverse Events of Special Interest (AESIs) for DTG

<table>
<thead>
<tr>
<th>AESI</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Preclinical toxicology studies showed upper and lower GI toxicity (m2.4), including vomiting, diarrhoea and gastric erosions observed in monkey toxicology studies (thought to be related to local toxicity). Certain AE Preferred Terms for the present studies that were considered indicative of general GI intolerability (e.g., nausea, vomiting, and diarrhoea) or peptic ulcers/serious GI erosions were reviewed in detail.</td>
</tr>
<tr>
<td>Rash with or without Systemic Involvement</td>
<td>Severe, potentially life-threatening, and fatal skin reactions (including cases of Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) and hypersensitivity reactions are listed events in the Local Country Prescribing Information for the first marketed INI, RAL. Few serious cases of rash have been reported for DTG during the Phase III clinical development programme.</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Two serious cases of possible drug-induced liver injury (DILI) have been previously described for ING113086 (m5.3.5.1 ING113086 Week 48 CSR), which was the first Phase III study. These cases involved concomitant increases of ALT &gt;3xULN and bilirubin &gt;2xULN, but alkaline phosphatase &lt;2xULN. One case was complicated by evidence of recent cholelithiasis and possible inflammation, and the other case was a hypersensitivity reaction with elements of hepatic involvement in a subject also treated with abacavir/lamivudine. Liver chemistry data and relevant clinical event data from the present studies were reviewed.</td>
</tr>
<tr>
<td>Renal Disorders</td>
<td>Mild non-progressive changes in serum creatinine have been previously described for DTG in the Phase Ib studies ING112276 (m5.3.5.1 ING112276 Week 96 CSR), ING112961 (m5.3.5.2 ING112961 Cohort I Week 96/Cohort II Week 48 CSR), and ING113086 (m5.3.5.1 ING113086 Week 48 CSR). Relevant laboratory data and clinical events for the present studies were reviewed.</td>
</tr>
<tr>
<td>Torsades de Pointes</td>
<td>Events relating to Torsade de Pointes (TdP) are of regulatory authority interest for any drug in development. Per ICH E14 Guidelines [ICH E14, 2005], although drug-induced prolongation of the QT/QTc interval is usually asymptomatic, an increased rate of certain AEs in patients taking an investigational agent can signal potential proarrhythmic effects. As such, Medical Dictionary for Regulatory Activities (MedDRA) AE preferred terms indicative of the clinical events (including but not limited to those specified below), were designated and analysed as AEs potentially related to Torsades de pointes: Torsades de pointes; Sudden death; Ventricular tachycardia; Ventricular fibrillation and flutter; Syncope; Seizures.</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Nervous system disorders (including headache and dizziness) are listed events in the Local Country Prescribing Information for the first marketed INI, RAL. Headache is also considered an expected event in the Sponsor's Development Core Safety Information for DTG, due to findings from the Phase Ib study ING112276 (m5.3.5.1 ING112276 Week 96 CSR), which was a dose ranging study for DTG compared to EFV in combination therapy to treat ART-naïve, HIV-infected subjects.</td>
</tr>
</tbody>
</table>
# Module 2.7.4 Summary of Clinical Safety

<table>
<thead>
<tr>
<th>AESI</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric Disorders including Suicidality</strong></td>
<td>Psychiatric disorders including suicide ideation and behaviours are listed events in the Local Country Prescribing Information for the first marketed INI, RAL. The risk of suicide among HIV-1 positive individuals is more than three times higher than the general population [Jia, 2012]. Subjects under particularly higher risk include the ones with more intensive and frequent hospital care. To date, psychiatric disorders are not considered a signal for DTG.</td>
</tr>
<tr>
<td><strong>Musculoskeletal, Connective Tissue and Bone Disorders</strong></td>
<td>Rhabdomyolysis and myositis are listed events in the Local Country Prescribing Information for the first marketed INI, RAL. To date, musculoskeletal, connective tissue and bone disorders, including rhabdomyolysis and myositis, are not considered a signal for DTG. Relevant clinical event data for the present studies were reviewed.</td>
</tr>
<tr>
<td><strong>Immune Reconstitution Inflammatory Syndrome</strong></td>
<td>A higher rate of immune reconstitution inflammatory syndrome (IRIS) is a potential concern with DTG due to rapid viral load decline and CD4+ cell count recovery. Further background is provided in Section1.1.7. These cases were adjudicated as IRIS events using definitions derived from the literature [Robertson, 2006].</td>
</tr>
<tr>
<td><strong>Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)</strong></td>
<td>An increased incidence of new, recurrent or progressive cancers was seen for RAL (3.5% [16/462]) vs. placebo (1.7% [4/237]) (relative risk [RR; 95% CI] of cancer was 1.5 [0.50, 6.34] in analysis of preliminary 16 Week data from BENCHMRK, investigating ART-experienced subjects, as included in the original submission [Steigbigel, 2008]. However, this signal was later mitigated on analysis of final data (relative risk [95% CI] of cancer was 0.75 [0.30, 1.91] in an analysis of 96 week safety data from STARTMRK and BENCHMRK [Teppler, 2011], indicating no difference between raltegravir and comparator).</td>
</tr>
<tr>
<td><strong>Cardiovascular Disorders</strong></td>
<td>Several studies have reported a higher risk of coronary heart disease in HIV patients receiving combination ART, particularly over longer periods. These studies have involved various methodologies, end-point definitions, patient populations and follow-up periods, as well as different treatment regimens, especially those containing NNRTIs and PIs. The D:A:D cohort provides the largest prospective study of cardiovascular risk with ART [Fris-Møller, 2003a; D:A:D, 2007; Worm, 2011]. The observed rate of myocardial infarction (MI) in this D:A:D study was 3.2/1000 patient years (PY) [Worm, 2011]. Earlier findings from this cohort (with fewer patient years of follow up) reported a higher incidence [Fris-Møller2003b, D:A:D, 2007]. Results from the D:A:D study indicate that, at least for up to 6 years of exposure, there was a relative increase in the incidence of MI of 26% per additional year of exposure to combination ART including a PI and/or a NNRTI [Fris-Møller, 2003b]. The observed rate of MI in HIV-infected patients in other studies has ranged from 1.4 to 11.1/1000 patient years [Calza, 2010; Currier, 2008].</td>
</tr>
</tbody>
</table>
2.1.5.1. Hypersensitivity and Rash

Severe, potentially life-threatening, and fatal skin reactions, including cases of SJS and TEN, and hypersensitivity reactions are listed events in the Local Country Prescribing Information for the first marketed INI, RAL [Isentress, 2012].

The ABC (600 mg)/3TC (300 mg) once daily FDC tablet was used in all of the three supportive/pivotal Phase IIb/III clinical trials in ART-naïve subjects, either as: randomized study medication (ING114467); or investigator-selected dual NRTI backbone (ING112276 and ING113086). The most important risk associated with the ABC component of the FDC is a well characterized drug-related hypersensitivity reaction (HSR), which is generally manageable. \textit{HLA-B*5701} has been shown to be highly associated with ABC HSR, and the practice of pre-therapy screening for and exclusion of patients with \textit{HLA-B*5701} reduces the risk of HSR [EPZICOM US Prescribing Information, 2012; KIVEXA EU Summary of Product Characteristics, 2011]. Thus, screening for and exclusion of subjects with \textit{HLA-B*5701} was required for all subjects in the DTG programme who received (or had the potential to receive due to blinding) ABC-containing products.

Drug hypersensitivity is about 100 times more common in HIV-1-infected patients than in the general population [Carr, 2000] and skin rash is associated with many antiretrovirals [NIA, 2012].

In the DTG clinical program, reporting rates for “Rash” of any grade were low for DTG, comparable with RAL, and lower than observed for EFV/Atripla. Cases of HSR and/or severe skin reactions with or without systemic involvement were rarely seen for DTG. Reporting rates were comparable to RAL and less than observed for EFV/Atripla. Cases reported for DTG and RAL were generally confounded by co-suspect medications that were considered to have contributed to the event. With the exception of the Atripla treatment group in ING114467, rash or hypersensitivity events leading to discontinuation of IP and withdrawal of subjects from study have been infrequent.
## Summary of Characteristics of Hypersensitivity Adverse Events of Special Interest – ART-Naïve Population

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Number of Subjects with Event(^a)</th>
<th>Number of Events</th>
<th>Event Characteristics</th>
<th>Outcome</th>
<th>Action Taken</th>
<th>Time of Onset of First Occurrence, Days</th>
<th>Duration of First Occurrence, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG Once Daily + 2 NRTI N=155</td>
<td>0</td>
<td>2</td>
<td>Drug-related: 0</td>
<td>Recovered/resolved: 0</td>
<td>Investigational product withdrawn: 0</td>
<td>Median: 16.0</td>
<td>Median: 0</td>
</tr>
<tr>
<td>EFV 600 mg Once Daily + 2 NRTI N=50</td>
<td>1 (2)</td>
<td>5</td>
<td>Serious: 0</td>
<td>Recovering/resolving: 0</td>
<td>Dose not changed: 0</td>
<td>Min.: 16</td>
<td>Min.: 0</td>
</tr>
<tr>
<td>DTG 50 mg Once Daily + 2 NRTI N=111</td>
<td>5 (1)</td>
<td>2</td>
<td>Fatal: 0</td>
<td>Not recovered/not resolved: 0</td>
<td>Dose interrupted/delayed: 0</td>
<td>Median: 46.5</td>
<td>Median: 5.0</td>
</tr>
<tr>
<td>RAL 400 mg BID + 2 NRTI N=111</td>
<td>2 (&lt;1)</td>
<td>4</td>
<td>Severe or Grade 3/4: 0</td>
<td>Recovered/resolved with sequelae: 0</td>
<td></td>
<td>Min.: 7</td>
<td>Min.: 5</td>
</tr>
<tr>
<td>DTG 50 mg + ABC/3TC Once Daily N=414</td>
<td>4 (&lt;1)</td>
<td>5</td>
<td>Moderate or Grade 2: 0</td>
<td>Dose not changed: 0</td>
<td></td>
<td>Max.: 138.0</td>
<td>Max.: 58</td>
</tr>
<tr>
<td>EFV/TDF/FTC Once Daily N=419</td>
<td>5 (1)</td>
<td>9</td>
<td>Mild or Grade 1: 0</td>
<td>Dose interrupted/delayed: 0</td>
<td></td>
<td>Max.: 11.0</td>
<td>Max.: 172</td>
</tr>
</tbody>
</table>

\(^a\) Events of special interest are those for which the preferred term contains 'hypersensitivity'.

Data Source: ISO Table 2.60 and ISO Table: 2.82
## Module 2.7.4 Summary of Clinical Safety

### Table 36 Summary of Characteristics of Rash Adverse Events of Special Interest – ART-Naïve Population

<table>
<thead>
<tr>
<th>Drug</th>
<th>N=155 (n (%))</th>
<th>N=50 (n (%))</th>
<th>N=411 (n (%))</th>
<th>N=414 (n (%))</th>
<th>N=419 (n (%))</th>
<th>N=980 (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>13 (8)</td>
<td>9 (18)</td>
<td>23 (6)</td>
<td>25 (6)</td>
<td>21 (5)</td>
<td>73 (17)</td>
</tr>
<tr>
<td><strong>Number of events</strong></td>
<td>14</td>
<td>9</td>
<td>29</td>
<td>28</td>
<td>23</td>
<td>80</td>
</tr>
<tr>
<td><strong>Event characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related</td>
<td>2 (15)</td>
<td>6 (67)</td>
<td>9 (36)</td>
<td>5 (24)</td>
<td>50 (68)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe or Grade 3/4</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate or Grade 2</td>
<td>0</td>
<td>3 (33)</td>
<td>6 (24)</td>
<td>4 (19)</td>
<td>29 (40)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Mild or Grade 1</td>
<td>13 (100)</td>
<td>6 (67)</td>
<td>20 (87)</td>
<td>18 (72)</td>
<td>17 (81)</td>
<td>63 (86)</td>
</tr>
<tr>
<td><strong>Number of occurrences per subject</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>12 (92)</td>
<td>9 (100)</td>
<td>18 (78)</td>
<td>22 (88)</td>
<td>19 (90)</td>
<td>66 (90)</td>
</tr>
<tr>
<td>Two</td>
<td>1 (8)</td>
<td>0</td>
<td>4 (17)</td>
<td>3 (12)</td>
<td>2 (10)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Three or more</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Action taken</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigational product withdrawn</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (10)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Dose not changed</td>
<td>13 (100)</td>
<td>9 (100)</td>
<td>22 (96)</td>
<td>24 (96)</td>
<td>19 (90)</td>
<td>65 (89)</td>
</tr>
<tr>
<td>Dose interrupted/delayed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered/resolved</td>
<td>12 (92)</td>
<td>9 (100)</td>
<td>20 (87)</td>
<td>20 (83)</td>
<td>17 (81)</td>
<td>63 (86)</td>
</tr>
<tr>
<td>Recovering/resolving</td>
<td>0</td>
<td>0</td>
<td>3 (13)</td>
<td>2 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not recovered/not resolved</td>
<td>1 (8)</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>3 (14)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Recovered/resolved with sequelae</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>7 (10)</td>
</tr>
<tr>
<td><strong>Time of onset of first occurrence, days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>211.0</td>
<td>11.0</td>
<td>56.0</td>
<td>77.0</td>
<td>68.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Min.</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Max.</td>
<td>620</td>
<td>495</td>
<td>412</td>
<td>506</td>
<td>336</td>
<td>362</td>
</tr>
<tr>
<td><strong>Duration of first occurrence, days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>22.5</td>
<td>7.0</td>
<td>14.0</td>
<td>32.5</td>
<td>23.5</td>
<td>13.5</td>
</tr>
<tr>
<td>Min.</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Max.</td>
<td>64</td>
<td>18</td>
<td>148</td>
<td>192</td>
<td>293</td>
<td>113</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.58 and ISO Table 2.80

a. Events of special interest are those for which the preferred term contains 'rash' or 'eruption'.
### Module 2.7.4 Summary of Clinical Safety

#### Table 37 Summary of Characteristics of Rash Adverse Events of Special Interest – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Event characteristics</th>
<th>ING111762 DTG 50 mg Once Daily + BR N=357 n (%)</th>
<th>RAL 400 mg BID + BR N=362 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with event</td>
<td>21 (6)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>Number of events</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Drug-related</td>
<td>6 (29)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe or Grade 3/4</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Moderate or Grade 2</td>
<td>2 (10)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Mild or Grade 1</td>
<td>19 (90)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered/resolved</td>
<td>14 (67)</td>
<td>21 (84)</td>
</tr>
<tr>
<td>Recovering/resolving</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Not recovered/not resolved</td>
<td>6 (29)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Action taken</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigational product withdrawn</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dose not changed</td>
<td>21 (100)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Dose interrupted/delayed</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Time of onset of first occurrence, days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>28.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Min.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Max.</td>
<td>197</td>
<td>250</td>
</tr>
<tr>
<td>Duration of first occurrence, days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>29.0</td>
<td>38.0</td>
</tr>
<tr>
<td>Min.</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Max.</td>
<td>134</td>
<td>227</td>
</tr>
</tbody>
</table>

Data Source: IS0 Table 2.537 and Table 2.544

a. Events of special interest are those for which the preferred term contains 'rash' or 'eruption'.
## Table 38  Summary of Characteristics of Rash Adverse Events of Special Interest – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th></th>
<th>ING112961</th>
<th>ING112574</th>
<th>TOTAL DTG 50 mg BID N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort I DTG 50 mg Once Daily + BR N=27</td>
<td>Cohort II DTG 50 mg BID + BR N=24</td>
<td>DTG 50 mg BID + BR N=183</td>
</tr>
<tr>
<td>Number of subjects with any event*</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Number of events</td>
<td>1</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td><strong>Event characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related</td>
<td>0</td>
<td>1 (50)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Fatality</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe or Grade 3 to 4</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Moderate or Grade 2</td>
<td>1 (100)</td>
<td>1 (50)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Mild or Grade 1</td>
<td>0</td>
<td>1 (50)</td>
<td>10 (67)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered/resolved</td>
<td>0</td>
<td>2 (100)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Recovering/resolving</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Not recovered/not resolved</td>
<td>1 (100)</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Recovered/resolved with sequelae</td>
<td>0</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td><strong>Action taken</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigational product withdrawn</td>
<td>0</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Dose not changed</td>
<td>1 (100)</td>
<td>2 (100)</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Dose interrupted/delayed</td>
<td>0</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td><strong>Time of onset of first occurrence, days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>421.0</td>
<td>253.5</td>
<td>18.0</td>
</tr>
<tr>
<td>Min.</td>
<td>421</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Max.</td>
<td>421</td>
<td>505</td>
<td>129</td>
</tr>
<tr>
<td><strong>Duration of first occurrence, days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NA</td>
<td>34.5</td>
<td>16.0</td>
</tr>
<tr>
<td>Min.</td>
<td>NA</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Max.</td>
<td>NA</td>
<td>59</td>
<td>69</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.59 and ISO Table 2.81

*Events of special interest are those for which the preferred term contains 'rash' or 'eruption'.

In ING113086, Subject 4529 (a 42 year old White male treated with DTG plus ABC/3TC) experienced an SAE of hypersensitivity. Flu like symptoms (fever and body aches) were noted approximately ten days after commencing IP, which progressed over the course of four days to include symptoms of rash (profuse, purpuric and coalescing), joint swelling and pain, palpable liver, jaundice and atrial fibrillation. The subject’s ALT peaked at >20xULN and his bilirubin at >4xULN. No additional evidence for liver dysfunction, including encephalopathy or prothrombin time prolongation, was observed. He improved clinically following the discontinuation of DTG and ABC/3TC and introduction of corticosteroid therapy. The investigator implicated DTG in causality; the Sponsor considers ABC/3TC co-suspect, but do not attribute events to an ABC HSR alone.
In ING114915, one SAE of clinically suspected ABC HSR was reported as of the cut-off date (non-serious AEs were not summarized for this data cut). Subject 486003 developed the single symptom of disseminated maculopapular rash 10 days after starting treatment with DRV, RTV and ABC/3TC. Study medications were permanently withdrawn as a result and events improved following treatment with chloropyramine. The investigator considered the event reasonably attributable to ABC/3TC and not DRV+RTV. A narrative for this case is provided in APPENDIX 6.

In ING116070, one subject (Subject 27) had reported a Grade 1 rash at the time of the cut-off date for the Week 2 analysis. This event was not attributed to study drug by the investigator and led to no action with study drug (Data Source: ING116070 Week 2 Synoptic CSR Listing 11). No cases of HSR were reported.

No episodes of serious rash such as SJS, TEN or erythema multiforme have been reported for the DTG development program to date.

There is no evidence for increased risk of rash with or without systemic symptoms with either DTG 50 mg once daily in INI-naïve subjects or DTG 50 mg twice daily in INI-resistant subjects. Due to identification of the case of HSR with organ dysfunction in an ART-naïve subject in ING113086 described above, and additional confounded cases identified in ART-experienced subjects, labelling for DTG is proposed to reflect a warning about hypersensitivity reactions, including monitoring for liver enzymes if HSR is observed for a patient on DTG.

2.1.5.2. Hepatobiliary Disorders

Refer to Section 3.1.1 (Liver Chemistries).

2.1.5.3. Renal Disorders

Refer to Section 3.1.2 (Renal Function).

2.1.5.4. Musculoskeletal Disorders

Refer to Section 3.1.3 (Creatine Phosphokinase).

2.1.5.5. Gastrointestinal Disorders

GI symptoms are among the most frequently encountered in HIV/AIDS, including diarrhea, nausea, vomiting, difficulty swallowing, weight loss and abdominal pain [Hill, 2009]. The more rare GI manifestations of HIV disease and opportunistic infections include upper gastrointestinal tract bleeding & ulceration of the esophagus, stomach and duodenum bleeding [Chalasani, 1999; Steininger, 2006]. Antiretrovirals are themselves commonly associated with GI symptoms [Parente, 1991; Chubineh, 2008].
2.1.5.5.1. Studies in ART-Naïve Adults

General GI Intolerance

Events indicative of general GI intolerance (i.e., diarrhoea, nausea, vomiting, and abdominal pain AE preferred terms only and no derivatives) were commonly reported at similar rates across all three individual Phase IIb/III studies investigating ART-naïve subjects, and between comparative treatment arms within each of the three individual studies. The proportion of general GI intolerance events that were considered reasonably attributable to IP by the reporting investigator were also similar across all three studies, between comparative treatment groups in ING113086 and ING114467, and compared to DTG overall (ISO Table 2.54). The exception to this was the DTG treatment group in Phase IIb study ING112276, in which drug-related general GI intolerance events occurred primarily on the lowest 10 mg DTG dose in this small study.

The majority of subjects developed single episodes of general GI intolerance events, regardless of treatment group, and there was no difference in the frequency of subjects with recurrent GI intolerance events across these three studies or between comparative treatment arms within each of these studies.

Only two general GI intolerance events were reported as SAEs. These were both non-fatal SAEs reported from ING113086, with one each from the DTG and RAL treatment groups (abdominal pain and diarrhoea, respectively). Very few subjects overall developed general GI intolerance events leading to either the temporary interruption or permanent withdrawal of IP (in each individual study and combined), however this was more common for subjects receiving Atripla in ING114467 compared to DTG. Very few subjects developed general GI intolerance events that were considered of severe intensity (i.e., Grade 3 to 4) and rates were similar for DTG, RAL and Atripla (Data Source: ISO Table 2.54).

The median time to onset (TTO) of the first occurrence of a general GI intolerance event with DTG was generally comparable across the three studies and between the comparative treatment arms for each of these studies, with the majority of events occurring within the first two weeks of treatment. Regardless of treatment group, the majority of these general GI intolerance events had resolved at the time of the data cut for this analysis. The duration of the first occurrence (Data Source: ISO Table 2.76) and total duration of all events (Data Source: ISO Table 2.98) were also generally similar across the three studies, and between comparative treatment arms within each of these studies, with the majority of events lasting approximately two to three weeks.

Considered individually, diarrhoea and nausea were the most commonly reported GI AESI, with similar reporting rates across all three individual studies, and between comparative treatment arms within each of the three individual studies (Data Source: ISO Table 2.54). However, cumulative incidence data showed noticeable differences in the incidence of diarrhoea (Data Source: ISO Figure 2.84), with a higher incidence for Atripla in ING114467 than observed for DTG (combined). The cumulative incidence
rates for nausea, abdominal pain, and vomiting were similar for all of these comparative groupings (Data Source: ISO Figure 2.82).

As for all AESIs suggestive of general GI intolerance, the majority of subjects developed single episodes of diarrhoea and/or nausea, regardless of treatment group, and there was no difference in the frequency of subjects with recurrent diarrhoea and/or nausea across the Phase III studies or for DTG combined, with the exception of fewer subjects with recurrent nausea for Atripla in ING114467 than observed for either DTG or RAL (Data Source: ISO Table 2.54).

Reporting rates for drug-related diarrhoea and nausea (as attributed by the investigator) observed for studies ING114467 and ING113086 were similar across treatment groups and with DTG combined.

In Phase IIb study ING112276, rates for investigator attributable nausea and diarrhoea were greater for the DTG group than the EFV group, however the size of this study was small (n=205). In addition, there was an inverse relationship between dose and GI AEs for this study (e.g., higher rate of GI events in subjects treated with lower DTG doses) and for the first 96 weeks, investigators were blinded to DTG dose but not EFV. The Phase III studies ING113086 and ING114467, with a larger study population, provide a more robust estimate for rates of investigator-attributable diarrhoea and nausea with DTG 50 mg once daily in ART-naïve subjects (Data Source: ISO Table 2.54).

Episodes of diarrhoea or nausea were rarely considered of severe intensity (i.e., Grade 3 to 4) and rarely required temporary interruption or permanent discontinuation of IP, suggesting that these symptoms were tolerated by ART-naïve subjects (Data Source: ISO Table 2.54). The majority of nausea events consistently occurred within the first week of treatment, regardless of study or treatment group. The majority of diarrhoea events reported for DTG and RAL in ING113086 and ING114467 occurred after the first 28 days of treatment, with a median TTO of approximately 48 days for DTG (range 1 to 592) and 67 days for RAL (range 1 to 482); the majority of diarrhoea events reported for Atripla occurred within the first 28 days of treatment with a median TTO of 22 days (range 1 to 373) (Data Source: ISO Table 2.76). The broad range of TTO for diarrhoea is suggestive of different causes of diarrhoea, with early events more likely to be drug-related and later events reflecting non-drug-related causes (e.g., incident infections). The majority of the diarrhoea and nausea events lasted for up to two and four weeks, respectively, regardless of treatment group (ISO Table 2.76 and ISO Table 2.98).

**Events Suggestive of GI Ulcerative Lesion**

Event preferred terms considered potentially indicative of GI ulcerative lesion (as identified from medical review of ISO Table 2.54) were rarely reported in ART-naïve subjects. One subject receiving DTG developed a duodenal ulcer (in association with a Grade 4 Burkitt’s like Non-Hodgkin Lymphoma of the GI tract) and one developed a gastric ulcer (subject had a past medical history of gastritis at Baseline) in ING112276 and ING113086, respectively. Neither event was considered reasonably attributable to IP by the reporting investigator. There were no gastric or duodenal ulcers reported for
comparator groups (ISO Table 2.15). Haemoglobin concentrations also increased over time on DTG regimen (Section 3.2.1), as would be expected from the positive effects of ART.

In ING114467, a higher number of subjects in the DTG 50 mg plus ABC/3TC fixed dose combination treatment group (n=10, 2%) developed gastro oesophageal reflux disease (GERD) compared to Atripla (n=1, <1%). However reporting rates for GERD in ING112276 and ING113086 were greater for EFV (n=2, 4%) and RAL (n=11, 3%), respectively, than they were for DTG (n=1 and n=4, respectively, <1%) (Data Source: ISO Table 2.15). The majority of these GERD episodes in ING114467 were Grade 1 to 2 in intensity. No serious cases were reported and no subjects were permanently discontinued from IP and WD from study due to GERD. The majority of the concerned subjects (n=9) had a medical history of GERD/gastrointestinal disorders (n=5), or were receiving concurrent medications, labelled for GERD or general GI intolerance as adverse drug reactions (specifically anxiolytics such as diazepam [n=1], alprozolam [n=1], and citalopram [n=2]) (Data Source: ING114467 Week 48 CSR Section 7.3.1).

2.1.5.5.2. Studies in ART-Experienced (INI-Naïve) Adults

More events indicative of general GI intolerance (i.e., diarrhoea, nausea, vomiting and abdominal pain) were reported for DTG than for RAL, however no real differences were observed when comparing rates for the individual terms (Data Source: ISO Table 2.535). Overall, rates were comparable to those observed for ART-naïve subjects (Data Source: ISO Table 2.54). The proportion considered drug-related were comparable between treatment groups and were lower than reported for ART-naïve subjects.

The majority of subjects developed single episodes of general GI intolerance events, regardless of treatment group, and there was no difference in the frequency of subjects with recurrent GI intolerance events.

One SAE was reported for this population, which was a Grade 2 abdominal pain in the DTG group that was not considered drug-related and did not require any action to be taken with IP. The majority of the events in either treatment group were of Grade 1 intensity, with few Grade 3 events reported. The majority of events required no action to be taken with IP and only one subject, in the RAL treatment group, was withdrawn to a general GI intolerance event (nausea). The majority of events occurred within the first two weeks of treatment, had resolved at the time of analysis, and had a duration of one to two weeks (Data Source: ISO Table 2.542).

When considered individually, few events of nausea, vomiting, or abdominal pain were reported and were comparable between treatment groups, with lower rates for nausea (Data Source: ISO Table 2.535) than observed in the ART-naïve population (i.e., 7% for DTG and 8% for RAL versus 14% for the combined DTG group, respectively, and between 13 to 15% for all comparative ART-naïve treatment groups (Data Source: ISO Table 2.54). Diarrhoea was the most common general GI intolerance event in this ART-experienced (INI-naïve) population, reported at equivalent rates for DTG and RAL; however, reporting rates were higher than observed for both DTG and RAL in ART-
 naïve subjects participating in ING113086 (i.e., 20% and 17% for DTG and RAL, respectively, in ING111762 versus 12% for both DTG and RAL, respectively, in ING113086). Diarrhoea for DTG 50 mg once daily in the ART-experienced (INI-naïve) population was also more frequent than observed for 50 mg BID in the ART-experienced (INI-resistant) population [i.e., 20% versus 14 to 16% (Data Source: ISO Table 2.55)]. This effect is likely related, in part, to use of ritonavir-boosted protease inhibitors in the treatment-experienced population (See Section 1.3.2.3.2).

As for general GI intolerance, the majority of subjects developed single episodes of diarrhoea, and there was no difference in the frequency of subjects with recurrent GI intolerance events regardless of treatment group. There were more episodes of drug-related diarrhoea for DTG (30 of 72 diarrhoea events, 42%) compared to RAL (22/62, 17%; ISO Table 2.535), and more treatment related episodes for DTG 50 mg once daily in this treatment population than observed for DTG 50 mg once daily in ART-naïve subjects participating in ING113086 [30/72 (42%) versus 14/49 (29%)], but similar to rates observed for 50 mg BID in the ART-experienced (INI-resistant) population [10/25 (40%; Data Source: ISO Table 2.55)].

The majority of episodes were considered of Grade 1 or 2 (mild to moderate) intensity regardless of treatment and none were reported as SAEs, regardless of treatment group. The majority of episodes for DTG occurred within the first week of treatment (with a median TTO of 7.5 days to first occurrence); whereas for RAL, the TTO for first occurrence was more variable, although the majority occurred within the first four weeks (median of 22 Days). The TTO for diarrhoea with DTG 50 mg once daily and comparator in this treatment population was earlier than observed for DTG 50 mg once daily and comparators in the ART-naïve treatment group (Data Source: ISO Table 2.76) and similar to observation for diarrhoea with 50 mg BID. The majority of diarrhoea episodes were resolved at the time of analysis, generally within one week, and none required any action to be taken with IP. (Data Source: ISO Table 2.535 and ISO Table 2.542).

**Events suggestive of GI ulcerative lesion**

No cases of gastric or peptic ulcer disease were reported and, following medical review, there were few events that were possibly suggestive of gastrointestinal ulcerative lesion in either treatment group (ISO Table 2.523). Haemoglobin concentrations also increased over time on DTG regimen (Section 3.2.2), as would be expected from the positive effects of ART.

**Pancreatitis**

Four cases of pancreatitis were reported, two from each treatment group, all of which were reported as SAEs (ISO Table 2.508). Two subjects, one in each treatment group, had a medical history significant for episodes of pancreatitis preceding the study. Only one episode, in the RAL group, was considered related to IP and also resulted in the permanent discontinuation of IP and withdrawal from the study. Narratives for these cases can be found in APPENDIX 6. Other than these four cases, only one additional
case of pancreatic AE was reported across the clinical program, that being a case of pancreatic pseudocyst in an ART-naïve subject receiving RAL in ING113086.

Similar rates of post-Baseline-emergent lipase elevations were observed between treatment groups in ING111762, including Grade 3 and Grade 4 elevations, with the majority of treatment-emergent elevations Grade 1 to 2 in intensity. The mean change from Baseline in lipase elevations was lower among those subjects in the DTG treatment arm than RAL subjects. None of the four pancreatitis cases mentioned above were diagnosed on the basis of lipase elevations alone, and all concerned subjects presented with abdominal pain with or without other general GI symptoms (e.g., nausea).

### 2.1.5.5.3. Studies in ART-Experienced (INI-Resistant) Adults

#### General GI intolerance

The incidence of AESIs indicative of general GI intolerance reported overall for DTG 50 mg BID in ART-experienced (INI-resistant) subjects, and specifically from Phase III clinical trial ING112574, and the incidence of those that were considered reasonably attributable to DTG by study investigators (drug-related), were less than observed for: 1) the equivalent treatment population in Phase IIb clinical trial ING112961; and 2) DTG 50 mg once daily in INI-naïve HIV-infected subjects at Week 48 in ING113086 and ING114467 (ART-naïve) and at Week 24 in ING11762 (ART-experienced) (Data Source: ISO Table 2.55). Although the duration of exposure for ING112574 is shorter in comparison to ING113086 and ING114467, drug-related episodes of diarrhoea, nausea, vomiting, and abdominal pain would generally be predicted to occur early in therapy.

The higher reporting rates observed in ING112961 appear to be driven by reports of abdominal pain (3/27) and diarrhoea (5/27) in Cohort I [affecting 7/27 (26%) subjects in total] and by reports of diarrhoea [9/24 (38%)] in Cohort II (Data Source: ISO Table 2.55).

The majority of subjects in ING112574 developed single episodes of general GI intolerance, and there was no difference in the frequency of subjects with recurrent GI intolerance events than observed for DTG 50 mg once daily in INI-naïve, HIV-infected subjects participating in ING113086, ING114467, and ING111762. No subjects in the ART-experienced (INI-resistant) treatment population were withdrawn from IP/study due to a general GI intolerance AESI (nor were any temporary interruptions of IP required; Data Source: ISO Table 2.55). Only one general GI intolerance AESI was reported as an SAE (diarrhoea in ING112961 Cohort II, which was not considered attributable to DTG 50 mg BID by the reporting investigator). All but one event was considered of mild to moderate intensity (i.e., Grade 1 to 2). Patterns for TTO and duration for the first occurrence and all episodes of general GI intolerance with DTG 50 mg BID in ING112574 were similar to those described for DTG 50 mg once daily in ART-naïve HIV-infected subjects (Data Source: ISO Table 2.77 and ISO Table 2.99).

Considered individually, diarrhoea was the most commonly reported GI AESI with DTG 50 mg BID. These events were reported at similar rates to those observed for DTG
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50 mg once daily in ART-naïve, HIV-infected subjects in ING113086 and ING114467 (Data Source: ISO Table 2.54) and lower than observed for DTG 50 mg once daily in ART-experienced (INI-naïve) subjects in ING11762 (Data Source: ISO Table 2.535). As noted for ART-experienced (INI-naïve) subjects, proportions of ART-experienced (INI-resistant) subjects with drug-related diarrhoea on DTG 50 mg BID in ING112574 were similar to those observed for DTG 50 mg in ART-experienced (INI-naïve) subjects, and more than observed in ART-naïve subjects (likely due in part to use of protease inhibitors in the background regimens for treatment-experienced subjects). The majority of subjects receiving DTG 50 mg BID developed single episodes of diarrhoea and/or nausea.

Diarrhoea tended to occur in the first two weeks of treatment with DTG 50 mg BID in ING112574, which was similar to observations for DTG 50 mg once daily in ART-experienced (INI-naïve) subjects, and earlier than observed with DTG 50 mg once daily in ART-naïve subjects (majority >28 days). Duration of diarrhoea on DTG 50 mg BID was similar to observations for DTG 50 mg once daily, lasting for up to three weeks (Data Source: ISO Table 2.55).

Higher reporting rates of diarrhoea were observed with DTG 50 mg BID (Cohort II) compared to DTG 50 mg once daily (Cohort I) in ING112961, but this finding was not observed in ING112574.

These observations for ING112961 were thought to be primarily due to chance (i.e., small population numbers) and notable differences in study population characteristics between the two cohorts, specifically in terms of associated medical history at Baseline and changes in drug regimens at Day 11 (with more new use of protease inhibitors in OBR). ING112574, with a larger study population, provides a more robust estimate for rates of diarrhoea with DTG 50 mg BID in ART-experienced (INI-resistant) subjects. This study showed rates for GI AEs that were generally comparable to DTG 50 mg once daily from 48 Week data in ART-naïve subjects participating ING113086 and ING114467.

Additionally, per Section 2.1.1, although diarrhoea was observed at a higher incidence for DTG 50 mg BID in the ART-experienced (INI-resistant) population (Table 19) compared to DTG 50 mg once daily in ART-naïve populations (Table 17), this was also true for DTG 50 mg once daily in the ART-experienced (INI-naïve) population (Table 18) when compared to DTG 50 mg once daily in ART-naïve populations (Table 17). This suggests that these differences in diarrhoea incidence are an artifact of treatment population [i.e., ART-experienced (both INI-naïve and INI-resistant) versus ART-naïve] rather than DTG dose. This again is likely due to the different background therapy that was used in the ART-experienced populations and generally contained PIs (Table 14 and Table 15), which are known to be associated with diarrhoea. In contrast, all ART-naïve patients received NRTIs in addition to DTG or comparator (Table 13).

Few events of nausea, vomiting, or abdominal pain were reported for DTG 50 mg BID in ART-experienced (INI-resistant) subjects, with lower rates for nausea (Data Source: ISO
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Table 2.55) than observed in the ART-naïve population (i.e., 9% for DTG 50 mg BID versus 14% for the combined DTG 50 mg once daily group; ISO Table 2.54).

**Events suggestive of GI ulcerative lesion**

Event preferred terms considered potentially indicative of GI ulcerative lesion (as identified from medical review of ISO Table 2.55) were rarely reported for INI-resistant subjects. One subject in ING112574 developed a gastric ulcer whilst receiving DTG 50 mg BID, though this was confounded by the use of aspirin. This event was not considered reasonably attributable to DTG by the reporting investigator. Haemoglobin concentrations also increased over time on DTG regimen (Section 3.2.3), as would be expected from the positive effects of ART.

**2.1.5.5.4. Other Completed and Ongoing Studies in Adults**

**ING116070:** The incidence of GI AESI was low. Two subjects (15%) reported nausea, one subject (8%) reported diarrhoea, one subject (8%) reported dyspepsia and one subject (8%) GERD prior to the Week 2 data cut-off. All events were Grade 1 in intensity and attributed to study medication (DTG and/or ABC/3TC) by the investigator. None of these events were reported as serious or led to treatment withdrawal (Data Source: ING116070 Week 2 Synoptic CSR Listing 11).

**ING114915:** One subject developed a SAE of hematemesis prior to the safety data lock point for this study. Subject 476019 was a 62-year-old female with no relevant medical history or risk factors who started receiving DTG 50 mg once daily. She had chronic pain secondary to arthritis and was taking Naprosyn (naproxen). On 31 April 2013, 53 days after the start of DTG, the subject developed grade 2 or moderate hematemesis that lasted for 10 minutes and was hospitalised. The subject had a chest X-ray, ultrasound of gallbladder, and an ECG on 01 April 2013, and all tests were normal. No treatment was needed. Treatment with DTG was continued uninterrupted and the event resolved. The investigator considered that there was no reasonable possibility that hematemesis may have been caused by DTG.

**2.1.5.6. Torsades de Pointes**

**2.1.5.6.1. AEs Related to Torsades de Points (TdP)**

No cases of TdP or sustained ventricular tachycardia have been reported across the DTG clinical program.

**Studies in ART-Naïve Adults**

Few AEs potentially related to Torsades de Points (TdP) were reported (as defined in Table 34). The rate of such events was similar across the treatment groups for the Phase IIb/III clinical trials and for DTG combined (ISO Table 2.15, Listing 2.44).

The most frequently reported events were syncope and tachycardia. All AEs were reported at a rate of <1%, except syncope (1%) for the total DTG treatment population in...
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ING112276. The syncope and tachycardia related events proved to be isolated, and no subjects reported sustained ventricular tachycardia or TdP. Five convulsion-related events were reported in total, one on DTG (confounded by alcohol consumption and lack of sleep), three on RAL (each confounded by alcohol withdrawal, alcohol mediated seizure with sleep deprivation and secondary to viral infection) and one on Atripla.

All these events were investigated and considered by the Sponsor to be unrelated to IP and not indicative of TdP.

Subject 3884 in ING113086 was noted to have an arrhythmia (non-sustained ventricular tachycardia). He was evaluated in clinic where an asymptomatic ECG revealed short runs of non-sustained ventricular tachycardia (NSVT). His blood pressure (BP) was stable. Investigational product was withdrawn pending further workup. Subsequent cardiac monitoring revealed NSVT, premature ventricular contractions and bigeminy without evidence of cardiac ischemia. Cardiac ECG and stress test were unremarkable. His laboratory workup was unremarkable. An external review of his cardiac rhythm suggested a diagnosis of Right Ventricular Outflow Tract Ventricular Tachycardia. This subject was subsequently withdrawn due to acute hepatitis C and liver chemistry elevations.

Studies in ART-Experienced (INI-Naïve) Adults

Few AEs potentially related to TdP were reported in the study (ING111762 Week 24 CSR Table 8.2). These events were investigated and considered by the investigator to be unrelated to IP and not indicative of TdP.

Studies in ART-Experienced (INI-Resistant) Adults

Only four AEs potentially related to TdP were reported from the INI-resistant treatment population (Data Source: ISO Table 2.16; Listing 2.45). Two subjects experienced convulsion (both receiving DTG 50 mg BID): one case was confounded by progressive multifocal leukoencephalopathy, and the other was confounded by a cerebral lesion localized in the right frontal region compatible with residual scarring of a previous neurotoxoplasmosis. Two subjects experienced syncope (one each on the 50 mg once daily and the BID DTG dose). These events were investigated and considered by the Sponsor to be unrelated to IP and not indicative of TdP.

2.1.5.6.2. ECG Findings

Studies in ART-Naïve Adults

No subjects had a Fridericia’s corrected QT interval (QTcF) >500 msec, and few subjects had change from Baseline in QTcF or Bazette’s corrected QT interval (QTcB) ≥60 msec. Additionally on review of data from ING112276 and limited data from ING113086 and ING114467, few clinically significant ECG abnormalities were reported, and no trends were observed in these abnormalities (see Section 4.2.1 for further information).
Studies in ART-Experienced (INI-Naïve) Adults

Most subjects in the both arms had QTcB and QTcF values ≤450 msec throughout the study. One subject receiving DTG and 2 subjects receiving RAL had QTcB or QTcF values >500 msec. Few subjects had change from Baseline in QTcF or QTcB >60 msec. Few clinically significant ECG abnormalities were reported, and no trends were observed in these abnormalities (see Section 4.2.2 for further information).

Studies in ART-Experienced (INI-Resistant) Adults

No subjects receiving DTG 50 mg BID had a Baseline-corrected QTcF >500 msec, and few subjects had a QTcF or Baseline-corrected QTcB change from Baseline ≥60 msec. Week 24 ECG results were available for 115 subjects in ING112574, and a small percentage had abnormal, clinically significant changes. No trends were noted in these abnormalities (see Section 4.2.3 for further information).

2.1.5.6.3. Thorough QTc Study

In thorough QTc study ING111856, a single supra-therapeutic dose of DTG (250 mg suspension) had no significant effect on cardiac repolarisation in a population of 42 healthy subjects, when compared to moxifloxacin (400 mg; active control) or placebo. In this study with demonstrated ability to detect small effects, the upper bound of the two-sided 90% confidence interval for the largest placebo adjusted, Baseline-corrected QTcF was below 10 ms, the threshold for regulatory concern. The maximum observed time-matched change from Baseline in QTcF for DTG 250 mg was at 4 hours (mean ΔΔQTcF of 1.99 msec, 90% CI: -0.55, 4.53 msec). The maximum observed time-matched change from Baseline in QTcF for moxifloxacin was at 4 hours (mean ΔΔQTcF 9.58 msec, 90% CI: 7.05, 12.11 msec). Since the study had adequate sensitivity to detect a positive QT effect with moxifloxacin, it is concluded that this study was valid to assess the effects of DTG on cardiac repolarisation. The dose of 250 mg using a suspension formulation yielded a maximum dolutegravir plasma concentration of 12.4 μg/mL (range: 5.33-20.5 μg/mL), which was ~2.4 fold above mean maximum observed concentration (Cmax) associated with the 50 mg once daily and 50 mg twice daily doses) (See m2.7.2, Section 2.2.2.1 for details).

2.1.5.6.4. Other Completed and Ongoing Studies

In ING116070, there were no AEs potentially related to TdP reported, and no scheduled post Baseline ECG data available, through to the data cut-off for the planned Week 2 analysis.

No SAEs consistent with possible TdP-associated events were reported from other studies.

For ING114916 EAP protocol and the ING115502 Named Patient Program, ECG data was not collected, and for ING114915 these data were not available at the time of the safety data lock point for this ISS.
2.1.5.7. **Nervous System Disorders**

Although headache was a frequently reported AE, the event rate was comparable between treatment arms in studies and across patient populations. Importantly, the PK/PD analysis of ING113086 Week48, ING111762 Week 24, and ING112574 Week 24 data showed no relationship between DTG exposure and the occurrence of headache (m2.7.2, Section 3.2.2).

2.1.5.7.1. **Studies in ART-Naive Adults**

Headaches were commonly reported for DTG at similar rates in both of the Phase III studies in ART-naive adult subjects and at rates similar to the comparative treatment arms. The proportion of headache events that were considered reasonably attributable to DTG by the reporting investigator were also similar across both Phase III studies and were comparable to RAL, and lower than the proportion of equivalent events observed for Atripla in ING114467 (Data Source: ISO Table 2.62).

One headache event confounded by complications of lumbar puncture was reported for DTG in ING112276 study as a non-fatal SAE, but did not result in DTG being withdrawn. One headache in the ING113086 study led to withdrawal of DTG; however, a higher rate of withdrawal due to headache was seen in the Atripla arm in the ING114467 study. The frequency of events, outcomes, maximum grade and action taken were similar for DTG in the Phase IIb/III studies and similar to that seen in general in the comparator arms (Data Source: ISO Table 2.62). The majority of episodes across all treatment group were considered of mild or moderate intensity (Grades 1 to 2).

The TTO for the majority of the events was generally within the first four weeks of treatment (although the median TTO for comparator in ING113086 and ING114467 was earlier than for DTG), were self limiting, resolving within two weeks without interruption of study regimens (Data Source: ISO Table 2.84).

In ING114467 a pre-specified, exploratory analysis compared nervous system disorder events of interest prior to unblinding. Subjects in the Atripla treatment group experienced a statistically significant higher rate for events of interest from the Nervous System Disorders SOC ($p<0.001$), consistent with the current labelling for Atripla. However, there was no difference in the rate of individual AE preferred term of headache between the two treatment groups ($p=1.000$), which is in contrast to the findings from ING112276 (in which the treatment assignment of DTG versus EFV was not blinded and there was a higher rate of headache in subjects receiving DTG, especially at the lowest dose). In addition, a higher rate of subjects reporting nervous system disorders leading to withdrawal was observed for the Atripla treatment group (13/419 [3%]) in ING114467, compared to the DTG 50 mg plus ABC/3TC FDC treatment group (0/414) (Data Source: ING114467 Week48 CSR Table 8.15).
2.1.5.7.2. Studies in ART-Experienced (INI-Naïve) Adults

Headache was commonly reported at the same rate in both treatment groups, at lower rates than observed for DTG or comparator in the ART-naïve population, and at comparable rates to those observed for DTG 50 mg BID in ART-experienced (INI-resistant) subjects. The majority of ART-experienced (INI-naïve) subjects had single episodes, and all were reported as Grade 1 to 2 (mild or moderate) intensity, regardless of treatment group. Few events were considered drug-related by the reporting investigators, and rates were comparable between treatment groups and the majority required no action to be taken with IP, with only one treatment interruption for DTG and no permanent discontinuations and withdrawals for either group. Only one event, in the RAL treatment group, was reported as an SAE (Data Source: ISO Table 2.539).

The TTO for the first occurrence for DTG was within four weeks for the majority of subjects, but slightly longer for those in the RAL treatment group, with the majority of episodes having resolved by the time of analysis regardless of treatment group (Data Source: ISO Table 2.546). The duration of first occurrence for the majority of subjects in either treatment group was within three weeks.

2.1.5.7.3. Studies in ART-Experienced (INI-Resistant) Adults

No dose-related effect was observed between DTG dosed once daily versus BID for the AESI of headache. The number of subjects reporting headache events in ING112961, Cohort I, was higher than those reported in Cohort II, but the numerical differences for these events between the two Cohorts were small. The number of subjects reporting headache events for ING112961, Cohort II, and ING112574 were lower than those reported in the Phase III studies in ART-naïve adult subjects. Headache events that were considered reasonably attributable to DTG by the reporting investigators were similar across INI-resistant treatment populations receiving DTG 50 mg BID, and comparable to 50 mg once daily in ART-naïve subjects participating in the Phase III studies. The majority of subjects in ING112961 and ING112574 receiving DTG 50 mg BID developed one episode of headache, and this was similar to observations for subjects receiving DTG 50 mg once daily in ART-naïve or ART-experienced (INI-naïve) subjects (Data Source: ISO Table 2.63).

As observed for ART-experienced (INI-naïve) subjects, and similar for ART-naïve subjects, the TTO for the first occurrence for DTG 50 mg BID was within four weeks for the majority of subjects, with the majority of episodes having resolved by the time of analysis regardless of treatment group, generally after a duration of up to three weeks (Data Source: ISO Table 2.85).

2.1.5.7.4. Other Completed and Ongoing Studies in Adults

ING116070: Headache was the most commonly reported AE (reported by 7/13 [54%] of subjects) and all were Grade 1 in intensity (Data Source: ING116070 Week 2 Synoptic CSR Table 8.4). Of these, two headaches were reported as being drug-related (Data Source: ING116070 Week 2 Synoptic CSR Table 8.6). None led to withdrawal.
Additionally, headache is a known AE associated with lumbar punctures and several of the headaches were reported to have a start date on or shortly after the date of the lumbar puncture (Data Source: ING116070 Week 2 Synoptic CSR Listing 11).

2.1.5.8. Psychiatric Disorders Including Suicidality

2.1.5.8.1. Psychiatric AESI Overall

Studies in ART-Naïve Adults

Psychiatric AESI were more commonly reported for Atripla and EFV than for DTG. In the Phase III study ING113086, reporting rates for such events were comparable between DTG and RAL. However, reporting rates and cumulative incidence for DTG combined was higher than for RAL, which appears to be driven by reporting rates for insomnia with DTG in the Phase III study ING114467 (Data Source: ISO Table 2.70 and ISO Figure 2.89). The majority of subjects reporting a psychiatric AESI developed single episodes, regardless of treatment group.

Over all, more psychiatric AESIs for Atripla were considered investigator-attributable than for any other treatment group, or for DTG overall (Data Source: ISO Table 2.70).

More psychiatric AESIs with Atripla and EFV required a dose interruption of IP, and more subjects on Atripla and EFV developed psychiatric AESIs leading to permanent discontinuation of IP and withdrawal from study. Events considered of severe intensity (i.e., Grade 3 to 4) and/or reported as SAEs were reported at low and comparable rates across all treatment groups and for the combined DTG population. One event of completed suicide was reported for RAL (see below) (Data Source: ISO Table 2.70).

In ING114467, a pre-specified, exploratory analysis of the Week 48 data indicated a statistically significantly higher rate of psychiatric AEs of interest over all (as identified by the GSK Medical Monitor prior to study unblinding) \( p=0.008 \), and for abnormal dreams specifically \( p<0.001 \), in the Atripla treatment group. In contrast, subjects in the DTG 50 mg plus ABC/3TC treatment group were significantly more likely to develop insomnia (i.e., RR values and 95% CI were >1) \( p=0.029 \) (Data Source: ING114467 Week 48 CSR Table 8.16).

Overall, TTO for the first occurrence of any psychiatric AESI was generally greater than 28 days for each treatment group in ING112276 and ING113086, but was notably earlier for Atripla and DTG+ABC/3TC in ING114467, with the majority of events in this study occurring within the first two weeks (median 3 days [range 1 to 401] and 15 days [range 1 to 344], respectively) (Data Source: ISO Table 2.92). This appears to be driven by differences in TTO for the individual AESI of insomnia in ING114467 compared to the other two studies (see below). Large proportions of events remained unresolved at the time of data cut for analysis, regardless of treatment group. For those that had resolved, the majority had a duration greater than 35 days. These observations for outcome and event duration are consistent with the nature of these types of events and any required psychiatric treatment (Data Source: ISO Table 2.92 and ISO Table 2.114).
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Considered individually (Data Source: ISO Table 2.70), reporting rates for psychiatric AESIs were generally comparable between treatment groups, with the exception of nightmare and abnormal dreams, which were more commonly reported for Atripla and EFV (Data Source: ISO Figure 2.89), and insomnia, which was reported at similar rates for DTG overall, Atripla, and and EFV, but higher than observed for RAL (Data Source: ISO Figure 2.89). Few sleep disorder, anxiety or depression, bipolar, or suicidal AESIs were reported, and these were generally reported at similar rates across all treatment groups.

When considering reporting rates for drug-related psychiatric AESIs (as assessed by the reporting investigators), these were more commonly reported for Atripla and EFV than for DTG, and DTG was comparable to RAL; this seems to be driven largely by nightmare and abnormal dreams. In ING113086, reporting rates for drug-related psychiatric AESIs were low and comparable for DTG and RAL. In ING114467, overall rates for drug-related psychiatric AESIs were higher for Atripla than for DTG, but the rate for DTG in this study was higher than observed for DTG in ING113086. This appears to be driven by rates of drug-related insomnia, nightmare and abnormal dreams with DTG in ING114467. It is possible that investigators more commonly attributed sleep disturbances to IP in this blinded study that contained Atripla (which is known to be associated with sleep disorders), as discussed further in Section 2.1.5.8.2.

Generally there were no consistent trends for TTO for the first occurrence for each of the individual psychiatric AESIs, especially in relation to DTG treatment, which suggests a general lack of association with the ART regimens investigated in these studies. The notable exception was the TTO for anxiety, which was shorter with Atripla (median 22 days [range 1 to 302]) and longer for RAL (median 205.5 days [range 3 to 46]) when compared to DTG (median 65 days [1 to 417] in ING113086 and 47.5 days [24 to 157] in ING114467).

Trends for outcome, duration of the first occurrence, and duration of all events for each of the individual psychiatric AESIs were generally similar to those described above for psychiatric AESIs overall (Data Source: ISO Table 2.92 and ISO Table 2.114).

Studies in ART-Experienced (INI-Naïve) Adults

Psychiatric AESI were infrequently reported for ART-experienced (INI-naïve) subjects, and rates were comparable for DTG and RAL, and lower than observed for ART-naïve subjects regardless of treatment group. The majority were of Grade 1 to 2 intensity with few Grade 3 to 4 events reported, regardless of treatment group. Fewer episodes were considered drug-related for DTG, but more were reported as SAEs, than compared to RAL. Only one event (in the RAL treatment group) led to the permanent discontinuation and withdrawal of IP. The majority of subjects had single psychiatric AESI, regardless of treatment group.

As for ART-naïve subjects, the TTO for the first occurrence for the majority of psychiatric AESI reported for ART-experienced (INI-naïve) subjects was >28 days (Data Source: ISO Table 2.548), although the median TTO with RAL was earlier than with
DTG. Large proportions of events remained unresolved at the time of data cut for analysis, regardless of treatment group. For those that had resolved, the majority had a duration of up to 21 days for DTG, which was shorter than observed for RAL, where the majority had a duration >35 days (Data Source: ISO Table 2.548).

When considered individually, psychiatric AESIs were reported at comparable rates between treatment groups, with insomnia and depression, bipolar, suicidal/suicide, hypomania events being the most commonly reported. Too few drug-related events were reported to make any meaningful comparisons between treatment groups for individual psychiatric AESIs (Data Source: ISO Table 2.541).

Observations for TTO, outcome, and duration for individual psychiatric AESIs were generally similar to those for all psychiatric AESIs combined (Data Source: ISO Table 2.541 and ISO Table 2.548).

**Studies in ART-Experienced (INI-Resistant) Adults**

Few psychiatric AESIs were reported for this treatment population. The incidence of psychiatric AESIs with DTG 50 mg BID in Phase III clinical trial ING112574 was comparable to rates observed for DTG 50 mg once daily in ART-experienced (INI-naïve) subjects and less than that observed for ART-experienced (INI-resistant) subjects in Phase IIb clinical trial ING112961 (both Cohort I [DTG 50 mg once daily] and Cohort II [DTG 50 mg BID]), and DTG 50 mg once daily in ART-naïve HIV-infected subjects. ING112961 involved small treatment populations, and ING112574, with a larger study population, provides a more robust estimate for psychiatric AESIs at the higher dose of DTG in ART-experienced (INI-resistant) subjects. The majority of subjects reporting psychiatric AESIs developed single episodes (Data Source: ISO Table 2.71).

Few psychiatric AESIs in ART-experienced (INI-resistant) subjects were considered drug-related, to meet seriousness criteria, or of severe intensity (i.e., Grade 3 to 4), and few resulted in temporary interruption or permanent discontinuation of IP (Data Source: ISO Table 2.71).

Too few psychiatric AESIs were reported to allow for meaningful interpretation of data for TTO and duration, which was also affected by smaller treatment populations (in comparison to the Phase III clinical trials in ART-naïve subjects) and differences in treatment duration (i.e., median exposure approximately 20 months for ING112961 and 24 weeks for ING112574). However, observations for DTG 50 mg BID in ING112574 appear to be similar to those for DTG 50 mg once daily in ART-naïve subjects (Data Source: ISO Table 2.93 and ISO Table 2.115).

When considered individually, the insomnia AE preferred terms were the most commonly reported psychiatric AESIs (Data Source: ISO Table 2.71), and are discussed in more detail in Section 2.1.5.8.2.
Very few events from the other individual psychiatric AESI categories were reported in the ART-experienced (INI-resistant) study populations. Depression, bipolar disorder, and suicidal events were rarely reported.

**Other Ongoing Studies**

**ING116070:** Two subjects reported a psychiatric AESI (one Grade 2 depression and one Grade 1 sleep disorder) prior to the Week 2 data cut-off. Both events were attributed to study medication (DTG and/or ABC+3TC) by the investigator. No action was taken with study medication and neither event was reported as serious (Data Source: ING116070 Week 2 Synoptic CSR Listing 11).

### 2.1.5.8.2. Insomnia

**Studies in ART-Naïve Subjects**

While insomnia appears to be a signal for DTG (based mainly on analysis of data from ING114467), the majority of events were considered of mild to moderate intensity (i.e., Grade 1 to 2), and did not require dose interruption or permanent discontinuation of IP. Recurrent episodes of insomnia only occurred in ING114467, although the majority of subjects reporting insomnia in this study developed a single episode. No episodes of insomnia were reported as SAEs in this ART-naïve treatment population (Table 39).
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Table 39 Summary of Characteristics of Insomnia Events of Special Interest – ART-Naïve Population

<table>
<thead>
<tr>
<th></th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG Once Daily + 2 NRTI N=155 n (%)</td>
<td>EFV 600 mg Once Daily + 2 NRTI N=50 n (%)</td>
<td>DTG 50 mg Once Daily + 2 NRTI N=411 n (%)</td>
</tr>
<tr>
<td>Number of subjects with eventa</td>
<td>13 (8)</td>
<td>6 (12)</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Number of events</td>
<td>13</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Event characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related</td>
<td>3 (23)</td>
<td>5 (83)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leading to withdrawal</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Number of occurrences</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>13 (100)</td>
<td>6 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Two</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered/resolved</td>
<td>6 (46)</td>
<td>3 (50)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Recovering/resolving</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Not recovered/not resolved</td>
<td>7 (54)</td>
<td>3 (50)</td>
<td>13 (59)</td>
</tr>
<tr>
<td>Recovered/resolved with sequelae</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum grade or intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild or Grade 1</td>
<td>10 (77)</td>
<td>5 (83)</td>
<td>16 (73)</td>
</tr>
<tr>
<td>Moderate or Grade 2</td>
<td>2 (15)</td>
<td>1 (17)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Severe or Grade 3</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Action taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigational product withdrawn</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Dose not changed</td>
<td>13 (100)</td>
<td>5 (83)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time of onset of first occurrence, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>122.0</td>
<td>101.0</td>
<td>77.0</td>
</tr>
<tr>
<td>Min.</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Max.</td>
<td>543</td>
<td>428</td>
<td>476</td>
</tr>
<tr>
<td>Duration of first occurrence, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61.0</td>
<td>12.0</td>
<td>48.5</td>
</tr>
<tr>
<td>Min.</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Max.</td>
<td>396</td>
<td>518</td>
<td>209</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.70 and ISO Table 2.92.

a. Events of special interest are those which contain insomnia

Despite there being a difference in the distribution of insomnia events between the DTG+ABC/3TC and Atripla treatment groups in ING114467, in terms of gender, time to onset, graded intensity, event duration, and event outcome (Data Source: ING114467 Week 48 CSR Table 8.4, Table 8.59, Table 8.60 and Table 8.61), these findings were not
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replicated when comparing data from ING114467 with ING113086, ING112276, or total DTG (Data Source: ISO Table 2.70 and ISO Table 2.47 [AEs by SOC and subgroup]).

The TTO for the first occurrence of insomnia was generally greater than 28 days in most treatment groups, with the exception of ING114467, in which the majority of episodes with DTG occurred in the first week, and there was no real trend for Atripla (Data Source: ISO Table 2.92). Median TTO for the first occurrence of insomnia was also shorter for ING114467 in comparison to the other two studies and for DTG combined.

Large proportions of events remained unresolved at the time of data cut for analysis, regardless of treatment group. For those that had resolved, the majority had a total duration of greater than 35 days (with the exception of EFV in ING112276; Data Source: ISO Table 2.92 and ISO Table 2.114). Median total duration was comparable, with the exception of RAL in ING113086 (which was longer) and EFV in ING112276 (which was notably shorter in this small treatment group; Data Source: ISO Table 2.92). Observations for outcome and duration were generally similar to those for the other psychiatric AESIs.

While insomnia was highlighted as a signal for DTG by data from ING114467, this was not duplicated by any of the other Phase IIb/III studies conducted with DTG. Despite the higher daily dose of DTG in ART-experienced (INI-resistant) subjects, the rate for insomnia in this treatment population was less that that observed overall for DTG 50 mg once daily in ART-naïve and ART-experienced (INI-naïve) subjects.

ING114467 was the only study in the DTG development programme that employed a Global Health Outcomes (GHO) Symptoms Impact CRF module that questioned subjects about specific potentially bothersome symptoms, including insomnia at Day 1, Week 4, Week 24, Week 48, and Week 96. It is possible that this also influenced subjects reporting insomnia to their Investigator/designee as AEs during routine study visits.

The incidence of Grade 2 and 3 episodes of insomnia combined in ING114467 was comparable between treatment groups (4% each, although no Grade 3 episodes were reported for the Atripla arm), and was also similar to rates seen for moderate to severe insomnia in the STARTMRK study (comparing RAL to EFV, both in combination with Truvada) at 48 weeks (RAL 4% vs. EFV 3%) [Isentress, 2012]. Rates seen for Grade 2 to 3 insomnia with Atripla in ING114467 (4%) were also comparable to rates cited in the Atripla Food and Drug Administration (FDA) prescribing information for Study 934 (5%), comparing Atripla to EFV + zidovudine/lamivudine over 144 weeks [Atripla, 2012]. Finally, insomnia events in ING114467 were generally not treatment-limiting: only one subject in the DTG+ABC/3TC arm discontinued due to insomnia versus two subjects in the EFV/TDF/FTC arm.

Over all, the available data suggest that the higher rate of insomnia with DTG in ING114467 was due to a chance statistical finding, over-reporting in this double-blinded study with Atripla (for which insomnia is a listed event in local country labelling), influenced by a GHO Symptoms Impact CRF module that was unique to this study and
questioned subjects about specific potentially bothersome symptoms (including insomnia), or a combination thereof.

**Studies in ART-Experienced (INI-Naïve) Adults**

Rates for insomnia were low and comparable for DTG and RAL (10/357 [3%] vs. 11/362 [3%]) in this ART-experienced (INI-naïve) population (ISO Table 2.541), and were also similar to rates of insomnia observed for ART-naïve, HIV-infected subjects participating in ING113086 and ART-experienced (INI-resistant) subjects participating in ING112574.

All episodes of insomnia in ART-experienced (INI-naïve) subjects were considered Grade 1 to 2 (mild to moderate) in intensity, and none were reported as serious, regardless of treatment group (Data Source: ISO Table 2.541). No events were considered related to DTG by reporting investigators, and only 1% of episodes were considered related to RAL. The majority of subjects developed single episodes, regardless of treatment group.

The TTO for the first occurrence of insomnia was generally greater than 28 days for both DTG and RAL (Data Source: ISO Table 2.548). Large proportions of events remained unresolved at the time of data cut for analysis, regardless of treatment group, but more so for RAL then for DTG (Data Source: ISO Table 2.541). For those that had resolved, the majority had a total duration of greater than 35 days for DTG and between 15 to 28 days for RAL, however there were so few events in total, and so few resolved, that meaningful analysis of duration is not possible.

**Studies in ART-Experienced (INI-Resistant) Adults**

As noted in Section 2.1.5.8.1, the insomnia AE preferred terms were the most commonly reported psychiatric AESIs (Data Source: ISO Table 2.71). However, the rate for insomnia AEs in ING112574 was comparable to that observed for DTG 50 mg one daily in ART-naïve, HIV-infected subjects in ING113086, and ART-experienced (INI-naïve) subjects in ING111762. The rates of insomnia for DTG in Phase III clinical trials ING112574, ING113086, and ING111762 were all less than the rate reported for DTG in ING114467 and the combined rate for DTG in ART-naïve subjects overall.

Few episodes of insomnia in ING112574 were considered drug-related, none were reported as SAEs or considered severe in intensity (i.e., Grade 3 to 4), and none resulted in the interruption or permanent discontinuation of IP. All ART-experienced (INI-resistant) subjects reporting insomnia events developed single episodes, regardless of dose (Data Source: ISO Table 2.71).

Insomnia mostly occurred within the first two weeks in ING112574 and for total DTG 50 mg BID, which was similar to observations for DTG 50 mg one daily in ART-naïve subjects participating in ING114467. Observations for outcome of insomnia events in ING112574 were similar to those for ART-naïve subjects in the Phase III studies (Data Source: ISO Table 2.71). For those that had resolved, the majority in ING112574 and on
DTG 50 mg BID (total) had a duration up to 28 days, which again is shorter than observed for ART-naïve subjects (Data Source: ISO Table 2.93 and ISO Table 2.115).

2.1.5.8.3. Suicidal Ideation and Behaviours

Studies in ART-Naïve Subjects

Nineteen subjects in total were reported with AEs considered indicative of suicide ideation and behaviours, with equivalently low reporting rates across treatment arms in the ART-naïve population (Data Source: ISO Table 2.15). One subject (in the RAL treatment arm for ING113086) completed suicide. All subjects in DTG and Atripla treatment groups, and the subject in EFV group, had a relevant medical history of psychiatric disorders with or without nervous system disorders (e.g., insomnia) and/or alcohol/illicit substance misuse. Two of the subjects receiving RAL, including the completed suicide case, did not have such relevant medical history recorded at Baseline, but events were considered as not related to RAL by the reporting investigators (ING113086 Week 48 CSR Table 8.7).

Studies in ART-Experienced (INI-Naïve) Adults

Seven subjects in total were reported with AEs considered indicative of suicide ideation and behaviours: five subjects for the DTG treatment group (1%) and two subjects in the RAL treatment group (<1%). These low rates were similar to those seen for DTG and comparators in the ART-naïve subjects. There were no events of completed suicide reported for either treatment group in this ART-experienced (INI-naïve population) (Data Source: ISO Table 8.2).

All subjects had a relevant ongoing medical history at Baseline of depression, with or without addition psychiatric/neurological disorders (i.e., insomnia), and with or without additional risk factors (e.g., alcohol and or illicit substance misuse).

Studies in ART-Experienced (INI-Resistant) Adults

There were no AEs indicative of suicidal ideation and behaviours reported from the Phase III clinical trial ING112574. One subject in ING112961 (Cohort II), with a medical history significant for depression, completed suicide (Section 2.1.2).

2.1.5.9. Immune Reconstitution Inflammatory Syndrome

2.1.5.9.1. IDMC Recommended Evaluation of Cases Indicative of IRIS

As discussed in Section 1.1.7, the IDMC recommended an evaluation of opportunistic infections (OIs) reported as HIV-related conditions within the first 2-3 months of starting antiretroviral therapy, to determine whether they were indicative of IRIS and coded accordingly. These cases, along with any AEs identified as related to IRIS were reviewed (before unblinding of treatment allocation) by either: two senior physicians from ViiV Healthcare (for ING113086), or the IDMC (for ING114467, ING111762, and ING112574), none of whom had any contact with sites or investigators. These cases
were adjudicated as IRIS events using definitions derived from the literature [Robertson, 2006].

Findings

ING113086: Four subjects, two each from the DTG and RAL groups, had AEs adjudicated as IRIS events; these were identified from eight subjects with nine AEs that were reported as an HIV-related condition within the first 100 days of enrollment (three DTG subjects and five RAL subjects) and from two subjects with IRIS reported as an AE (one each for DTG and RAL).

The two adjudicated cases for DTG subjects involved IRIS associated with a pre-existing HBV infection (Subject 3170) and IRIS associated with tuberculous meningitis (Subject 4075). On the RAL arm, the two adjudicated cases were IRIS associated with CMV pneumonia (Subject 3128) and IRIS associated with a pre-existing HBV infection (Subject 4052).

Two AEs initially were reported as IRIS for RAL, but were not judged to be recognized IRIS or to meet criteria used for adjudication: acneiform rash described as ‘immune restoration acne’ (Subjects 3544), and pustular lesions on the trunk and left side of the head with periorbital cellulitis and conjunctivitis described as a ‘staphylococcal syndrome’ (4523). Additional description can be found in the ING113086 Week 48 CSR Section 7.3.5.

ING114467: There were seven cases classified by the IDMC as definite or possible IRIS: three definite in the DTG group, and one definite and three possible in the Atripla group. The cases in the DTG group included the adjudicated definite IRIS cases of central nervous system toxoplasmosis (Subject 5913), tuberculosis (Subject 6059), and mycobacterium avium complex infection (Subject 6775). The cases in the Atripla group included an adjudicated definite IRIS case of cryptococcal meningitis (Subject 6772), and the adjudicated possible IRIS cases of extrapulomary cryptococcosis (Subject 5123) and AST and ALT elevations secondary to HCV flares (Subject 5119 and Subject 6033). Additional description can be found in the ING114467 Week 48 CSR Section 7.3.10.

ING111762: Six subjects in the DTG group were identified by the IDMC as having IRIS (Subjects 2528, 942, 1112, and 2467) or possible IRIS (Subjects 2418 and 2474). Five of these six were considered to have HB and/or HCV IRIS. The sixth subject (Subject 2528) had IRIS reported by the investigator (and agreed on IDMC adjudication) as an AE (Source Data: CSR ING111762 Table 8.2). Subject 2528, a 39 year old White male, developed Grade 3 IRIS, Grade 3 disseminated histoplasmosis, and Grade 1 disseminated intravascular coagulation, approximately 21 days aftercommencing study medications, which resulted in hospitalization. The investigator did not consider the events related to IP. The case narrative for this SAE is included in APPENDIX 6.

The IDMC considered three subjects receiving RAL to have IRIS; these were Subject 2054 [progressive multifocal leukoencephalopathy (PML)], Subject 2425 (possible HCV IRIS, with alcohol consumption a competing possibility), and Subject 2371 (with
immunoblastic lymphoma as possible IRIS). The PML for Subject 2054 and lymphoma for Subject 237, were reported as SAEs; the case narratives for these subjects are included in APPENDIX 6.

**ING112574:** There were five cases classified by the IDMC as definite (n=1) or possible IRIS (n=4). These compromised the adjudicated definite IRIS case of progressive multifocal leucoencephalopathy (Subject 1001), and the adjudicated possible IRIS cases of pyrexia (Subject 007), herpes zoster (Subject 663), herpes ophthalmic (Subject 1038), and cryptogenic IRIS (Subject 1202).

### 2.1.5.9.2. Analysis of Integrated Safety Data

AEs of IRIS were rarely reported across each treatment group from the Phase III clinical trials in ART-naïve subjects and for DTG combined group in this treatment population, as well as for 50 mg BID in the ART-experienced (INI-resistant) treatment population. In ART-experienced (INI-naïve) subjects, one subject in the DTG group (Subject 2528), and no subjects in the RAL group, had IRIS reported as AEs (Data Source: ING111762 Week 24 CSR Table 8.2). No cases of IRIS were reported in the only clinical pharmacology study that enrolled HIV-infected subjects (ING111521). In ING116070, there were no reported AEs of IRIS and no HIV-associated conditions reported prior to the Week 2 data cut-off (Data Source: ING116070 Week 2 Synoptic CSR Listing 7 and ICH Listing 11). One IRIS event was reported in the ING115502 Named Patient Program: cytomegalovirus retinitis (subject BRA-001-001) and was considered possibly related to CD4+ cell counts and IRIS. This subject had Grade 4 pulmonary haemorrhage resulting in death (unknown date); the event was considered related to IRIS.

### 2.1.5.10. Neoplasms, Benign, Malignant, and Unspecified (including Cysts and Polyps)

#### 2.1.5.10.1. Studies in ART-Naïve Adults

The majority of the AEs reported from the Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) SOC were non-malignant, and the rate was comparable between the treatment groups (Data Source: ISO Table 2.15). The most frequently reported AEs in this SOC were anogenital warts and benign skin papillomas, occurring at similar rates across the treatment groups. All other events were reported at a rate of <1%.

Few subjects developed malignant or potentially malignant events. All were isolated and occurred in only one subject, except basal cell carcinoma and Kaposi’s sarcoma, which each occurred in two subjects in the DTG population (Data Source: ISO Table 2.15).

#### 2.1.5.10.2. Studies in ART-Experienced (INI-Naïve) Adults

The most frequently reported AEs in this SOC were benign skin papillomas and anogenital warts, occurring at similar rates between the treatment groups (Data Source:
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ING111762 Week 24 CSR Table 8.2). All other events were isolated and occurred in only one subject.

Four subjects developed malignant events, all in the RAL arm.

2.1.5.10.3. Studies in ART-Experienced (INI-Resistant) Adults

The most frequently reported events in this SOC were benign skin papillomas and anogenital warts, all other events were reported at a rate of <1%. Few subjects developed malignant or potentially malignant events; all were isolated and occurred in only one subject (Data Source: ISO Table 2.16).

2.1.5.10.4. Other Completed and Ongoing Studies in Adults

ING116070: No AEs from the neoplasms benign, malignant and unspecified (including cysts and polyps) SOC were reported prior to the Week 2 data cut-off (Data Source: ING116070 Week 2 Synoptic CSR Table 8.2).

ING114915: One AE from the Neoplasms Benign, Malignant and Unspecified (including cysts and polyps) SOC was reported. Subject 477302 was a year-old male who was receiving DTG 50 mg once daily. On 16 February, 50 days after the start of DTG, the subject developed Grade 3 or severe anemia, and Grade 3 or severe dehydration, and was hospitalised. The subject was found with haemorrhoids, abdominal and pelvic lymphadenopathy, and hepatosplenomegaly, which led to the diagnosis of Hodgkin's lymphoma. He was treated with multiple medications. Treatment with DTG was discontinued permanently and the subject was withdrawn from the study. The event was resolving at the time of writing. The investigator considered that there was no reasonable possibility that Hodgkin’s lymphoma may have been caused by DTG.

2.1.5.11. Cardiovascular Disorders

2.1.5.11.1. Studies in ART-Naïve Adults

Few subjects developed ischemic cardiac disease related events, regardless of treatment group (Data Source: ISO Table 2.15).

Subject 4047 (Framingham risk: <10%) received DTG 50 mg once daily in study ING113086 and developed angina pectoris two days after starting therapy. This was confounded by a medical history of vascular disorders not otherwise specified (NOS). Subject 55 (Framingham risk: <10%) from study ING112276 developed an acute myocardial infarction 655 days after starting therapy with DTG plus TDF/FTC, followed by a second fatal episode on Day 935 (see Section 2.1.2). This case was confounded by a medical history of diet-controlled hyperlipidemia and 30-pack-year history of smoking.

The single case for Atripla involved Subject 5923 (Framingham risk: <10%) in ING114467, who had an AE of coronary artery disease recorded seven days after starting therapy; this subject also had a history of smoking.
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Four cases were observed in subjects on RAL in ING113086. Subject 4337 (Framingham risk: <10%) had angina pectoris 156 days after starting therapy, with the case confounded by a medical history of hypertriglyceridemia. The other three subjects had angina pectoris without medical risk factors recorded at Baseline as follows: Subject 3270 (Framingham risk assessment not calculated) had a TTO of 144 days; Subject 3851 (Framingham risk: <10%) had a TTO of 256 days; Subject 3853 (Framingham risk: 10 to 20%) had a TTO of 459 days.

2.1.5.11.2. Studies in ART-Experienced (INI-Naïve) Adults

Two subjects developed ischemic cardiac disease-related events. One was in the DTG group (Subject 93), with a TTO of 37 days and Framingham risk of 10 to 20%, who experienced angina pectoris confounded by a medical history of hypertension and metabolic disorder NOS, and the other was in the RAL group (Subject 2224), with a TTO of 319 days and Framingham risk of >20%, who experienced coronary artery disease confounded by a medical history of hypertriglyceridemia and hypercholesterolemia.

2.1.5.11.3. Studies in ART-Experienced (INI-Resistant) Adults

Few subjects developed ischemic cardiac disease-related events, all of which were receiving DTG 50 mg BID (Data Source: ISO Table 2.16).

Subjects 2202 and 2431 from ING112961 (Cohort II) both developed coronary artery disease and angina pectoris. The case for Subject 2202 (Framingham risk: 10 to 20%) had a TTO of 484 days and was confounded by a history of smoking, hypercholesterolemia, and hypertriglyceridemia. Subject 2431 (Framingham risk: <10%) had a TTO of 384 days and was confounded by hypertension, diabetes mellitus, and a family history of coronary artery disease. Subject 1272 (Framingham risk assessment not calculated) in ING112574 had an event of myocardial infarction reported 170 days after starting DTG therapy. This event was initially described as “posterior inferior cardiac necrosis”, which was subsequently coded to myocardial infarction. The site later clarified that it was an incidental ECG finding, probably a previous silent event in an asymptomatic patient.

2.1.5.11.4. Other Completed and Ongoing Studies in Adults

ING115502: As of the cut-off date, one cardiovascular SAE, Grade 3 angina pectoris (Subject ITA-002-001), had been reported.

2.2. Narratives

Full case narratives for all fatal SAE are included in APPENDIX 5 (also see Section 2.1.2 for brief narratives of deaths related to AEs of Special Interest).

Case narratives for all SAEs received by the company through are included in APPENDIX 6.
3. CLINICAL LABORATORY EVALUATIONS

3.1. Clinical Chemistry

**Studies in ART-Naïve Adults:** The majority of subjects (82%) had post-Baseline-emergent graded clinical chemistry toxicities. A small proportion, 12 to 15%, had Grade 3 to 4 toxicities and the incidence was similar in all treatment groups across all the studies (Data Source: ISO Table 2.275). All the treatment arms in the studies of ART-naïve subjects had essentially neutral effects on the lipid profile. Grade 2 to 4 events were recorded for a minority of subjects (10% for DTG overall, 9% for RAL, and 11% for Atripla; Data Source: ISO Table 2.167). Grade 3 to 4 events were reported for 3% or fewer subjects. This was reflected by small mean increases in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides up to Week 48 (Data Source: ISO Table 2.159 and Table 2.167). There were no clinically significant effects on the total cholesterol/HDL cholesterol ratio in any group. Lipase elevations have been noted, most have been transient and asymptomatic, and none have resulted in a clinical diagnosis of pancreatitis. Similar rates were observed across the treatment groups, including Grade 3 and Grade 4 elevations (Data Source: ISO Table 2.167).

**Studies in ART-Experienced (INI-Naïve) Adults:** Similar to ART-naïve subjects, the majority of DTG (82%) and RAL (86%) subjects had post-Baseline-emergent graded abnormalities. A small proportion (15% for DTG, 16% for RAL) had Grade 3 to 4 toxicities (Data Source: ING111762 Week 24 CSR Table 8.24). There were similar changes in mean values for lipid parameters across both treatment groups (ING111762 Week 24 CSR Table 8.19) and similar grades and distribution of treatment-emergent toxicities (Data Source: ING111762 Week 24 CSR Table 8.24). There were increases in mean total cholesterol, LDL cholesterol, and HDL cholesterol in both groups, but little change in the HDL/cholesterol ratio. Lipase elevations have been noted, most have been transient and asymptomatic. Four subjects in total had a diagnosis of pancreatitis; two in DTG and two in RAL arms (see Section 2.1.5.5.2 for further information on these cases). Similar rates were observed between the treatment groups including Grade 3 and Grade 4 elevations (Data Source: ING111762 Week 24 CSR Table 8.24).

**Studies in ART-Experienced (INI-Resistant) Adults:** Although a high proportion of subjects (85%) had a post-Baseline-emergent graded change in clinical chemistry, the majority were Grade 1 and Grade 2 with few Grade 3 to 4 events (Data Source: ISO Table 2.276). For study ING112574 only 114 of the 183 subjects were included in the Week 24 analysis. Patients who were taking lipid lowering agents at Baseline were excluded from the lipid change from Baseline analysis and only fasting values were analysed. DTG had a similar neutral effect on lipid profiles in the ART-experienced (INI-resistant) population, with 10% of subjects reporting Grade 2 to 4 toxicities and 2% Grade 3 to 4 toxicities overall (Data Source: ISO Table 2.168). There were only small, clinically insignificant changes in mean values of lipid parameters up to Week 24 (Data Source: ISO Table 2.155). Lipase elevations have been noted; most have been transient and asymptomatic, and none have resulted in a clinical diagnosis of pancreatitis including those with Grade 4 elevations (Data Source: ISO Table 2.168).
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Module 2.7.4 Summary of Clinical Safety

**Electrolytes, Across All Studies:** No clinically significant patterns of changes in electrolytes (sodium, potassium, chloride, and bicarbonate) were identified (Data Source: ISO Table 2.154, ISO Table 2.155, ISO Table 2.256 and ISO Table 2.257).

**Metabolism Indices, Across All Studies:** No clinically significant patterns of changes in metabolism indices (glucose, calcium and phosphorous) were identified (Data Source: ISO Table 2.154, ISO Table 2.155, ISO Table 2.256 and ISO Table 2.257).

3.1.1. Liver Chemistries

Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) narratives and datasets, as specified by the FDA, are provided in m.5.3.5.3, along with corresponding patient profiles containing all study-related information collected in the electronic case report from (eCRF) and by the central laboratory. This data will be provided as requested to the FDA only.

The PDF patient profiles submitted for eDISH are a snapshot of the data from the safety analysis data cut-off dates with the exception of ING112574, which is based on a later date. Any blinded reference in the header can be ignored since actual treatment is reported in the accompanying statistical analysis software (SAS) dataset.

In the following sections, individual events as well as summaries of graded events are provided in tabular format. “Maximum post Baseline” refers to the highest liver chemistry value encountered after Day 1 of each study. These events do not necessarily represent treatment-emergent events, as subjects with ALT values up to five times the upper limit of normal were allowed to enrol in the Phase IIb and III studies. “Post Baseline-emergent” does represent treatment-emergent events, and subjects were included in these tables when they experienced graded lab abnormalities at a higher level than those observed at Day 1 (Baseline).

3.1.1.1. Studies in ART-Naïve Adults

There were few adverse events reported from the Hepatobiliary SOC and the incidence was comparable between groups (Data Source: ISO Table 2.15).

The graded liver chemistry abnormalities for the ART-naïve population are available in ISO Table 2.167. The incidence of Grade 3/4 toxicities was low and similar (<2%) for all chemistries in all arms of the three studies.

The summary of subjects meeting the hepatobiliary laboratory abnormality criteria suggested in the FDA guidance 2009 [FDA, 2009] is shown for the ART-naïve population in Table 40 and a plot of ALT versus total bilirubin using the ratio to the ULN (eDISH) for the ART-naïve population is shown in Figure 1. The percentage of subjects with ALT>3xULN was similar for DTG versus RAL (ING113086) and lower for DTG compared with EFV or DTG+ABC+3TC compared with Atripla (ING114467).
### Table 40  Summary of Subjects Meeting Hepatobiliary Laboratory Abnormality Criteria At Any Post Baseline Visit – ART-Naïve Population

<table>
<thead>
<tr>
<th>Parameter/criteria</th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>Total DTG Once Daily N=980 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/AST &gt;3XULN AND TOT. BILI. &gt; 2XULN</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT/AST &gt;3XULN &amp; ALK. PHOS.&lt;2XULN &amp; TOT BILI. &gt;2XULN</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT/AST &gt;3XULN &amp; TOT BILI. &gt;1.5XULN</td>
<td>0</td>
<td>0</td>
<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT+AST &gt;=20XULN</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT+AST &gt;=10XULN</td>
<td>0</td>
<td>1 (2)</td>
<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT+AST &gt;=5XULN</td>
<td>0</td>
<td>1 (2)</td>
<td>7 (2)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>ALT+AST &gt;3XULN</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>12 (3)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>ALT &gt;=20XULN</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT &gt;=10XULN</td>
<td>0</td>
<td>1 (2)</td>
<td>5 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>ALT &gt;=5XULN</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>9 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>ALT &gt;=3XULN</td>
<td>6 (4)</td>
<td>5 (10)</td>
<td>15 (4)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>AST &gt;=20XULN</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>AST &gt;=10XULN</td>
<td>0</td>
<td>1 (2)</td>
<td>5 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>AST &gt;=5XULN</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>13 (3)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>AST &gt;=3XULN</td>
<td>8 (5)</td>
<td>1 (2)</td>
<td>24 (6)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Total Bili. &gt;2xULN</td>
<td>2 (1)</td>
<td>0</td>
<td>3 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Total Bili. &gt;1.5xULN</td>
<td>4 (3)</td>
<td>0</td>
<td>11 (3)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Alk. Phos. &gt;1.5xULN</td>
<td>2 (1)</td>
<td>6 (12)</td>
<td>7 (2)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.198

**Post Baseline ALT and/or AST >3xULN with Total Bilirubin >2xULN and Alkaline Phosphatase <2xULN**

Three subjects, all from study ING113086, had a combination of ALT >3xULN with total bilirubin >2xULN and alkaline phosphatase <2xULN, two of these subjects were on DTG (4529 and 4319) and one subject was on RAL (4052). Brief narratives for these
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Module 2.7.4 Summary of Clinical Safety

Subjects are provided below, and more detailed summaries are available from the clinical study report.

Subject 4529 (SAE - hypersensitivity) is a 29-year-old White male (Baseline HIV-1 RNA viral load of 166,000 c/mL and CD4+ cell count of 344 cells/µL and negative HBsAg, HCV AB) who was randomized to DTG 50 mg once daily with investigator selected ABC/3TC. Flu like symptoms (fever and body aches) were noted approximately ten days after commencing IP, which progressed over the course of four days to include symptoms of rash (profuse, purpuric and coalescing), joint swelling and pain, palpable liver, jaundice and atrial fibrillation. The subject’s ALT peaked at >20xULN and his bilirubin at >4xULN. No additional evidence for liver dysfunction, including encephalopathy or prothrombin time prolongation, was observed. He improved clinically following the discontinuation of DTG and ABC/3TC and introduction of corticosteroid therapy. This subject was investigated extensively for non-drug causes of his hypersensitivity reaction, including testing for hepatitis A/B/C/D/E, cytomegalovirus, Epstein-Barr virus (EBV), syphilis and autoimmune disease and repeat HLA-B*5701 testing (negative), but an alternative cause could not be identified. The investigator implicated DTG alone, however the Sponsor cannot rule out a contribution by ABC, although features of the case would be considered atypical for ABC HSR. This case was described in an Investigational New Drug Application (IND) Safety Report to FDA.

Subject 4319 (SAE – hepatitis) is a 48-year-old White female (Baseline HIV-1 RNA viral load of 2,193 c/mL and CD4+ cell count of 345 cells/µL) who was randomized to DTG 50 mg once daily with investigator selected ABC/3TC. At the Week 16 visit, the subject was asymptomatic but was noted to have an ALT of 272 U/L (normal: 0-48 U/L) and AST of 302 U/L (normal: 0-42 U/L), with normal total bilirubin of 8 µmol/L [normal range (NR): 0-22] and alkaline phosphatase of 70 U/L (NR: 20-125 U/L). Follow up AST/ALT/BiliT/ALP, performed approximately two weeks later were within normal limits. One month later, the subject was noted to have scleral icterus and hepatomegaly with an AST of 777 U/L, ALT of 552 U/L, ALP of 139 U/L, total bilirubin of 169 µmol/L, direct bilirubin 80 µmol/L (normal: 0-6 µmol/L). IP was withdrawn. The subject denied any other symptoms, alcohol intake, new herbal therapies, over the counter or prescription medications, or any other novel exposures. Hepatitis A/B/C/E, Epstein-Barr virus (EBV), cytomegalovirus (CMV), rapid plasma reagin (RPR), antinuclear antibody (ANA) testing was negative. Drugs of abuse screening and acetaminophen testing was negative. Abdominal ultrasound revealed multiple gallstones including one in the gallbladder neck and concluded ‘outcome of acute cholecystopancreatitis and disabled gallbladder’. No common bile duct stone was observed at the time of the ultrasound. The subject’s AST/ALT/Bilirubin trended downward over the following month and she remained asymptomatic. The Investigator and Sponsor could not rule out drug-induced liver injury (DILI) as a contributing factor in this case. The observed gallstone disease was considered a co-suspect contributing factor. This case was described in an IND Safety Report to FDA.
**Subject 4052 (RAL)** is a 51 year old American Indian or Alaskan Native, male, [height, 163 cm and weight 52.4 kilogram (kg)], with Baseline HIV-1 RNA viral load of 9118 c/mL and CD4+ cell count of 454 cells/μL, who was randomized to RAL 400 mg BID on 28 December with investigator selected backbone of TDF/FTC. Screening HBsAg was positive, HCV antibody was negative. His viral load was fully suppressed to <50 c/mL at Week 4 with a rise in CD4+ cells to 638 cells/μL. His ALT was elevated to Grade 1 at screening and rose to reach liver event stopping criteria at Week 8 (ALT 465 U/L= 9.7xULN with normal bilirubin). Due to a central laboratory error, this result was not flagged to the site or monitors. At the Week 12 visit the ALT had fallen to 122 U/L. A liver event screen did not reveal any other pathology. The flare in his hepatitis was attributed to HBV IRIS. The Ethics Committee was informed of the protocol violation and the subject continued in the study. His transaminases had returned to normal levels by Week 14 but his bilirubin rose to 43 μmol/L (Direct bilirubin 8 μmol/L) at Week 24 and remained elevated (40 – 47 μmol/L, ULN=22 μmol/L) at all subsequent visits. As the direct bilirubin remained relatively low (7-9 μmol/L), the hyperbilirubinemia is related to indirect hyperbilirubinemia and, therefore, may be related to a condition such as Gilbert’s syndrome, especially as the total bilirubin was elevated at Screening (26 μmol/L).

**Post Baseline ALT>10xULN**

A summary table for subjects with the most extreme elevations of ALT post Baseline is presented in Table 41. Five of the ten subjects had an acute HCV infection as the cause of the liver inflammation. In two other cases, chronic HCV and a concurrent medication...
seemed the more likely causes of the liver chemistry elevations. Both subjects remained in the study and improved with withdrawal of the concurrent medications. There were two cases where drug-induced liver injury was implicated in causality (Subject 4319 on DTG and Subject 4068 on RAL, both in study ING113086). A narrative for these subjects are provided in APPENDIX 6APPENDIX 7.

Table 41 Listing of Subjects with Maximum Post Baseline ALT >10xULN - ART-Naive Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT /ULN</th>
<th>Bilirubin /ULN</th>
<th>Comment</th>
<th>Study Withdrawal? Yes/No (Y/N), Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY ING112276</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>621</td>
<td>EFV</td>
<td>30.00</td>
<td>0.86</td>
<td>Acute HCV</td>
<td>Y, Liver Stopping Criteria</td>
</tr>
<tr>
<td>STUDY ING113086</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3170</td>
<td>DTG 50 mg once daily</td>
<td>27.77</td>
<td>0.91</td>
<td>HBV IRIS</td>
<td>Y, Liver Stopping Criteria</td>
</tr>
<tr>
<td>3884a</td>
<td>DTG 50 mg once daily</td>
<td>15.00</td>
<td>1.09</td>
<td>Acute HCV</td>
<td>Y, AEb</td>
</tr>
<tr>
<td>3950</td>
<td>DTG 50 mg once daily</td>
<td>12.88</td>
<td>1.00</td>
<td>Acute HCV</td>
<td>Y, AEb</td>
</tr>
<tr>
<td>4068</td>
<td>RAL 400 mg BID</td>
<td>12.38</td>
<td>0.68</td>
<td>Possible DILI</td>
<td>Y, Liver Stopping Criteria</td>
</tr>
<tr>
<td>4319</td>
<td>DTG 50 mg once daily</td>
<td>11.50</td>
<td>10.86</td>
<td>Possible DILI</td>
<td>Y, Liver Stopping Criteria</td>
</tr>
<tr>
<td>4946</td>
<td>DTG 50 mg once daily</td>
<td>11.06</td>
<td>0.91</td>
<td>HCV + amoxycillin/clavulanate; resolved despite continued DTG</td>
<td>N</td>
</tr>
<tr>
<td>3815</td>
<td>RAL 400 mg BID</td>
<td>10.06</td>
<td>0.77</td>
<td>Acute HCV</td>
<td>Y, Liver Stopping Criteriaa</td>
</tr>
<tr>
<td>STUDY ING114467</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5334</td>
<td>Atripla once daily</td>
<td>17.13</td>
<td>0.82</td>
<td>Acute HCV</td>
<td>Y, AEb</td>
</tr>
<tr>
<td>5259</td>
<td>DTG 50 mg +ABC/3TC once daily</td>
<td>10.38</td>
<td>0.36</td>
<td>HCV, naltrexone; resolved despite continued study drugs</td>
<td>N</td>
</tr>
</tbody>
</table>

Data Source: ING112276 Week 96 CSR ICH Listing 2, Other Listing 24; ING113086 Week 48 CSR ICH Listing 3, Other Listing 20; ING114467 Week 48 CSR ICH Listing 3, Other Listing 21; ISO Listing 2.10

a. IP stopped and the subject was withdrawn from study due to arrhythmia prior to developing elevated transaminases
b. Also met liver stopping criteria but investigator listed AE as reason for withdrawal.
c. NOTE: updated since ING113086 Week 48 CSR.

Summary tables for subjects with post Baseline-emergent ALTs >5xULN but <10xULN and >3xULN but <5xULN are presented in Table 42 and Table 43. The majority of these elevations of liver chemistries were associated with co-infection with hepatitis viruses, alcohol abuse, steatohepatitis, concomitant medications or supplements or combinations of these. Drug induced liver injury was implicated in two cases. Subject 4529 (DTG) in study ING113086 had a hypersensitivity reaction; a narrative is provided in APPENDIX 6.
### Table 42  Listing of Subjects with Maximum Post Baseline ALT >5xULN but <10xULN - ART-Naïve Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT /ULN</th>
<th>Bilirubin /ULN</th>
<th>Comment</th>
<th>Study Withdrawal? Yes/No (Y/N), Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY ING112276</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>DTG</td>
<td>5.21</td>
<td>0.64</td>
<td>ALT lower on treatment</td>
<td>Y, Withdraw consent</td>
</tr>
<tr>
<td>781</td>
<td>DTG</td>
<td>5.17</td>
<td>0.64</td>
<td>Acute HCV</td>
<td>N</td>
</tr>
<tr>
<td>STUDY ING113086</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4052a</td>
<td>RAL 400 mg BID</td>
<td>9.69</td>
<td>2.14</td>
<td>HBV iRIS</td>
<td>N</td>
</tr>
<tr>
<td>4389</td>
<td>DTG 50 mg once daily</td>
<td>9.06</td>
<td>1.64</td>
<td>HCV reactivation</td>
<td>Y, AEc</td>
</tr>
<tr>
<td>4934</td>
<td>DTG 50 mg once daily</td>
<td>8.00</td>
<td>0.59</td>
<td>HBV and Acute HAV</td>
<td>N</td>
</tr>
<tr>
<td>4529b</td>
<td>DTG 50 mg once daily</td>
<td>7.27</td>
<td>4.73</td>
<td>Possible DILI</td>
<td>Y, AEc</td>
</tr>
<tr>
<td>3173</td>
<td>RAL 400 mg BID</td>
<td>6.92</td>
<td>0.64</td>
<td>Acute HCV</td>
<td>Y, Virologic Failure</td>
</tr>
<tr>
<td>4734</td>
<td>DTG 50 mg once daily</td>
<td>6.25</td>
<td>0.41</td>
<td>No definitive diagnosis</td>
<td>N</td>
</tr>
<tr>
<td>4955</td>
<td>RAL 400 mg BID</td>
<td>6.04</td>
<td>0.59</td>
<td>Possible DILI</td>
<td>Y, AE</td>
</tr>
<tr>
<td>3095</td>
<td>RAL 400 mg BID</td>
<td>5.31</td>
<td>0.45</td>
<td>Alcohol</td>
<td>N</td>
</tr>
<tr>
<td>4532</td>
<td>RAL 400 mg BID</td>
<td>5.02</td>
<td>0.55</td>
<td>Steatohepatitis</td>
<td>N</td>
</tr>
<tr>
<td>STUDY ING114467</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5644</td>
<td>Atripla once daily</td>
<td>5.42</td>
<td>0.36</td>
<td>Anabolic steroids</td>
<td>N</td>
</tr>
</tbody>
</table>

Data Source: ING112276 Week 96 CSR ICH Listing 2 and Other Listing 24; ING113086 Week 48 CSR ICH Listing 3 and Other Listing 20; ING114467 Week 48 CSR ICH Listing 3 and Other Listing 21

a. Not a Hy's law case as alternative diagnosis established.
b. Additional diagnosis identified
c. Also met liver stopping criteria but investigator listed AE as reason for withdrawal.
## Module 2.7.4 Summary of Clinical Safety

### Table 43 Listing of Subjects with Maximum Post Baseline ALT >3x ULN but <5x ULN - ART-Naïve Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT/ULN</th>
<th>Bilirubin/ULN</th>
<th>Comment</th>
<th>Study Withdrawal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>818</td>
<td>DTG</td>
<td>4.96</td>
<td>1.09</td>
<td>Chronic HCV</td>
<td>Y, AE (Fatal Traffic Accident)</td>
</tr>
<tr>
<td>906</td>
<td>EFV</td>
<td>3.56</td>
<td>0.55</td>
<td>Transient increase</td>
<td>N</td>
</tr>
<tr>
<td>930</td>
<td>EFV</td>
<td>3.50</td>
<td>0.45</td>
<td>Chronic HCV</td>
<td>Y, Withdrew consent</td>
</tr>
<tr>
<td>75</td>
<td>DTG</td>
<td>3.21</td>
<td>0.73</td>
<td>Diagnosis not established</td>
<td>N</td>
</tr>
<tr>
<td>605</td>
<td>EFV</td>
<td>3.19</td>
<td>0.50</td>
<td>Transient, Diagnosis not established</td>
<td>N</td>
</tr>
<tr>
<td>55</td>
<td>DTG</td>
<td>3.10</td>
<td>1.00</td>
<td>Alcohol</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>EFV</td>
<td>3.10</td>
<td>0.36</td>
<td>Chronic HCV; transaminases elevated at screening</td>
<td>N</td>
</tr>
<tr>
<td>65</td>
<td>DTG</td>
<td>3.04</td>
<td>0.36</td>
<td>Exercise related changes in transaminases</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT/ULN</th>
<th>Bilirubin/ULN</th>
<th>Comment</th>
<th>Study Withdrawal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>3655</td>
<td>RAL 400 mg BID</td>
<td>4.58</td>
<td>0.64</td>
<td>Treated HCV</td>
<td>N</td>
</tr>
<tr>
<td>4371</td>
<td>RAL 400 mg BID</td>
<td>4.35</td>
<td>0.41</td>
<td>HBV</td>
<td>N</td>
</tr>
<tr>
<td>3669</td>
<td>RAL 400 mg BID</td>
<td>3.90</td>
<td>0.64</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>4337</td>
<td>RAL 400 mg BID</td>
<td>3.88</td>
<td>1.05</td>
<td>HCV + alcohol</td>
<td>N</td>
</tr>
<tr>
<td>4361</td>
<td>RAL 400 mg BID</td>
<td>3.79</td>
<td>0.73</td>
<td>HCV + alcohol</td>
<td>N</td>
</tr>
<tr>
<td>3702</td>
<td>RAL 400 mg BID</td>
<td>3.54</td>
<td>0.55</td>
<td>HBV</td>
<td>N</td>
</tr>
<tr>
<td>4304</td>
<td>DTG 50 mg once daily</td>
<td>3.52</td>
<td>0.50</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>3252</td>
<td>RAL 400 mg BID</td>
<td>3.50</td>
<td>0.64</td>
<td>Muscle source</td>
<td>N</td>
</tr>
<tr>
<td>3697</td>
<td>DTG 50 mg once daily</td>
<td>3.48</td>
<td>0.68</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>4557</td>
<td>RAL 400 mg BID</td>
<td>3.42</td>
<td>0.55</td>
<td>Steatohepatitis</td>
<td>N</td>
</tr>
<tr>
<td>4370</td>
<td>RAL 400 mg BID</td>
<td>3.35</td>
<td>0.27</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>3046</td>
<td>DTG 50 mg once daily</td>
<td>3.06</td>
<td>0.55</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>4060</td>
<td>DTG 50 mg once daily</td>
<td>3.04</td>
<td>0.68</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>4338</td>
<td>RAL 400 mg BID</td>
<td>3.04</td>
<td>0.55</td>
<td>ABC HSR</td>
<td>Y, AE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT/ULN</th>
<th>Bilirubin/ULN</th>
<th>Comment</th>
<th>Study Withdrawal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>5580</td>
<td>DTG 50 mg +ABC/3TC once daily</td>
<td>4.63</td>
<td>1.00</td>
<td>Grade 1 ALT at Baseline</td>
<td>N</td>
</tr>
<tr>
<td>6033</td>
<td>Atripla once daily</td>
<td>4.58</td>
<td>0.91</td>
<td>HCV, Possible IRIS</td>
<td>Y, Virologic Failure</td>
</tr>
<tr>
<td>5119</td>
<td>Atripla once daily</td>
<td>4.27</td>
<td>0.55</td>
<td>HCV, Possible IRIS</td>
<td>N</td>
</tr>
<tr>
<td>5484</td>
<td>Atripla once daily</td>
<td>4.21</td>
<td>0.45</td>
<td>Muscle source</td>
<td>N</td>
</tr>
<tr>
<td>6078</td>
<td>Atripla once daily</td>
<td>4.08</td>
<td>0.27</td>
<td>Possible DILI</td>
<td>N</td>
</tr>
<tr>
<td>6401</td>
<td>Atripla once daily</td>
<td>3.92</td>
<td>0.23</td>
<td>Transient increase on two occasions</td>
<td>N</td>
</tr>
<tr>
<td>5315</td>
<td>Atripla once daily</td>
<td>3.83</td>
<td>0.45</td>
<td>Systemic candida, multi-organ failure.</td>
<td>Y, AE</td>
</tr>
<tr>
<td>6195</td>
<td>Atripla once daily</td>
<td>3.83</td>
<td>0.36</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>5084</td>
<td>Atripla once daily</td>
<td>3.73</td>
<td>0.36</td>
<td>Cholecystitis</td>
<td>N</td>
</tr>
<tr>
<td>5283</td>
<td>Atripla once daily</td>
<td>3.65</td>
<td>0.27</td>
<td>HCV, concurrent drugs</td>
<td>N</td>
</tr>
<tr>
<td>5622</td>
<td>Atripla once daily</td>
<td>3.54</td>
<td>0.27</td>
<td>Possible DILI</td>
<td>N</td>
</tr>
</tbody>
</table>
### Module 2.7.4 Summary of Clinical Safety

#### 3.1.1.1.1. ART-Naïve Adults Co-Infected with HBV and/or HCV

In the ART-naïve population for all groups, subjects with HBV and/or HCV infection at Baseline had a higher incidence of post-Baseline-emergent Grade 2-4 liver chemistry toxicities compared with subjects who had neither infection (Table 44). For ALT and AST, the incidence of toxicities in subjects with hepatitis virus infection treated with DTG was lower than both the RAL and Atripla treated subjects. The incidence of liver chemistry toxicities for subjects without hepatitis virus infection was similar in all treated groups.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT /ULN</th>
<th>Bilirubin /ULN</th>
<th>Comment</th>
<th>Study Withdrawal? Yes/No (Y/N), Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>5225</td>
<td>Atripla once daily</td>
<td>3.44</td>
<td>0.45</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>5722</td>
<td>Atripla once daily</td>
<td>3.29</td>
<td>0.45</td>
<td>HCV</td>
<td>Y, AE</td>
</tr>
<tr>
<td>7796</td>
<td>Atripla once daily</td>
<td>3.29</td>
<td>0.64</td>
<td>Primary Biliary Cirrhosis</td>
<td>N</td>
</tr>
<tr>
<td>6736</td>
<td>DTG 50 mg +ABC/3TC once daily</td>
<td>3.08</td>
<td>0.73</td>
<td>Alcohol</td>
<td>N</td>
</tr>
<tr>
<td>5179</td>
<td>DTG 50 mg +ABC/3TC once daily</td>
<td>3.02</td>
<td>0.64</td>
<td>Non-alcoholic fatty liver disease</td>
<td>Y, Virologic Failure</td>
</tr>
</tbody>
</table>

Data Source: ING112276 Week 96 CSR ICH Listing 2 and Other Listing 24; ING113086 Week 48 CSR ICH Listing 3 and Other Listing 20; ING114467 Week 48 CSR ICH Listing 3 and Other Listing 21

Subject 55 in ING112276 died of a myocardial infarction after the Week 96 CSR data cut-off but before the data cut-off for this safety summary.
### Table 44  Summary of Post Baseline-Emergent ALT, AST and Total Bilirubin Toxicities for Subjects Co-Infected with HBV and/or HBC or Neither – ART-Naïve Population

<table>
<thead>
<tr>
<th></th>
<th>HBV and/or HCV coinfected</th>
<th>No HBV or HCV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOTAL DTG ART-Naïve</td>
<td>RAL ART-Naïve</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>90</td>
<td>43</td>
</tr>
<tr>
<td><strong>ALT n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>29 (32)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>13 (14)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>5 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>16 (18)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>8 (9)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>AST n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>28 (31)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>10 (11)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18 (20)</td>
<td>15 (35)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (8)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>BILI n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>3 (3)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (2)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Data Source:** ISO Table 2.227

### 3.1.1.2. Studies in ART-Experienced (INI-Naïve) Adults

There were few events in the Hepatobiliary SOC except for jaundice, which was similar in both groups and likely reflected the use of boosted atazanavir and the well-described indirect hyperbilirubinemia related to use of this drug (Data Source: ISO Table 2.523).

Graded liver chemistry toxicities are provided in CSR ING11762 Table 8.24. The overall profiles were similar for DTG and RAL, although there were numerically more Grade 3/4 events for ALT and AST in the DTG group than in the RAL group (9 versus 6 and 12
versus 5, respectively). The percentages were greater for all groups compared with the ART-naïve population, likely reflecting the inclusion of a higher percentage of subjects with viral hepatitis co-infection and other co-morbidities, the longer duration of disease in this ART-experienced population, and the greater number of concomitant medications. There was also a higher incidence of total bilirubin toxicities, particularly Grade 3/4 toxicities, which seemed attributable to the inclusion of boosted atazanavir in the OBR of approximately 13 to 15% of the subjects and the known indirect hyperbilirubinemia associated with its use.

There was a similar proportion of subjects in each treatment group with ALT ≥3xULN (DTG: 6%; RAL: 4%) and ALT ≥5xULN (DTG: 3%; RAL: 2%, Table 45).

Table 45 Summary of Subjects Meeting Hepatobiliary Laboratory Abnormality Criteria At Any Post Baseline Visit - ART-Experienced (INI-Naive) Population

<table>
<thead>
<tr>
<th>Parameter/criteria</th>
<th>DTG 50 mg Once Daily</th>
<th>RAL 400 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects meeting at least one criterion</td>
<td>71 (20)</td>
<td>65 (18)</td>
</tr>
<tr>
<td>ALT and/OR AST &gt;3XULN and Alkaline Phosphatase &lt; 2xULN and Total Bilirubin &gt;= 2xULN</td>
<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT and/OR AST &gt;3XULN and total bilirubin &gt;2xULN</td>
<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT and/OR AST &gt;3XULN and total bilirubin &gt;1.5xULN</td>
<td>4 (1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>ALT+AST &gt;=20XULN</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT+AST &gt;=10XULN</td>
<td>3 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT+AST &gt;=5XULN</td>
<td>8 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>ALT+AST &gt;=3XULN</td>
<td>15 (4)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>ALT &gt;=20XULN</td>
<td>2 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>ALT &gt;=10XULN</td>
<td>4 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT &gt;=5XULN</td>
<td>9 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>ALT &gt;=3XULN</td>
<td>20 (6)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>AST &gt;=20XULN</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>AST &gt;=10XULN</td>
<td>6 (2)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>AST &gt;=5XULN</td>
<td>12 (3)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>AST &gt;=3XULN</td>
<td>18 (5)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Total Bilirubin &gt;2XULN</td>
<td>27 (8)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Total Bilirubin &gt;1.5XULN</td>
<td>38 (11)</td>
<td>34 (9)</td>
</tr>
<tr>
<td>Alk. Phos. &gt;1.5XULN</td>
<td>18 (5)</td>
<td>19 (5)</td>
</tr>
</tbody>
</table>

Data Source: CSR ING111762 Table 8.44
**Post Baseline ALT and/or AST >3xULN with Total Bilirubin >2xULN and Alkaline Phosphatase <2xULN**

Three subjects on DTG (Subjects 283, 2640, and 9098) and one subject on RAL (Subject 2166) had a combination of ALT >3xULN with total bilirubin ≥2xULN and ALP <2xULN. All 4 of these subjects met the protocol-defined liver stopping criteria and are briefly described below.

**Subject 283 (DTG),** a □-year-old male, had medical history not significant for hepatobiliary disorders and was negative to hepatitis B and hepatitis C (including HCV RNA) at Day 1. The subject started presenting elevated ALT (71 U/L; normal 0 to 48) at study visit week 8. AST was normal and total bilirubin was 44 µmol/L (normal 0 to 22), with normal direct bilirubin. At Week 16 ALT increased to 102 U/L and total bilirubin was 52 µmol/L. On 29 November □ ALT was 470 U/L, AST was 370 U/L and total bilirubin was 86 µmol/L, with direct bilirubin of 34 µmol/L. On 01 December a* antiretrovirals were interrupted. Laboratory results from 01-Dec-a* disclosed an HCV RNA 54,300 IU/mL. ALT was 456 U/L, AST was 323 U/L, alkaline phosphatase was 137 U/L (1.1 x ULN), and total bilirubin was 138 µmol/L (43% due to direct bilirubin). The subject liver tests were closely followed until 12-Jan-b*, when he returned to the withdrawal visit and ALT was 237 U/L, AST 58 U/L, and total bilirubin was 10 µmol/L. HCV RNA for that visit was of 991 IU/mL. This subject’s liver abnormalities were considered related to acute hepatitis C and were documented in an SAE of liver disorder.

**Subject 2640 (DTG),** a □-year-old male, had medical history of hepatitis B since q* (HBV DNA PCR at Day 1 was <116 copies/mL). The treatment regimen discontinued at the time of study entry included tenofovir, tipranavir/ritonavir, maraviroc and zidovudine/lamivudine. On Day 1 of the study, the background regimen was darunavir/ritonavir and etravirine. On 28 February □ at week 12 visit (23 February a*) ALT was 681 U/L (normal 0 to 48), AST was 567 U/L (normal 0 to 42), and total bilirubin was 24 µmol/L (normal 0 to 22). On 29 February a* the subject was complaining of mild abdominal pain and choloria and presented with ALT of 1888 U/L, AST of 1574 U/L, and total bilirubin was 82 U/L (direct bilirubin of 36 U/L). At the same date Hepatitis B surface Ag and hepatitis B-Core IgM antibodies were positive and HBV DNA PCR >989,000,000 copies/mL. Antiretroviral therapy was interrupted. On 06 March a* he was started on 1.0 mg oral Entecavir once daily. Liver biopsy from 08-Mar-a* showed hepatitis with intense inflammatory component. The subject improved progressively and on 04-Jul-a* HBV DNA was 1,240 IU/mL, ALT was 31 U/L, AST was 31 U/L and total bilirubin was 8 µmol/L. Antiretroviral therapy was restarted on 05-Jul-a* with the same regimen (darunavir/ritonavir, etravirine and DTG). There was no recurrence of liver chemistry elevations following rechallenge with DTG. This subject was considered to have presented with an hepatitis B flare, which was described in an SAE of liver disorder.

**Subject 9098 (DTG),** a □-year-old AA/AH male, experienced Grade 4 hepatotoxicity on Day 57 of the study. This subject had a Baseline HIV-1 RNA of 2,959 c/mL (Screening HIV-1 RNA – 169,713 c/mL) and CD4 cell count of 266 cells/µL, and in
addition to DTG, was receiving LPV/RTV. Baseline ALT was 15 U/L with AST of 21 U/L and total bilirubin was 5 μmol/L. The subject’s medical history was significant for hepatitis B, with a positive hepatitis B surface antigen at Screening. The treatment regimen discontinued at the time of study entry included 3 (zidovudine/3TC and EFV). At Week 8 the subject had asymptomatic liver chemistry elevations as follows: ALT 1011 U/L (normal 0-48), AST 909 U/L (normal 0-42), and total bilirubin 34 μmol/L (normal 0-22) with direct bilirubin of 16 μmol/L (normal 0-6). Corresponding HIV-1 RNA was 160 c/mL and CD4+ cell count was 358 cells/μL. Antiretroviral therapy, including IP, was interrupted ~1 week after the liver chemistry elevation was noted. The subject denied use of concomitant medications, including herbals, or alcohol intake. An abdominal ultrasound was performed and was unremarkable. Additional hepatitis virus workup was negative. HBV DNA at Day 1 was 250 c/mL, and at the time of the liver chemistry elevation, was noted to be 3,030,000 c/mL. The subject was closely followed and progressively improved. Twenty-three days after the initial elevation, ALT was 51 U/L, AST was 29 U/L and total bilirubin was 20 μmol/L. This case was considered by the Sponsor as a hepatitis B flare after removal of hepatitis B therapy (3TC) and a possible IRIS (with decline in HIV-1 RNA and increase in CD4+ cell count). The IDMC did not classify this as an IRIS event but noted the flare in HBV after discontinuation of lamivudine. The investigator felt that the SAE was reasonably related to DTG.

Subject 2166 (RAL), a year-old male, had medical history significant for hepatitis C and type 2 diabetes. Baseline ALT (normal 0 to 48) and AST (normal 0 to 42) were mildly abnormal (57 U/L and 86 U/L, respectively). On 13 April, at study visit week 4 the ALT was 80 U/L, AST was 155 U/L, and total bilirubin was 56 μmol/L (normal 0 to 22) with direct bilirubin of 25 μmol/L (normal 0 to 6). The investigator associated the liver abnormalities to ethanol abuse and the subject was counseled. At week 8, the same pattern of liver enzymes was observed and at week 12 (08 June a*) ALT improved to 21 U/L, with AST of 44 U/L with total bilirubin of 34 μmol/L (16 μmol/L of direct bilirubin). Transaminases continued within normal ranges until week 48 with the exception of Week 32 AST, which was 64 U/L. Total bilirubin also improved with time and was noted as Grade 1 on Week 16 and Week 24, decreasing to values within normal ranges from Week 32 onwards. This subject also presented with low blood red cell count from Baseline up to Week 40, macrocytosis from Baseline to week 32 and elevated lipase, which ranged from normal and Grade 2 throughout the study period (maximum of 108 U/L). The pattern of AST>ALT (moderately elevated), elevated lipase values, and macrocytosis was considered by the sponsor to suggest a link between the subject’s abnormalities in liver function tests and ethanol abuse, with possible concomitant influence of the subject’s hepatitis C. These events were not reported as an SAE.

The relationship between post-Baseline-emergent increases in ALT and total bilirubin is shown in Figure 2.

*a* The year
Figure 2  eDish plot of Maximum Post Baseline Total Bilirubin vs Maximum Post Baseline ALT (/ULN) – ART-Experienced (INI-Naïve) Population

Data Source: ISO Figure 2.511

Post Baseline ALT >10xULN

The subjects with maximum ALT values ≥10xULN are summarised in Table 46. All of these subjects met protocol-defined liver chemistry criteria for stopping IP.
Table 46 Listing of Subjects with Maximum Post Baseline ALT ≥10xULN – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT ULN</th>
<th>Bilirubin ULN</th>
<th>Comment</th>
<th>Study Withdrawal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>2418</td>
<td>DTG</td>
<td>14.9</td>
<td>0.45</td>
<td>Possible Hepatitis C IRIS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes, Liver Stopping Criteria</td>
</tr>
<tr>
<td>2467</td>
<td>DTG</td>
<td>10.0</td>
<td>1.77</td>
<td>Hepatitis C IRIS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes, Liver Stopping Criteria</td>
</tr>
<tr>
<td>2640</td>
<td>DTG</td>
<td>54.0</td>
<td>20.09</td>
<td>Hepatitis B flare after tenofovir/lamivudine discontinuation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>9098</td>
<td>DTG</td>
<td>26.9</td>
<td>3.64</td>
<td>Hepatitis B flare after discontinuation of lamivudine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes, Liver Stopping Criteria</td>
</tr>
<tr>
<td>9972</td>
<td>RAL</td>
<td>15.7</td>
<td>7.45</td>
<td>Choledocolithiasis and post cholecystectomy complications</td>
<td>Yes, Adverse Event&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR ICH Listing 3 and Other Listing 25 and Table 8.58, Table 8.59
a. DTG 50 mg Once Daily; RAL 400 mg BID
b. Based on Quest Laboratory values.
c. Adjudicated by IDMC
d. Also met liver stopping criteria but investigator listed AE as reason for withdrawal.

Post Baseline ALT >5xULN but <10xULN

Subjects with ALT elevations >5xULN but <10xULN are shown in Table 47. A total of eleven subjects met these criteria [DTG: 5 (1%); RAL: 6 (2%)].
## Listing of Subjects with Maximum Post Baseline-Emergent ALT >5xULN but <10xULN – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatmenta</th>
<th>ALT ULN(^b)</th>
<th>Bilirubin ULN</th>
<th>Comment</th>
<th>Study Withdrawal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>283</td>
<td>DTG</td>
<td>9.79</td>
<td>6.27</td>
<td>Acute hepatitis C virus(^c)</td>
<td>Yes, Liver Stopping Criteria</td>
</tr>
<tr>
<td>291</td>
<td>RAL</td>
<td>5.54</td>
<td>0.55</td>
<td>Chronic hepatitis C(^c)</td>
<td>No</td>
</tr>
<tr>
<td>346</td>
<td>RAL</td>
<td>6.50</td>
<td>0.55</td>
<td>Excessive alcohol intake</td>
<td>No</td>
</tr>
<tr>
<td>501</td>
<td>DTG</td>
<td>8.04</td>
<td>0.45</td>
<td>Possibly tipranavir (TPV)/RTV, DTG could not be ruled out</td>
<td>Yes, Liver Stopping Criteria</td>
</tr>
<tr>
<td>742</td>
<td>RAL</td>
<td>6.94</td>
<td>0.45</td>
<td>Hepatitis C, RAL could not be ruled out; not IRIS(^c)</td>
<td>Yes, AE</td>
</tr>
<tr>
<td>942</td>
<td>DTG</td>
<td>9.92</td>
<td>1.36</td>
<td>HBV IRIS, followed by hepatitis B flare off treatment(^c)</td>
<td>Yes, Liver Stopping Criteria</td>
</tr>
<tr>
<td>1112</td>
<td>DTG</td>
<td>5.85</td>
<td>0.82</td>
<td>Hepatitis B IRIS, hepatitis C IRIS(^c),</td>
<td>No</td>
</tr>
<tr>
<td>2209</td>
<td>RAL</td>
<td>4.96</td>
<td>1.91</td>
<td>Liver chemistry elevations beyond treatment discontinuation; HCV flare without temporal relationship to start of drug(^c)</td>
<td>Yes, Liver Stopping Criteria</td>
</tr>
<tr>
<td>9012</td>
<td>RAL</td>
<td>7.60</td>
<td>1.55</td>
<td>Acute infectious disease with multi organ failure, RAL could not be ruled out(^d)</td>
<td>Yes, Death</td>
</tr>
<tr>
<td>9040</td>
<td>DTG</td>
<td>6.65</td>
<td>1.32</td>
<td>Hepatitis B flare in absence of treatment(^c)</td>
<td>No</td>
</tr>
<tr>
<td>9142</td>
<td>RAL</td>
<td>5.58</td>
<td>0.82</td>
<td>Hepatitis C with fluctuating low grade elevation of AST/ALT(^c)</td>
<td>No</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR ICH Listings 3 and 20 and Table 8.58, Table 8.59

### Post Baseline ALT >3xULN but <5xULN

Subjects with ALT ≥5 times the upper limit of normal were excluded from the study. A summary of subjects with ALT elevations >3xULN but <5xULN at any time from Baseline onward is provided in Table 48. A total of 17 subjects met these criteria (DTG: 11 (3%); RAL: 6 [2%]).
### Table 48  
**List of Subjects with Maximum Post Baseline ALT >3x ULN but <5x ULN – ART-Experienced (INI-Naïve) Population**

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT ULN</th>
<th>Bilirubin ULN</th>
<th>Comment</th>
<th>Study Withdrawal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>224</td>
<td>DTG</td>
<td>3.42</td>
<td>0.82</td>
<td>Hepatitis C infection, Grade 2 at Baseline and Grade 1-2 through Week 24 (exception: normal Week 16)</td>
<td>No</td>
</tr>
<tr>
<td>561</td>
<td>RAL</td>
<td>4.54</td>
<td>0.55</td>
<td>Grade 2 at Baseline and Week 24 only</td>
<td>No</td>
</tr>
<tr>
<td>862</td>
<td>DTG</td>
<td>3.98</td>
<td>0.55</td>
<td>Grade 2 at Week 16 only – with concurrent hepatotoxisci</td>
<td>No</td>
</tr>
<tr>
<td>923</td>
<td>DTG</td>
<td>3.08</td>
<td>0.55</td>
<td>Grade 2 at Baseline</td>
<td>No</td>
</tr>
<tr>
<td>979</td>
<td>RAL</td>
<td>4.1</td>
<td>0.73</td>
<td>Hepatitis C infection, Grade 2 at Baseline and to Week 40</td>
<td>No</td>
</tr>
<tr>
<td>1127</td>
<td>DTG</td>
<td>3.48</td>
<td>0.36</td>
<td>Grade 2 at Week 12 and Week 12 retest only</td>
<td>No</td>
</tr>
<tr>
<td>1149</td>
<td>DTG</td>
<td>3.23</td>
<td>0.45</td>
<td>Grade 1 at Baseline, Grade 2 at Week 2; no other elevations</td>
<td>No</td>
</tr>
<tr>
<td>1905</td>
<td>DTG</td>
<td>4.33</td>
<td>1.0</td>
<td>Grade 1 Week 12 and Week 16 only</td>
<td>No</td>
</tr>
<tr>
<td>2030</td>
<td>DTG</td>
<td>4.78</td>
<td>0.68</td>
<td>Single Grade 2 elevation at Week 24</td>
<td>No</td>
</tr>
<tr>
<td>2425</td>
<td>RAL</td>
<td>3.00</td>
<td>1.50</td>
<td>HCV IRIS; Alcohol consumption a competing possibilityc</td>
<td>Yes, LTFU</td>
</tr>
<tr>
<td>2474</td>
<td>DTG</td>
<td>3.02</td>
<td>0.64</td>
<td>HCV IRIS; Alcohol consumption a competing possibilityc.</td>
<td>Yes, withdrew consent</td>
</tr>
<tr>
<td>2677</td>
<td>RAL</td>
<td>3.23</td>
<td>0.55</td>
<td>Grade 2 at Baseline, and Grade 1-2 through Week 24</td>
<td>No</td>
</tr>
<tr>
<td>2740</td>
<td>DTG</td>
<td>3.79</td>
<td>0.46</td>
<td>Single Grade 2 elevation at Week 12</td>
<td>No</td>
</tr>
<tr>
<td>2812</td>
<td>DTG</td>
<td>3.63</td>
<td>0.55</td>
<td>Grade 2 at Follow-up visit</td>
<td>Yes, PDVF</td>
</tr>
<tr>
<td>2851</td>
<td>RAL</td>
<td>4.08</td>
<td>0.91</td>
<td>Chronic hepatitis B infection, Grade 2 at Baseline</td>
<td>Yes, PDVF</td>
</tr>
<tr>
<td>2984</td>
<td>DTG</td>
<td>2.96</td>
<td>0.36</td>
<td>Grade 1 at all visits Week 2 through Week 24 (exception Grade 2 at Week 16)</td>
<td>No</td>
</tr>
<tr>
<td>9429</td>
<td>RAL</td>
<td>3.16</td>
<td>1.36</td>
<td>? Hyperlipidemia / fatty liver</td>
<td>No</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR ICH Listings 3 and 20 and Table 8.58, Table 8.59

a. DTG 50 mg Once Daily; RAL 400 mg BID
b. Based on Quest Laboratory values
c. Adjudicated by IDMC.

LTFU = lost to follow-up; PDVF = protocol-defined virologic failure

### 3.1.1.2.1. ART-Experienced (INI-Naïve) Adults Co-Infected with HBV and/or HCV

The maximum graded liver chemistry toxicities for subjects with and without viral hepatitis at Baseline are shown in Table 49. The post-Baseline-emergent liver chemistry toxicities for subjects with either HBV or HCV at Baseline are shown in Table 50.
### Table 49  Summary of Post Baseline-Emergent ALT, AST, and Total Bilirubin Toxicities for Subjects Co-Infected with HBV and/or HBC or Neither – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th></th>
<th>HBV and/or HCV co-infected</th>
<th>Neither</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG 50 mg Once Daily + BR</td>
<td>RAL 400 mg BID + BR</td>
</tr>
<tr>
<td>n</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>All parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>21 (42)</td>
<td>35 (54)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>15 (30)</td>
<td>19 (29)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>7 (14)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6 (12)</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>8 (16)</td>
<td>14 (22)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (4)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>5 (10)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>15 (30)</td>
<td>21 (32)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>11 (22)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>7 (14)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (8)</td>
<td>17 (26)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>4 (8)</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>16 (32)</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>10 (20)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>7 (14)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6 (12)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3 (6)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>4 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>8 (16)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>6 (12)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>2 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (8)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.534

a. Subjects with missing HBV and/or HCV status are not included.
For subjects who had data available to confirm HBV or HCV status:

- In the DTG group, 14/15 subjects with Grade 3 post-Baseline-emergent total bilirubin elevations were receiving ATV and 2/3 subjects with Grade 4 post-Baseline-emergent total bilirubin elevations were receiving ATV.

- In the RAL group, 7/8 subjects with Grade 3 post-Baseline-emergent total bilirubin elevations were receiving ATV and 1/2 subjects with Grade 4 post-Baseline-emergent total bilirubin elevations were receiving ATV.

There were 3 additional subjects receiving ATV, with Grade 3 bilirubin elevations, who had missing data to confirm their HBV/HCV status (1 on DTG, 2 on RAL).

Forty two subjects were missing data on HBV and HCV status. Of those, 17 (5%) were receiving DTG, and 25 (7%) were receiving RAL.
### Table 50  Summary of Post Baseline-Emergent ALT, AST, and Total Bilirubin Toxicities for Subjects Co-Infected with HBV or HCV - ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th></th>
<th>HBV infected</th>
<th>HCV infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG 50 mg Once Daily + BR</td>
<td>RAL 400 mg BID + BR</td>
</tr>
<tr>
<td>n</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>All parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>8 (47)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>6 (35)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>4 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (12)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (12)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (18)</td>
<td>0</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>5 (29)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>4 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>4 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1 (6)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>6 (35)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>4 (24)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>4 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (12)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>6 (35)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>4 (24)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (12)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.534

Use of antiretroviral background therapy containing hepatitis B active agents (i.e., tenofovir, lamivudine, emtricitabine) and use of other hepatitis B therapy (e.g., entecavir, telbivudine) varied widely across the study with 11 subjects (6 on DTG, 5 on RAL) on no active hepatitis B therapy at Day 1 and/or discontinuing HBV-active therapy despite being hepatitis B surface antigen positive at Screening or Day 1.
Of the 6 subjects on DTG with chronic active hepatitis B and no hepatitis B therapy and/or discontinuation of HBV-active therapy at Day 1, 3 subjects (2640, 9098 and 942) developed liver event stopping criteria and 1 subject (9040) developed Grade 3 ALT and AST elevations. Subject 2640 had temporary discontinuation of DTG and other HIV medications, and entecavir was added with eventual improvement in the liver enzymes and decline in the HBV DNA. DTG was restarted and liver enzymes remained within normal limits. Subject 9040 had TDF/FTC added to their DTG and BR at Week 40 and the liver enzyme elevations resolved after this additional therapy was provided. One additional DTG subject (2889) was lost to follow-up at Week 2. The remaining subject experienced HIV virologic suppression and had normal liver enzymes throughout the study.

With regards to virologic response in the group of subjects with hepatitis B co-infection, 3/17 (18%) subjects receiving RAL experienced protocol-defined virologic failure (PDVF) and 1/18 (6%) subjects on DTG experienced PDVF. A post-hoc analysis of treatment-related discontinuation equals failure (TRDF) for hepatitis B subjects was completed and showed no differences in efficacy based on TRDF, although numbers of subjects are small in both groups (Data Source: ING111762 Week 24 CSR Figure 7.12).

Overall, four subjects (DTG: 2, RAL: 2) with acute (n=1) or chronic (n=3) hepatitis C met liver stopping criteria and were withdrawn for liver chemistry elevations. One additional subject (742) on DTG was withdrawn, although this subject did not meet liver stopping criteria. HCV co-infected subjects in both treatment arms were also noted to have Grade 1 and 2 elevations in liver transaminases at Baseline and during the course of treatment, which were not treatment-limiting or progressive, and in some cases were sporadic or self-limiting. A post-hoc analysis of TRDF for hepatitis C virus co-infected subjects was completed and suggested a possible efficacy difference in favour of DTG at Week 24 and beyond (Data Source: ING111762 Week 24 CSR Table 8.61).

### 3.1.1.3. Studies in ART-Experienced (INI-Resistant) Adults

There was no pattern of concern to the events reported from the hepatobiliary SOC in the ART-experienced (INI-resistant) population. Only hepatomegaly and hyperbilirubinaemia appeared in more than one subject on DTG 50 mg BID, and the remaining events were those that might be expected in this treatment-experienced population with many co-morbid conditions (Data Source: ISO Table 2.16).

The graded liver chemistry abnormalities for the ART-experienced (INI-resistant) population is shown in ISO Table 2.168. The incidence of Grade 3/4 toxicities was low (≤3%) for the total population.

The summary of subjects meeting the Hepatobiliary Laboratory Abnormality Criteria suggested in FDA 2009 guidance [FDA, 2009] is shown for the ART-experienced (INI-resistant) population in Table 51, and a plot of ALT versus total bilirubin using the ratio to the ULN (eDISH) for the ART-experienced (INI-resistant) population is shown in Figure 3.
## Table 51 Summary of Subjects Meeting Hepatobiliary Laboratory Abnormality Criteria At Any Post Baseline Visit - ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>Parameter/criteria</th>
<th>Cohort I DTG 50 mg Once Daily + BR N=27</th>
<th>Cohort II DTG 50 mg BID + BR N=24</th>
<th>DTG 50 mg BID + BR N=183</th>
<th>Total DTG 50 mg BID N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects meeting at least one criteria</td>
<td>6 (22)</td>
<td>7 (29)</td>
<td>28 (15)</td>
<td>35 (17)</td>
</tr>
<tr>
<td>ALT/AST &gt; 3XULN AND TOT. BILI. &gt; 2XULN</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>ALT/AST &gt;3XULN &amp; ALK. PHOS.&lt; 2XULN &amp; TOT BILI.&gt;=2XULN</td>
<td>0</td>
<td>1 (4)</td>
<td>3 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>ALT/AST &gt; 3XULN &amp; TOT BILI. &gt;1.5XULN</td>
<td>0</td>
<td>1 (4)</td>
<td>4 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>ALT+AST &gt;=20XULN</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT+AST &gt;=10XULN</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT+AST &gt;=5XULN</td>
<td>0</td>
<td>0</td>
<td>4 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>ALT+AST &gt;=3XULN</td>
<td>0</td>
<td>1 (4)</td>
<td>5 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>ALT &gt;=20XULN</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>ALT &gt;=10XULN</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>ALT &gt;=5XULN</td>
<td>0</td>
<td>1 (4)</td>
<td>7 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>ALT &gt;=3XULN</td>
<td>0</td>
<td>2 (8)</td>
<td>15 (8)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>AST &gt;=20XULN</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>AST &gt;=10XULN</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>AST &gt;=5XULN</td>
<td>0</td>
<td>1 (4)</td>
<td>6 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>AST &gt;=3XULN</td>
<td>0</td>
<td>2 (8)</td>
<td>9 (5)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>TOTAL BILI. &gt;2XULN</td>
<td>2 (7)</td>
<td>3 (13)</td>
<td>2 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>TOTAL BILI. &gt;1.5XULN</td>
<td>2 (7)</td>
<td>5 (21)</td>
<td>8 (4)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>ALK. PHOS. &gt;1.5XULN</td>
<td>4 (15)</td>
<td>0</td>
<td>10 (5)</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.199
Data Source: ISO Figure 2.27

A higher proportion of subjects in this treatment-experienced population developed ALT elevations greater than three times the upper limit of normal compared with the number reported in the ART-naïve populations (8% vs. 3%). Only three of these subjects were thought to have possible drug-induced liver injury (DILI) related to the ART regimen (Subjects 226, 461 and 568).

**Post Baseline ALT >3xULN with Total Bilirubin >2xULN and Alkaline Phosphatase <2xULN**

Three subjects had a combination of ALT >3xULN with total bilirubin >2xULN and alkaline phosphatase <2xULN in ING112574 (1263, 1201, and 568). All three subjects met protocol-defined liver event stopping criteria. One subject in ING112961, Subject 2203 Cohort II with chronic HCV, had an elevated AST and bilirubin at Baseline (both Grade 1), and both fluctuated between Grades 1 and 2 throughout 96 weeks. The investigator did not think the changes in liver chemistries were related to study drug, and the subject has remained asymptomatic with full virological suppression to <50 copies/ml.

**Subject 1263** is a 47 year old White male (Baseline HIV-1 RNA viral load of 11216 c/mL and CD4+ cell count of 360 cells/µL) who received DTG 50 mg BID, along with enfuvirtide, stavudine, and darunavir. He had a past history of infection with HBV and HCV and was positive for HCV antibody at Baseline with ALT of 322 U/L, AST 238 U/L and bilirubin 21 µmol/L. He responded well with suppression of his HIV viral
load to <40 c/mL at Week 4 and a fall in his transaminases. At Week 12 it was noted that although his transaminases remained below the Baseline value, his bilirubin had increased to 30 μmol/L and by Week 19 this had risen to just above 2xULN at 45 μmol/L. Although this technically met liver stopping criteria, as the subject was clinically well with no evidence of hepatic impairment and as his transaminases remained below Baseline his DTG was continued. His transaminases continued to fall slowly and his bilirubin fell to his Baseline (normal) levels. At Week 24 his ALT was 162 U/L, AST 115 U/L and bilirubin 23 μmol/L.

Subject 568 (SAE – Grade 3 drug eruption, Grade 3 hyperbilirubinemia, Grade 2 alanine aminotransferase increased) is a 21 year old White male (Baseline HIV-1 RNA viral load of 197,051 c/mL and CD4+ cell count of 20 cells/μL), with no relevant medical history, who received DTG 50 mg BID initially with Truvada. Treatment with DTG was well tolerated during the functional mono therapy phase, during the first seven days, of the study. On Day 8, the subject commenced etravarine (ETR) and DRV/RTV as OBR. After 15 days DTG treatment and seven days treatment with ETR and DRV/RTV the subject developed a full body drug rash with fever, nausea and vomiting. Four days later he developed elevated ALT and hyperbilirubinemia. ALT was 4.6xULN, with AST and creatinine marginally increased, alkaline phosphatase 3xULN and direct bilirubin 6.5xULN. Collectively, events were considered indicative of a hypersensitivity reaction. DTG, ETR, DRV/RTV permanently discontinued and the subject withdrawn from the study. Treatment with triamcinolone and promethazine was initiated and the events resolved within two weeks. It was noted that the subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the week prior to onset of the reported events. The subject consumed 2 units per week of alcohol on average. The subject had no liver disease medical conditions (drug-related or otherwise) and no other relevant medical conditions. Diagnostic imaging and liver biopsy were not performed. The investigator considered there to be a reasonable possibility that the reported events were caused by DTG and his OBR.

Subject 1201 (SAE – Hepatitis acute) is a 57 year old White male (Baseline HIV-1 RNA viral load of 154,899 c/mL and CD4+ cell count of 80 cells/μL) who received DTG 50 mg BID, along with maraviroc (MVC), T-20, and KIVEXA™. The subject had a history of infection with hepatitis A, B and C but had subsequently cleared the infections and had negative serology. One hundred and fifteen days after starting DTG he developed acute hepatitis characterised by ALT/AST >30xULN, bilirubin 5xULN and HBV DNA>110,000,000 IU/mL. Frozen plasma from Day 1 was positive for total HBs antibody (including IgG) indicating pre-existing HBV exposure. The subject was treated with dextrose and DTG was interrupted. His TDF/FTC was restarted to treat his HBV and there was a rapid fall in his HBV DNA, with the event resolving after ~10 weeks. His acute hepatitis was not thought to be related to treatment with DTG, but a reactivation of hepatitis B following the withdrawal of TDF/FTC.
Post Baseline ALT >10xULN

Two subjects had maximum ALT values greater than 10xULN, both in ING112574 and are summarized in Table 52. Subject 1201 has been discussed above. The other subject, Subject 226 is discussed below and also met protocol-defined stopping criteria.

Subject 226 is a 53 year old White male (Baseline HIV-1 RNA viral load of 36340 c/mL and CD4+ cell count of 160 cells/μL) who received DTG 50 mg BID, along with darunavir, ritonavir and TDF/FTC. His Week 16 ALT showed a rise to 499 U/L, AST 119 U/L but at his previous, Week 12 visit, both transaminases were 18 U/L. His bilirubin had been normal since withdrawal of atazanavir at Day 8. His screening labs were non-reactive for both HCV and HBV. He had a history of Hodgkin’s lymphoma but nothing else of note. He was clinically well with no specific complaints. His toxicology screen was positive for opiates and marijuana metabolites only and there was no evidence of other viral (HAV, HBV, HCV, EBV or CMV) infection or syphilis. All ART was withdrawn and his liver chemistry returned to normal levels. After withdrawal from the study he was subsequently rechallenged with DRV/RTV and TDF/FTC with a similar rise of ALT to 455 U/L and AST to 159 U/L after eight weeks.

Table 52 Summary of Subjects with Maximum Post Baseline-Emergent ALT >10xULN – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT /ULN</th>
<th>Bilirubin /ULN</th>
<th>Comment</th>
<th>Study Withdrawal? Yes/No (Y/N), Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1201</td>
<td>DTG 50 mg BID</td>
<td>35.69</td>
<td>14</td>
<td>Reactivation HBV when TDF/FTC withdrawn</td>
<td>N</td>
</tr>
<tr>
<td>226</td>
<td>DTG 50 mg BID</td>
<td>10.40</td>
<td>1.81</td>
<td>DILI on DTG and DRV with positive re-challenge to DRV</td>
<td>Y, AEa</td>
</tr>
</tbody>
</table>

Data Source: ISO Listing 2.11; ING112574 Week 24 CSR ICH Listing 2 and 20.

a. Also met liver stopping criteria but investigator listed AE as reason for withdrawal.

Post Baseline ALT >5xULN but <10xULN

Six subjects had increases in ALT >5xULN but <10xULN. They are summarized in Table 53. Only one of these subjects was thought to have possible DILI.
Table 53  Summary of Subjects with Maximum Post Baseline ALT >5xULN but <10xULN – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT /ULN</th>
<th>Bilirubin /ULN</th>
<th>Comment</th>
<th>Study Withdrawal? Yes/No (Y/N), Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>2463</td>
<td>DTG 50 mg BID</td>
<td>5.29</td>
<td>0.73</td>
<td>Chronic HCV</td>
<td>Y, suicide</td>
</tr>
<tr>
<td>461</td>
<td>DTG 50 mg BID</td>
<td>8.96</td>
<td>0.64</td>
<td>Underlying fatty liver; Possible DILI</td>
<td>Y, Liver Stopping Criteria</td>
</tr>
<tr>
<td>1611</td>
<td>DTG 50 mg BID</td>
<td>5.94</td>
<td>0.82</td>
<td>Chronic HCV</td>
<td>N</td>
</tr>
<tr>
<td>1263</td>
<td>DTG 50 mg BID</td>
<td>5.85</td>
<td>2.05</td>
<td>Chronic HCV</td>
<td>N</td>
</tr>
<tr>
<td>41</td>
<td>DTG 50 mg BID</td>
<td>5.27</td>
<td>0.27</td>
<td>Macro CK type 1</td>
<td>Y, AE</td>
</tr>
<tr>
<td>1076</td>
<td>DTG 50 mg BID</td>
<td>5.04</td>
<td>1.00</td>
<td>No cause established. Returned to normal. Investigations normal.</td>
<td>N</td>
</tr>
</tbody>
</table>

Data source: ING112961 Week 48 CSR Listing 3 and 20; ING112574 Week 24 CSR Listing 2s and 20; ISO Listing 2.11

Post Baseline ALT >3xULN but <5xULN

One subject in ING112961 and eight subjects in ING112574 had increases of ALT >3xULN but <5xULN and these are summarized in Table 54. One of these subjects (568 in ING112574) was thought to have possible DILI. This subject was discussed above.
### Module 2.7.4 Summary of Clinical Safety

**Table 54** Summary of Subjects with Maximum Post Baseline ALT >3xULN but <5xULN – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment</th>
<th>ALT /ULN</th>
<th>Bilirubin /ULN&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Comment</th>
<th>Study Withdrawal? Yes/No (Y/N), Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDY ING112961</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2430</td>
<td>DTG 50 mg BID</td>
<td>4.75</td>
<td>1.00</td>
<td>Diabetic, non-alchoholic steatohepatitis</td>
<td>Y, virological failure</td>
</tr>
<tr>
<td>STUDY ING112574</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1038</td>
<td>DTG 50 mg BID</td>
<td>4.77</td>
<td>0.32</td>
<td>Alcohol</td>
<td>N</td>
</tr>
<tr>
<td>568</td>
<td>DTG 50 mg BID</td>
<td>4.65</td>
<td>3.45</td>
<td>Possible DILI</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>DTG 50 mg BID</td>
<td>4.50</td>
<td>0.73</td>
<td>Improved whilst on treatment. Diagnosis not established.</td>
<td>Y, virological failure</td>
</tr>
<tr>
<td>1011</td>
<td>DTG 50 mg BID</td>
<td>3.98</td>
<td>0.59</td>
<td>Grade 1 ALT at Baseline. Diagnosis not established. Variable, low level elevation ALT and AST.</td>
<td>N</td>
</tr>
<tr>
<td>1821</td>
<td>DTG 50 mg BID</td>
<td>3.60</td>
<td>0.64</td>
<td>Abnormal at Screening/Baseline with no significant deterioration.</td>
<td>Y, virological failure</td>
</tr>
<tr>
<td>507</td>
<td>DTG 50 mg BID</td>
<td>3.27</td>
<td>0.27</td>
<td>Transient increase attributed to viral illness</td>
<td>N</td>
</tr>
<tr>
<td>1902</td>
<td>DTG 50 mg BID</td>
<td>3.27</td>
<td>0.45</td>
<td>HCV</td>
<td>N</td>
</tr>
<tr>
<td>1274</td>
<td>DTG 50 mg BID</td>
<td>3.15</td>
<td>0.68</td>
<td>Underlying hepatic disease of uncertain aetiology</td>
<td>N</td>
</tr>
</tbody>
</table>

Data source: ING112961 Week 48 CSR Listing 3 and 22; ING112574 Week 24 CSR Listings 2 and 20

a. Also met liver stopping criteria but investigator listed AE as reason for withdrawal.
3.1.1.3.1. ART-Experienced (INI-Resistant) Adults Co-Infected with HBV and/or HCV

Table 55 Summary of Post Baseline-Emergent ALT, AST, and Total Bilirubin Toxicities for Subjects Co-Infected with HBV and/or HCV or Neither – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>TOTAL DTG 50 mg BID</th>
<th>HBV and/or HCV co infected</th>
<th>No HBV or HCV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>46</td>
<td>157</td>
</tr>
<tr>
<td>ALT n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>9 (20)</td>
<td>22 (14)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>4 (9)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>2 (4)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>5 (11)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2 (4)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>AST n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>12 (26)</td>
<td>26 (17)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>4 (9)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>8 (17)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (9)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>BILI n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>6 (13)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>5 (11)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>1 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (9)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (2)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.228

Of note, three subjects in ING112961, Cohort II, and 1 subject in ING112574 were missing data on HBV and/or HCV status and are excluded from the table above.

In the ART-experienced (INI-resistant) population treated with DTG BID, the incidence of post Baseline-emergent Grade 2-4 ALT and AST toxicities in subjects with hepatitis virus infection was lower than the ART-naïve population and only marginally higher than for those without hepatitis virus infection. However, the incidence of total bilirubin
toxicities was highest in the ART-experienced (INI-resistant) population, but similar in all other groups. The bilirubin toxicities in the ART-experienced (INI-resistant) population were in most cases related to viral hepatitis or associated with concurrent treatment with atazanavir.

### 3.1.1.4. Other Completed and Ongoing Studies in Adults

**ING114915:** Week 2 data is available for this study, and the maximum post-Baseline-emergent clinical liver chemistry toxicities are shown in Table 56. There were few graded toxicities in either group, (DTG or DRV/RTV) and no Grade 3 or 4 elevations of transaminases.

#### Table 56 Summary of Maximum Post Baseline-Emergent Clinical Liver Chemistry Toxicities – Study ING114915

<table>
<thead>
<tr>
<th></th>
<th>DTG 50 mg Once Daily + ABC/3TC or TDF/FTC N=239 n (%)</th>
<th>DRV/RTV 800/100 mg Once Daily + ABC/3TC or TDF/FTC N=244 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine amino transferase (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>6 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate amino transferase (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>7 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ING114915 Table 4

**ING116070:** One Grade 2 and one Grade 3 ALT elevation and 1 Grade 1 AST elevation were reported in the Week 2 analysis.
### Table 57 Summary of Maximum Post Baseline-Emergent Clinical Liver Chemistry Toxicities – Study ING116070

<table>
<thead>
<tr>
<th>Maximum Post Baseline Emergent Toxicity</th>
<th>DTG 50 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=13  n (%)</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (15)</td>
</tr>
</tbody>
</table>

Data Source: ING116070 Week 2 Synoptic CSR Table 8.21

**ING115502**: For Subject FRA-001-002, on 15MAY, 126 days after the start of DTG, the subject developed a Grade 4 elevation of ALT and AST. The subject had no relevant medical history or risk factors and his transaminases had been normal at previous visits. Concomitant medications included darunavir, ritonavir, etravirine, maraviroc and lamivudine. On 22May a* his ALT had increased to 1125 U/L and AST to 344 U/L. Treatment with DTG and all ARVs was interrupted on 24MAY a*. Tests for hepatitis A, B, C, and E were negative. CMV and EBV were also negative. The subject had been taking methandienone (Dianabol) for three weeks prior to the event. The subject was completely asymptomatic. The event improved on 01JUN a* with a fall in ALT to 476 U/L and AST to 91 U/L and treatment with DTG and other ARVs was re-started on the same day. The event resolved on 03AUG a*, when the transaminases returned to baseline. The investigator and Sponsor assessed the event as attributable to the anabolic steroids (boosted by ritonavir) that the patient had been taking in the three weeks prior to the event.

### 3.1.2. Renal Function

#### 3.1.2.1. Studies in ART-Naïve Adults

**Adverse Events**

There was a low incidence of adverse events in the Renal SOC for DTG and comparators, with the total events for the AESI being the same as the overall total (Data Source: ISO Table 2.15). There were very few serious or Grade 3/4 events, and the only fatal event occurred in the Atripla group in the ING114467 study.

There were few reports of renal failure or renal impairment (5/980 subjects treated with DTG and 4/419 treated with Atripla). None of the events in subjects treated with DTG were judged by the investigator to be related to IP.

Three subjects treated with DTG had renal failure reported. Subject 727 from ING112276 (ABC/3TC backbone) had elevated creatinine at Baseline, which varied from Grade 1 to 2 throughout the study. This was attributed to his underlying chronic renal dysfunction.

---

*a*: The year
failure from polycystic kidney disease. Subject 3200 from ING113086 (initial backbone TDF/FTC) had a pre-existing renal disorder, diabetes, hypertension, and proteinuria, and did not have any graded increases in creatinine, although an AE of ‘chronic renal failure’ was reported. Subject 7802 (backbone ABC/3TC) from ING114467 had pre-existing diabetes, hypertension and proteinuria. His diabetes was poorly controlled with his blood glucose showing frequent elevations to Grades 2 and 3. His creatinine rose to a maximum of Grade 1 at Week 32 and he was withdrawn after his Week 48 visit with his creatinine still at Grade 1. Two subjects treated with DTG had renal impairment reported (Subjects 3507 and 4549 from ING113086). Subject 3507, who was also being treated with tenofovir/emtricitabine had fluctuating creatinine levels up to Grade 1 and Subject 4549 (initial backbone ABC/FTC) had a serious AE of septic arthritis and transient renal impairment related to treatment with vancomycin.

Three subjects treated with Atripla in ING114467 had renal failure reported and one subject had renal impairment reported. Subject 5315 died from renal and respiratory failure due to septic shock and candidemia (see narrative in Section 2.1.2). Subject 6056 had chronic renal failure and anaemia attributed to an underlying cryoglobulinaemia, which was not thought to be related to Atripla. Subject 6772 had an episode of acute renal failure while being treated in hospital for cryptococcal meningitis and a staphylococcal abscess (see narrative in Section 9.5.1.3). Subject 5971 had a transient increase in creatinine reported as renal insufficiency and attributed to treatment with ibuprofen.

**Creatinine and Creatinine Clearance**

In the ART-naïve population, small increases in mean and median creatinine were observed on the DTG arms. These were evident from Week 1 but plateaued with no evidence of subsequent increase (Figure 4 and Table 58).
There were few graded post Baseline-emergent creatinine results, 21 (2%) Grade 1 and only 5 (<1%) Grade 2 with no Grade 3 or 4 in subjects treated with DTG. Three of the subjects (receiving DTG) with Grade 2 levels were from the ING114467 study and in all three the elevation occurred on a single occasion, but was not confirmed on repeat analyses. One subject on DTG from the ING113086 study had increases in creatinine related to concomitant medications. The final subject was from the ING112276 study and had an underlying renal disorder with a low creatinine clearance at Baseline. His creatinine varied between Grades 1 and 2 throughout the study, related to periods of dehydration or concomitant illness such as pneumonia. None of these subjects had associated increases in urinary albumin/creatinine ratio.
Table 58  Maximum Post Baseline-Emergent Toxicity and Mean Change from Baseline in Creatinine and Creatinine Clearance - ART-Naïve Population

<table>
<thead>
<tr>
<th></th>
<th>ING112276 DTG= Once Daily + 2 NRTI N=155</th>
<th>ING113086 DTG 50 mg Once Daily + 2 NRTI N=50</th>
<th>ING114467 RAL 400 mg BID + 2 NRTI N=411</th>
<th>DTG 50 mg + ABC/3TC Once Daily N=414</th>
<th>EFV/TDF/FTC Once Daily N=419</th>
<th>TOTAL DTG Once Daily N=980</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine Maximum Post Baseline-Emergent Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1, n (%)</td>
<td>3 (2)</td>
<td>0</td>
<td>10 (2)</td>
<td>7 (2)</td>
<td>8 (2)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Grade 2, n (%)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>3 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Grade 4, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Creatinine (μmol/L) Chg from BL</strong></td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>155 84.07 50 79.5</td>
<td>411 74.7</td>
<td>411 75.24</td>
<td>414 75.05</td>
<td>419 74.62</td>
<td>980 76.33</td>
</tr>
<tr>
<td>Week 1</td>
<td>151 9.81 50 1.12</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Week 2</td>
<td>153 10.78 46 3.20</td>
<td>199 10.86</td>
<td>193 3.55</td>
<td>388 11.61</td>
<td>377 0.99</td>
<td>740 11.24</td>
</tr>
<tr>
<td>Week 8</td>
<td>150 9.40 45 1.89</td>
<td>397 12.14</td>
<td>400 3.80</td>
<td>388 11.61</td>
<td>380 0.71</td>
<td>935 11.48</td>
</tr>
<tr>
<td>Week 16</td>
<td>150 9.11 45 0.82</td>
<td>389 11.53</td>
<td>388 3.95</td>
<td>384 12.34</td>
<td>361 2.13</td>
<td>923 11.47</td>
</tr>
<tr>
<td>Week 24</td>
<td>148 6.59 43 -1.98</td>
<td>390 12.76</td>
<td>387 4.89</td>
<td>387 13.02</td>
<td>363 0.54</td>
<td>925 11.88</td>
</tr>
<tr>
<td>Week 48</td>
<td>147 3.37 45 -5.98</td>
<td>374 12.34</td>
<td>354 4.66</td>
<td>369 10.18</td>
<td>342 -0.70</td>
<td>890 9.96</td>
</tr>
<tr>
<td>Week 96</td>
<td>133 5.22 39 -2.36</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Creatinine Clearance – Cockcroft-Gault (mL/min) Chg from BL</strong></td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
<td>n Mean</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>155 116.8 50 118.5</td>
<td>411 125</td>
<td>411 127.8</td>
<td>414 129.7</td>
<td>419 130.5</td>
<td>980 125.7</td>
</tr>
<tr>
<td>Week 24</td>
<td>148 -6.8 43 4.7</td>
<td>389 -17.5</td>
<td>384 -6.4</td>
<td>384 -18.2</td>
<td>362 -1.2</td>
<td>921 -16.1</td>
</tr>
<tr>
<td>Week 48</td>
<td>147 -3.9 45 10.3</td>
<td>369 -16.5</td>
<td>353 -5.4</td>
<td>366 -13.1</td>
<td>339 2.1</td>
<td>882 -13.0</td>
</tr>
<tr>
<td>Week 96</td>
<td>133 -5.5 38 1.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.154, and Table 2.167
Only once daily 50 mg data included.
Analysis of Changes in Creatinine and Creatinine Clearance by Background NRTI

The changes in creatinine and creatinine clearance when DTG was combined with ABC/3TC (n=634) were compared with DTG combined with TDF/FTC (n=346), Table 59. The median changes and interquartile range over time were similar with no evidence of a deterioration in the renal tolerability of DTG due to concomitant TDF.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Initial NRTI Abacavir/Lamivudine Treatment Total DTG N=634</th>
<th>Initial NRTI Tenofovir/Emtricitabine Treatment Total DTG N=346</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Baseline</td>
<td>634</td>
<td>74.9 (65.4, 84.8)</td>
</tr>
<tr>
<td>Week 2</td>
<td>521</td>
<td>11.4 (6.2, 16.0)</td>
</tr>
<tr>
<td>Week 12</td>
<td>604</td>
<td>12.2 (6.2, 17.65)</td>
</tr>
<tr>
<td>Week 24</td>
<td>593</td>
<td>12.0 (6.2, 16.8)</td>
</tr>
<tr>
<td>Week 48</td>
<td>565</td>
<td>9.4 (3.5, 15.2)</td>
</tr>
<tr>
<td>Week 60</td>
<td>374</td>
<td>8.9 (4.2, 13.8)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.158

There were few graded changes in creatinine in either group, no increase in the subjects treated with the TDF/FTC combination and no Grade 3 or 4 increase in either group (Table 60).

Table 60 Summary of Maximum Post Baseline-Emergent Creatinine Toxicities by Background ART – ART-Naïve Population

<table>
<thead>
<tr>
<th>Maximum Post Baseline-Emergent Toxicity</th>
<th>Initial NRTI Abacavir/Lamivudine Treatment Total DTG N=634 n (%)</th>
<th>Initial NRTI Tenofovir/Emtricitabine Treatment Total DTG N=346 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>16 (3)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.171

DTG does not increase serum concentrations of tenofovir, an antiretroviral known to be associated with renal tubular toxicity (m2.7.2, Section 2.1.3.5). Importantly, the in vitro and in vivo evidence to date suggests that DTG does not impact renal tubule transporters responsible for tenofovir elimination. DTG’s effect on creatinine secretion is via OCT2, which affects cation transport into the renal tubule. DTG has not been shown to affect the transport of anions. Organic anion transporter (OAT) 1 and OAT3 are responsible for anion (e.g., tenofovir) transport into the renal tubule. As serum tenofovir concentrations are not increased with co-administration with DTG, OAT inhibition by DTG is highly
unlikely. Multidrug resistance-associated protein (MRP) 2 and MRP4 are anion transporters responsible for the transport of anions (e.g., tenofovir) from the renal tubule to the urine, and DTG has been shown not to inhibit MRP2 (m2.6.5), which also makes inhibition of MRP4 by DTG unlikely. Polymorphic MRP4 that decreases tenofovir renal clearance by 15% also increases plasma tenofovir concentrations by 32% [Kiser, 2008], which was not observed in the drug interaction study assessing the impact of DTG on tenofovir PK. Based on these data, an interaction with tenofovir at the renal tubule is considered unlikely.

Additionally, as noted in Table 60, 6/346 (2%) of subjects receiving DTG + TDF/FTC and 20/634 (3%) of subjects receiving DTG + ABC/3TC had post-Baseline-emergent Grade 1 or 2 creatinine elevations, and no subjects had post-Baseline-emergent Grade 3 or 4 elevations in creatinine on either NRTI backbone co-administered with DTG. Therefore, there is currently no clinical evidence that DTG potentiates the nephrotoxicity observed with tenofovir. An analysis of changes in Division of AIDS (DAIDS) toxicity grades and change from Baseline for creatinine, estimated creatinine clearance by the Cockcroft-Gault formula, and blood urea nitrogen (BUN) was done for subjects with the renal risk factors of a history of renal disease, hypertension, diabetes or hepatitis C virus co-infection (Data Source: ISO Table 2.229, Table 2.230, Table 2.231 and Table 2.232). There was no evidence of an adverse effect of DTG in the subjects with renal risk factors compared to those without risk factors. A summary of change from Baseline in serum creatinine for subjects with and without renal risk factors is available in ISO Table 2.229.

Urine Albumin/Creatinine Ratio and Dipstick Protein Assessments

The normal range for albumin/creatinine ratios is <3.4 mg/mmoL. Albumin/creatinine ratios of 3.4 to 34 mg/mmoL are designated microalbuminuria and ratios >34 mg/mmoL macroalbuminuria. Macroalbuminuria is an indication for further investigation and consideration of referral to a nephrologist for possible institution of treatment. The change from Baseline in albumin/creatinine ratio for the three populations is shown in Table 63.

Albuminuria was initially assessed by dipstick testing in the Phase IIb studies. However, the dipstick results appeared unreliable, particularly in the EFV-controlled studies, and the more accurate measurement of albumin/creatinine ratio confirmed there was no difference in the effect of DTG on albumin excretion compared with EFV or RAL.

The change from Baseline in urine albumin/creatinine ratio could only be assessed in the Phase III studies, as this measurement was added to the Phase IIb studies by protocol amendments (no values were available for the Baseline). There were marginal changes in the median urine albumin/creatinine ratio in the DTG and comparator groups. Mean changes were occasionally skewed by large outliers, but there was no increase in the DTG treated groups.
Table 61  Summary of Change from Baseline in Albumin/Creatinine Ratio (mg/mmoL)

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>Time</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Q1</th>
<th>Q3</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART-Naive Population:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG 50 mg Once-Daily + 2 NRTI N=411</td>
<td>Baseline</td>
<td>357</td>
<td>3.04</td>
<td>16.318</td>
<td>0.60</td>
<td>0.40</td>
<td>1.10</td>
<td>0.2</td>
<td>229.3</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>312</td>
<td>-0.75</td>
<td>11.150</td>
<td>0.00</td>
<td>-0.20</td>
<td>0.20</td>
<td>-187.9</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>298</td>
<td>-1.18</td>
<td>11.414</td>
<td>0.00</td>
<td>-0.30</td>
<td>0.20</td>
<td>-188.1</td>
<td>7.6</td>
</tr>
<tr>
<td>RAL 400 mg BID + 2 NRTI N=411</td>
<td>Baseline</td>
<td>366</td>
<td>2.34</td>
<td>9.142</td>
<td>0.60</td>
<td>0.40</td>
<td>1.10</td>
<td>0.2</td>
<td>129.7</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>310</td>
<td>-0.59</td>
<td>9.998</td>
<td>0.00</td>
<td>-0.20</td>
<td>0.20</td>
<td>-108.7</td>
<td>73.8</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>285</td>
<td>-0.31</td>
<td>9.975</td>
<td>0.00</td>
<td>-0.20</td>
<td>0.20</td>
<td>-68.1</td>
<td>119.1</td>
</tr>
<tr>
<td>ING114467</td>
<td>Baseline</td>
<td>356</td>
<td>1.70</td>
<td>5.477</td>
<td>0.70</td>
<td>0.40</td>
<td>1.10</td>
<td>0.2</td>
<td>73.0</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>280</td>
<td>0.29</td>
<td>3.014</td>
<td>0.10</td>
<td>-0.20</td>
<td>0.40</td>
<td>-20.6</td>
<td>28.3</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>274</td>
<td>0.93</td>
<td>7.680</td>
<td>0.05</td>
<td>-0.20</td>
<td>0.30</td>
<td>-19.5</td>
<td>101.5</td>
</tr>
<tr>
<td>Total for ART-Naive Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG 50 mg Once-Daily N=980</td>
<td>Baseline</td>
<td>705</td>
<td>2.78</td>
<td>13.345</td>
<td>0.70</td>
<td>0.40</td>
<td>1.20</td>
<td>0.2</td>
<td>229.3</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>603</td>
<td>-0.69</td>
<td>9.238</td>
<td>0.00</td>
<td>-0.20</td>
<td>0.20</td>
<td>-187.9</td>
<td>40.5</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>567</td>
<td>-0.05</td>
<td>13.831</td>
<td>0.00</td>
<td>-0.30</td>
<td>0.20</td>
<td>-188.1</td>
<td>234.2</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.238

The percentage of patients with an increase of albumin/creatinine ratio at Week 48 was similar in the DTG and comparator groups (Data Source: ISO Table 2.252). The increases were small; for the pooled DTG ART-naive population, 75% were less than 0.2 mg/mmoL. Of those assessed with urine albumin creatinine ratios within the normal range at Baseline, only 4% of DTG and comparator treated subjects had increased to >ULN at Week 48 (Data Source: ISO Table 2.253).

There was no evidence that DTG adversely affected subjects with an increased urine albumin/creatinine ratio at Baseline. The percentage of these subjects with an increase in the DTG treated group was comparable to RAL (10% DTG, 30% RAL) and Atripla (31% DTG, 33% Atripla) (Data Source: ISO Table 2.252).

The dipstick urinalysis results in ING113086 reflected the analysis of urine albumin/creatinine ratio. There were few subjects who had shifts in their results from low levels to the clinically significant level of 2+ or above (DTG 6 subjects, RAL 9 subjects). In ING114467, the results from the dipstick analysis of proteinuria were somewhat discrepant from the spot urine albumin/creatinine ratios, with more patients showing an increase from Baseline in the dipstick protein measurement in the DTG group vs. the Atripla group. However a shift upwards in dipstick results was not confirmed by a urine albumin/creatinine ratio above normal for the majority of subjects. Thirteen subjects had a urine albumin/creatinine ratio above normal for the majority of subjects. Thirteen subjects had a urine albumin/creatinine ratio above normal range at Week 48 out of the 90 subjects with an upward shift in the dipstick result in the DTG arm (13/90, 14%). In the Atripla arm, 10 subjects had an albumin/creatinine ratio above the normal range at
Week 48 out of the 30 subjects with an upward shift in the dipstick result (10/30, 33%) (Data Source: ING114467 Week 48 CSR).

The Sponsor also examined whether treatment-emergent proteinuria was more prevalent or problematic in subjects with diabetes. In ING114467 there were more subjects with diabetes randomized by chance to the DTG arm and a higher number of these subjects had elevated albumin/creatinine ratios at Baseline than in the Atripla arm (9/19 versus 2/12; Data Source: ING114467 Listing 30 and Listing 31 and ING114467 Listing 30 and Listing 31). The Baseline ratios were also greater in the subjects in the DTG arm.

In both groups a majority of the subjects either showed a decline in albumin creatinine ratio during the trial, or had only small increases (0.3 mg/mmol or less; Data Source: ING114467 Listing 30 and Listing 31 and ING114467 Listing 30 and Listing 31). Subject 6051 who showed the highest increase in the DTG arm had decreased at Week 24, but the sample at Week 48 was contaminated with blood and bacteria following a lithotripsy operation to remove a kidney stone. The three subjects with the next three most marked increases all had concurrent hypertension and elevations of their albumin/creatinine ratios at Baseline. Subject 5070 with the fifth highest increase had a normal ratio at Baseline but also had concurrent hypertension. These data do not suggest that patients with diabetic nephropathy and proteinuria are adversely affected by treatment with DTG.

3.1.2.2. Studies in ART-Experienced (INI-Naïve) Adults

Adverse Events

There were few subjects recorded with AE preferred terms from the Renal and Urinary Disorders SOC, and incidence was comparable between the treatment groups (DTG: 15/357, 4%; RAL: 16/362, 4%). Only three subjects had acute renal failure (Data Source: ING111762 Week 24 CSR Table 8.4). Of those subjects, two had Grade 2 and one had Grade 3 acute renal failure. These cases are discussed below.

Subject 9026 (DTG 50 mg once daily): This 40-year-old Asian male developed Grade 2 SAE of hepatic tuberculosis 18 days after the start of investigational product and subsequently had all antiretroviral therapy (stavudine, lopinavir/ritonavir) stopped 4 days later. Prior to hospitalization, this subject was noted to have a creatinine elevation at Week 2 (126.8 µmol/L) compared to Baseline (103.6 µmol/L). The Grade 2 acute renal failure was noted as an AE during the hospitalization for the hepatic tuberculosis but details of the creatinine values during hospitalization were not provided by the site. The acute renal failure resolved in 4 days. Approximately 2 weeks after hospitalization, the creatinine was 132.2 µmol/L, and the creatinine at Follow-up was 100.1 µmol/L two months later. Both events, hepatic tuberculosis and acute renal failure, were not considered related to investigational product by the investigator. A detailed narrative of the hepatic tuberculosis is provided in APPENDIX 6.

Subject 2809 (DTG 50 mg once daily): This 41-year-old Hispanic male from Chile, developed Grade 3 or severe myositis and Grade 3 or severe acute renal failure with concomitant ART of tenofovir and atazanavir and concomitant medication of salbutamol. A Grade 3 creatine phosphokinase (CPK) of 4179 U/L was documented at Week 24, with
subsequent reporting by this subject of muscle pain. The subject’s work involves lifting/carrying objects of a certain weight, and he associated the pain with excess of work. The subject stopped DTG and background ART medications for approximately 2 weeks, with an interim CPK of 363 U/L, and then restarted DTG and background ART. After two doses of DTG and ART, he reported lower extremity myalgia and weakness. Clinical assessment revealed adequate diuresis and no alterations in the colour of his urine. DTG and ART were stopped. Upon re-assessment, the subject’s labs showed a serum creatinine of 1.5 mg/dL, a creatinine clearance of 58.1 mL/min and CPK of 441 U/L for which he was hospitalized and subsequently diagnosed with myositis and acute renal failure. The admission urinalysis showed mild leukocyturia and mild hematuria, and no clinically significant derangement in serum electrolytes were noted (e.g., serum sodium 142 mEq/L, calcium 8.6 mg/dL) during hospitalization. The subject was discharged after two days with significant improvement of clinical symptoms and renal function parameters. The subject was subsequently re-challenged with a regimen containing tenofovir, atazanavir/RTV and enfuvirtide with no recurrence of his signs and symptoms. The investigator attributed these events to DTG. The Sponsor felt that the diagnosis of acute renal failure was not consistent with the laboratory parameters reported by the site during the hospitalization, as the creatinine increase at hospitalization was <2-fold the value at Screening (75.1 µmol/L or 0.85 mg/dL) and was not accompanied by serum electrolyte abnormalities. The Sponsor assessed the clinical findings as consistent with renal insufficiency. Additional details of the SAE are included in APPENDIX 6.

Subject 9012 (RAL 400 mg BID): This subject died as a result of hepatic failure (Grade 4) and renal failure (Grade 2). The investigator did not consider these events related to IP. A detailed narrative is included in APPENDIX 6.

Creatinine and Creatinine Clearance

Subjects receiving DTG had small mean increases in serum creatinine evident by Week 4 that remained stable through Week 24. This was reflected by small decreases in the calculated creatinine clearance (Table 62, Figure 5). The RAL group showed smaller increases in creatinine, which also remained stable.

There were a small number of post Baseline-emergent Grade 1 creatinine toxicities in both groups (DTG: 12/357; 3%; RAL: 7/362; 2%). Five subjects in each treatment arm had post Baseline-emergent Grade 2 increases in creatinine and 1 subject in the RAL group had Grade 3 increased creatinine. There were no other graded creatinine abnormalities in either treatment group. In both treatment arms, small increases (DTG: +11.4 µmol/L; RAL: +6.5 µmol/L) in mean creatinine were noted at Week 24 compared with Baseline (Table 62). The 24-week creatinine clearance (CrCl) assessment (Cockcroft-Gault) showed a small decrease in CrCl in both treatment groups (DTG: -15.0 mL/min; RAL: -6.4 mL/min) (Table 62).
### Table 62  Summary of Maximum Post Baseline-Emergent Toxicity and Mean Change from Baseline in Creatinine and Creatinine Clearance – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th></th>
<th>DTG 50 mg Once Daily + BR N=357</th>
<th>RAL 400 mg BID + BR N=362</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Maximum Post Baseline-Emergent Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1, n (%)</td>
<td>12 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Grade 2, n (%)</td>
<td>5 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Creatinine (µmol/L), Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>71.5 (19.20); n=357</td>
<td>72.4 (19.62); n=362</td>
</tr>
<tr>
<td>Week 4</td>
<td>9.7 (13.84); n=340</td>
<td>4.7 (9.79); n=351</td>
</tr>
<tr>
<td>Week 12</td>
<td>10.2 (15.97); n=333</td>
<td>4.5 (9.99); n=342</td>
</tr>
<tr>
<td>Week 24</td>
<td>11.4 (15.15); n=322</td>
<td>6.5 (17.88); n=327</td>
</tr>
<tr>
<td>Estimated Creatinine Clearance – Cockcroft-Gault (mL/min), Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>120.9 (36.66); n=357</td>
<td>122.4 (37.65); n=362</td>
</tr>
<tr>
<td>Week 4</td>
<td>-14.4 (17.20); n=338</td>
<td>-6.7 (14.05); n=350</td>
</tr>
<tr>
<td>Week 12</td>
<td>-14.0 (19.34); n=330</td>
<td>-6.0 (15.89); n=341</td>
</tr>
<tr>
<td>Week 24</td>
<td>-15.0 (19.96); n=317</td>
<td>-6.4 (17.51); n=320</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 8.19, Table 8.24

### Figure 5  Mean Change (± SD) in Serum Creatinine (µmol/L) over Time – ART-Experienced (INI-Naïve) Population

Data Source: ING111762 Week 24 CSR Figure 8.20
Urine Albumin/Creatinine Ratio and Dipstick Protein Assessments

The median urine albumin/creatinine ratios were similar in the two treatment groups at Baseline and remained stable up to Week 24 (Table 63). There were some changes in the mean values with a similar decrease in both arms. Most subjects in both treatment groups experienced a decrease in albumin/creatinine ratio at Week 24 (DTG: 58%; RAL: 57%, Data Source: ING111762 Week 24 CSR Table 8.34).

Table 63 Summary of Change from Baseline in Albumin/Creatinine Ratio (mg/mmol)

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>Time</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Q1</th>
<th>Q3</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG 50 mg</td>
<td>Baseline</td>
<td>331</td>
<td>7.68</td>
<td>37.523</td>
<td>1.00</td>
<td>0.50</td>
<td>2.60</td>
<td>0.2</td>
<td>601.2</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>279</td>
<td>-2.95</td>
<td>16.484</td>
<td>-0.20</td>
<td>-0.90</td>
<td>0.20</td>
<td>-139.4</td>
<td>63.8</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>131</td>
<td>-0.46</td>
<td>36.672</td>
<td>-0.10</td>
<td>-0.60</td>
<td>0.30</td>
<td>-118.8</td>
<td>333.0</td>
</tr>
<tr>
<td>RAL 400 mg</td>
<td>Baseline</td>
<td>333</td>
<td>8.13</td>
<td>30.181</td>
<td>1.10</td>
<td>0.60</td>
<td>3.30</td>
<td>0.1</td>
<td>374.7</td>
</tr>
<tr>
<td>BID + BR</td>
<td>Week 24</td>
<td>289</td>
<td>-0.33</td>
<td>37.000</td>
<td>-0.20</td>
<td>-1.20</td>
<td>0.20</td>
<td>-240.4</td>
<td>539.8</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>115</td>
<td>-3.01</td>
<td>12.920</td>
<td>-0.10</td>
<td>-1.20</td>
<td>0.10</td>
<td>-102.6</td>
<td>19.6</td>
</tr>
</tbody>
</table>

Data Source: CSR ING111762 Table 8.34

3.1.2.3. Studies in ART-Experienced (INI-Resistant) Adults

Adverse Events

There were few subjects with events from the renal Rin this population; only four subjects had events of renal failure or renal impairment (ISO Table 2.57). Narratives for these subjects are presented below.

Subject 2 from ING112574 is a 57-year-old White, male, (height, 177 cm and weight 82.1 kg); with Baseline HIV-1 RNA viral load of 9905 c/mL and CD4 cell count of 310 cells/μL. He had a history of hypercholesterolaemia, hypertriglyceridaemia and stroke, but no prior renal dysfunction. His OBR consisted of tenofovir/emtricitabine, DRV/RTV and maraviroc. At Day 1 (15 June), his creatinine (107.8 μmol/L) and his albumin/creatinine ratio (1.5 mg/mmol) were within normal limits. His viral load was rapidly suppressed to <40 c/mL by Week 4. His inorganic phosphorus was towards the lower limit of normal throughout 0.7 to 0.95 mmol/L but fell to 0.45 mmol/L (Grade 3) at Week 32. His urea and electrolytes were otherwise normal (creatinine 108.7 μmol/L) at this visit. No explanation was found for his low phosphorus although it was noted he had been on tenofovir/emtricitabine since j*. At Week 40 (21 March b*) he developed suspected virological failure with an increase in viral load to 988 c/mL. At Week 48 (17 May b*) his lab results reflected an acute renal insufficiency. His serum creatinine was 467.6 μmol/L (Grade 4), his calculated creatinine clearance was 18 mL/min (it had been 86 mL/min at Week 32), and his serum bicarbonate was 18 mmol/L (from 23 mmol/L at Week 40). His urinalysis showed 2+ protein (it had been 1+ at Baseline) and also showed 1+ glucose, which was new, but his inorganic phosphorus was within normal limits (1.2 mmol/L). His viral load had fallen to 287 c/mL. He expressed no complaints at the Week 48 visit; however, he was diagnosed with a thyroid malignancy in the same

b*: Following year
j*: 6 years ago
month. His non-ART concurrent medications included no known renal-damaging drugs. He stopped DTG on 26 May b*. He was placed on a renal dose of tenofovir/emtricitabine. He was seen by a nephrologist on 05 June b*, and again on 14 June b*. Per that consult, his serum creatinine was decreasing (off DTG) to 334.2 µmol/L, then to 247.5 µmol/L. The final diagnosis was glomerulonephritis, “adverse effect of antiviral drugs”, acidosis and electrolyte abnormalities. Since then, the subject has taken once daily maraviroc and darunavir, and tenofovir/emtricitabine every three days. His local lab creatinine was 161.8 µmol/L on 26 June b*. His viral load was down to 140 c/mL. It was subsequently reported that the subject had “doubled up” on his tenofovir/emtricitabine dosing in May because of concerns about his viral load for about two weeks before the acute rise in creatinine, and he had had surgical “cure” of his papillary thyroid cancer. The investigator had not been informed of the patient’s decision to change his dose of tenofovir/emtricitabine.

Subject 1057 from ING112574 is a 43-year-old White, male, (height, 179 cm and weight 131.0 kg), with Baseline (30 November ) HIV-1 RNA viral load of 57974 c/mL and CD4 cell count of 310 cells/µL. He was known to have HIV related Nephropathy with chronic renal failure and proteinuria since June 1* and essential hypertension since s*. It was also reported that he had morbid obesity with metabolic syndrome and hypertriglyceridemia as cardiovascular risk factors. His creatinine at Baseline was 169 µmol/L (Grade 2) with an elevated urinary albumin/creatinine ratio of 301.2 mg/mmol. His creatinine rose to 227.8 µmol/L (Grade 3) at Day 8 (the highest creatinine value recorded previously was 204 µmol/L in September a*). His OBR consisted of etravirine, DRV/RTV, tenofovir/emtricitabine, maraviroc and enfuvirtide. His viral load was fully suppressed to <40 c/mL from Week 8. There were fluctuations in his creatinine between Grade 2 and Grade 3 which were attributed to his diuretic therapy. An elective renal biopsy was performed on 19 December a* and this confirmed the previous diagnosis of ‘chronic renal failure of multi-vascular disease origin’. In March b*, he had a nephrology consultation, when his creatinine was 203 µmol and there was an increase in his 24 h urine proteinuria from 2.17 g in December a* to 9.3 g/24h in March b*; that was considered secondary to an episode of ‘tophus’ (treated by colchicine). At his Week 32 visit (12 July b*) his creatinine had increased to 268.5 µmol/L. The site calculated his creatinine clearance using the MDRD formula because of his obesity. His creatinine clearance had fallen from 34 to 22.5 mL/min and there was an associated increase in his proteinuria to 10 g/24 h (done in the local laboratory). The subject was clinically asymptomatic with no peripheral oedema. For the nephrologist the probable cause of his deterioration was his uncontrolled hypertension despite a regimen of three drugs. The decision was taken to increase his diuretic dose and to institute a strict low salt diet. The TDF/emtricitabine and maraviroc dosages were adjusted according to the creatinine clearance.

Subject 1214 from ING112574 is a 33 year old White, male, (height, 177 cm and weight 72.5 kg), with Baseline HIV-1 RNA viral load of 14830 c/mL and CD4 cell count of 170 cells/µL. He had a past history of IV heroin use and was diagnosed with HIV in s*. He had been treated with Peg Interferon for acute HCV (genotype 4a) in n* and had an acute myocardial infarction in April a*, when it was determined that he had progressive liver disease with cirrhosis. He had chronic renal failure attributed to HIV and he was noted to have congestive heart failure and worsening of chronic renal

*a*: The year  
b*: Following year  
l*: 8 years ago  
n*: 11 years ago  
s*: 16 years ago
insufficiency in May, a*. The subject had been hospitalized in August a* for worsening of chronic renal insufficiency and ascites before his Day 1 visit on 12 September. His Day 1 creatinine was 209 µmol/L (Grade 2), increased from the screening value of 123 µmol/L and there was a further increase to 221 µmol/L at Day 8. On 29 September a* the subject was admitted to hospital for elective hernia repair but was noted to have recurrent pleural effusions with ascites and an increase in creatinine to 226 µmol/L (Grade 3). This resolved with treatment on 04 October b*. On 09 January b* he was admitted to hospital with diarrhoea and hypotension. He was found to have a right basal pneumonia, massive ascites and a streptococcus viridians sepsicaemia. His creatinine in the local laboratory was 311 µmol/L. His diuretic therapy was optimised and his ascites drained and he was discharged. At Week 16 his creatinine was 267 µmol/L (Grade 3). On 20 February b* he was hospitalized with ascites secondary to chronic cirrhosis associated with worsening of his chronic renal insufficiency on 23 February b*. This resolved with treatment on 08 March b*. The subject had been withdrawn from the study on 05 March b* for non-compliance after confirmed virological failure. His creatinine at his withdrawal visit was 322 µmol/L (Grade 3) but this decreased to 167 µmol/L (Grade 2) at follow up on 05 April b*.

Subject 1662 from ING112961 is a -year-old AA/AH male, (height, 178 cm and weight 79.0 kg), with Baseline HIV-1 RNA viral load of 5587 copies/mL and CD4+ cell count of 190 cells/µL, who started DTG 50 mg once daily on 20 October and optimized background at Day 11. His past medical history was noteworthy for myocardial infarction, hypertension and hyperlipidaemia and an episode of acute tubular necrosis. Although his HIV-1 RNA viral load was fully suppressed to <50 c/mL by Week 4 he has had suspected protocol defined virological failure on seven occasions. During the study he had intermittent mild elevations of his creatinine up to Grade 2. On 21/Jun/c* he developed a sudden increase in creatinine and was admitted to hospital. A renal biopsy showed fibrosis of the kidney and acute tubular necrosis. The conclusion was acute renal failure with underlying chronic renal failure, with probable renal hypoperfusion due to dehydration, low blood pressure and non steroid anti-inflammatory treatment. He subsequently recovered and his creatinine had decreased to 130 µmol/L by the 25 June c*.

**Creatinine and Creatinine Clearance**

The same pattern with a small mean change in creatinine and creatinine clearance was evident in the INI-resistant population (Table 64), including those treated with DTG 50 mg BID, suggesting that 50 mg once daily achieved maximal inhibition OCT2. The majority of the Graded increases in creatinine were also Grade 1, although there were two subjects with Grade 3 and two subjects with Grade 4 levels in ING112574.

a*: The year
b*: Following year
c*: 2 years later

*新薬承認情報提供時に置き換え*
Table 64 Maximum Post-Baseline-Emergent toxicity and Mean Change from Baseline in Creatinine and Creatinine Clearance - ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th>ING112574</th>
<th></th>
<th>TOTAL</th>
</tr>
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<tr>
<td></td>
<td>Cohort I</td>
<td>Cohort II</td>
<td></td>
<td></td>
<td>N=207</td>
</tr>
<tr>
<td></td>
<td>DTG 50 mg Once Daily + BR</td>
<td>DTG 50 mg BID + BR</td>
<td></td>
<td></td>
<td>N=183</td>
</tr>
<tr>
<td>N=27</td>
<td>N=24</td>
<td></td>
<td>N=183</td>
<td></td>
<td></td>
</tr>
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</table>

Creatinine Maximum Post Baseline-Emergent Toxicity

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<th>Grade, n (%)</th>
<th>Cohort I</th>
<th>Cohort II</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1, n (%)</td>
<td>1 (4)</td>
<td>3 (13)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Grade 2, n (%)</td>
<td>3 (11)</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
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<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Grade 4, n (%)</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1)</td>
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</table>

Creatinine (µmol/L) Chg from BL

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th></th>
<th>n</th>
<th>Mean</th>
<th></th>
<th>n</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>27</td>
<td>88.7</td>
<td>24</td>
<td>87.79</td>
<td>183</td>
<td>81.24</td>
<td>207</td>
<td>82.0</td>
</tr>
<tr>
<td>Week 1</td>
<td>27</td>
<td>6.44</td>
<td>24</td>
<td>8.0</td>
<td>178</td>
<td>10.19</td>
<td>202</td>
<td>9.93</td>
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<tr>
<td>Week 2</td>
<td>27</td>
<td>7.81</td>
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<td>NA</td>
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<td>9.17</td>
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<td>24</td>
<td>10.29</td>
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<td>9.61</td>
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<td>22</td>
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<td>24</td>
<td>10.08</td>
<td>131</td>
<td>10.26</td>
<td>155</td>
<td>10.24</td>
</tr>
<tr>
<td>Week 24</td>
<td>17</td>
<td>11.29</td>
<td>22</td>
<td>10.41</td>
<td>109</td>
<td>11.8</td>
<td>131</td>
<td>11.57</td>
</tr>
<tr>
<td>Week 48</td>
<td>15</td>
<td>6.67</td>
<td>20</td>
<td>11.05</td>
<td>11</td>
<td>45.8</td>
<td>31</td>
<td>23.38</td>
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<td>Week 96</td>
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<td>-1.62</td>
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<td>0.8</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td>0.8</td>
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</table>

Creatinine Clearance – Cockcroft-Gault (mL/min) Chg from BL

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
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<th>Mean</th>
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<th>n</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>183</td>
<td>109.1</td>
<td>183</td>
<td>109.1</td>
</tr>
<tr>
<td>Week 24</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>101</td>
<td>-8.6</td>
<td>101</td>
<td>-8.6</td>
</tr>
<tr>
<td>Week 48</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
<td>-17.5</td>
<td>11</td>
<td>-17.5</td>
</tr>
<tr>
<td>Week 96</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.155, and Table 2.168

The apparently high mean change in creatinine at Week 48 in ING112574 is due to the inclusion of one subject with renal failure (Subject 2) with a Grade 4 emergent toxicity, which was associated with a doubling of the dose of tenofovir by the subject without the investigator’s knowledge. The change was accompanied by an increase in proteinuria and normoglycaemic glycosuria suggesting proximal tubule dysfunction. This subject’s renal function improved with interruption of DTG and a reduction in the dose of tenofovir to once every three days.

The remaining subjects with emergent increases in creatinine to Grades 2, 3, or 4 all had underlying renal disease and the changes were thought to be related to the natural history of their disease or concurrent co-morbidities such as cirrhosis, hypertension and heart failure, or concurrent drug treatment for co-morbidities. Narratives for these subjects are included in the clinical study report.
Urine Albumin/Creatinine Ratio and Dipstick Protein Assessments

In the treatment-experienced subjects, the Baseline urine albumin/creatinine ratio was elevated in many patients with a median higher than in the treatment-naive population, and interquartile range extending above the upper limit of normal (3.399 mg/mmol, Table 65). There was no increase in median albumin/creatinine ratio to Week 24. Results were only available for nine patients at Week 48.

Table 65 Summary of Change from Baseline in Albumin/Creatinine Ratio (mg/mmol) in ING112574

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>Time</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Q1</th>
<th>Q3</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG 50 mg BID N=183</td>
<td>Baseline</td>
<td>160</td>
<td>20.35</td>
<td>59.411</td>
<td>1.75</td>
<td>0.80</td>
<td>8.75</td>
<td>0.2</td>
<td>409.7</td>
</tr>
<tr>
<td></td>
<td>Week 1</td>
<td>149</td>
<td>-5.79</td>
<td>23.947</td>
<td>-0.20</td>
<td>-2.30</td>
<td>0.30</td>
<td>-155.3</td>
<td>46.1</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>90</td>
<td>-1.31</td>
<td>53.352</td>
<td>-0.10</td>
<td>-1.60</td>
<td>0.70</td>
<td>-290.8</td>
<td>283.5</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>9</td>
<td>6.38</td>
<td>9.024</td>
<td>2.60</td>
<td>0.60</td>
<td>8.00</td>
<td>-1.4</td>
<td>22.7</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.239

3.1.2.4. Other Completed and Ongoing Studies in Adults

ING114915: There were no Serious Adverse Events in the Renal SOC and only one Grade 1 and one Grade 2 post-Baseline-emergent creatinine toxicities, with no Grade 3 or Grade 4 in the DTG group (Data Source: ING114915 Table 3 and Table 4).

ING116070: No AEs from the Renal SOC were reported prior to the Week 2 data cut-off (Data Source: ING116070 Week 2 Synoptic CSR Table 8.2). Similar to the Phase IIb/III studies in ART-naive subjects, small increases in mean and median creatinine were observed which were evident from Week 2. However, no graded creatinine elevations were observed through the Week 2 data cut-off. Concomitant small decreases in creatinine clearance were also observed (Source Data: ING116070 Week 2 Synoptic CSR Table 8.16).

3.1.3. Creatine Phosphokinase (CPK)

CPK elevations in subjects receiving DTG in the ART-naive population were comparable to that seen with RAL and EFV-containing regimens. Most CPK elevations were asymptomatic and investigators were able to confirm high degrees of physical activity preceding the CPK elevations in the majority of cases. In the ART-experienced (INI-naive) population, few subjects had Grade 3 or Grade 4 increases in CPK, and most of these increases were transient. A similar pattern and incidence of CPK elevations were observed for ART-experienced (INI-resistant) subjects, despite the higher daily dose of DTG administered to these subjects.

The incidence of musculoskeletal events was low and similar across all treatment groups in the ART-naive population. In the ART-experienced (INI-naive) population, more subjects receiving RAL reported musculoskeletal disorders versus those receiving DTG, with fewer subjects on DTG experiencing Grade 3 or 4 events. The incidence of events reported for the ART-experienced (INI-resistant) population was lower than in the INI-
naïve (ART-naïve and ART-experienced) population, despite the higher daily dose of DTG. Finally, no cases of drug-related rhabdomyolysis have been reported on DTG across the clinical program.

Therefore, no increased risk for clinically significant or serious musculoskeletal disorders has been identified for DTG.

### 3.1.3.1. Studies in ART-Naïve Adults

The incidence of events in the Musculoskeletal and Connective Tissue Disorders SOC was similar across all groups in the ART-naïve population. Only 2% of subjects reported muscles spasm, musculoskeletal pain or myalgia. All other events were reported in <1% of subjects. There was only one case of myositis, which occurred in the Atripla group. There were no cases of rhabdomyolysis in either group (Data Source: ISO Table 2.15).

The incidence of musculoskeletal adverse events of special interest was low and comparable for the DTG treated groups and comparators (Data Source: ISO Table 2.64). Only two subjects reported serious events (Subject 5919 on DTG in ING114467 and Subject 3441 on RAL in ING113086). Subject 3441 had an elevated CPK due to a seizure. Subject 5919 had two days of ‘muscle pain’ but no abnormalities were detected, and it resolved spontaneously while DTG was continued. No withdrawals or treatment interruptions were observed in the DTG groups.

### Table 66 Summary of Maximum Post Baseline-Emergent Creatine Phosphokinase Toxicities – ART-Naïve Population

<table>
<thead>
<tr>
<th></th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>TOTAL</th>
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<tr>
<td></td>
<td>DTG</td>
<td>EFV</td>
<td>RAL</td>
<td>EFV/TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>Once Daily + 2 NRTI</td>
<td>Once Daily + 2 NRTI</td>
<td>Once Daily + 2 NRTI</td>
<td>Once Daily + 2 NRTI</td>
</tr>
<tr>
<td>N=155</td>
<td>n=50</td>
<td>N=411</td>
<td>N=414</td>
<td>N=419</td>
</tr>
<tr>
<td>Grades 1 to 4</td>
<td>30 (19)</td>
<td>5 (10)</td>
<td>65 (16)</td>
<td>57 (14)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>15 (10)</td>
<td>1 (2)</td>
<td>32 (8)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>8 (5)</td>
<td>0</td>
<td>24 (6)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>15 (10)</td>
<td>4 (8)</td>
<td>33 (8)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (5)</td>
<td>1 (2)</td>
<td>8 (2)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (2)</td>
<td>0</td>
<td>8 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>5 (3)</td>
<td>0</td>
<td>16 (4)</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.167

### 3.1.3.2. Studies in ART-Experienced (INI-Naïve) Adults

Very few subjects had Grade 3 or Grade 4 increases in CPK (DTG: 7/357; 1%; RAL: 4/362; <1%); of those, only two subjects in each treatment group had Grade 4 increases in CPK. Most of these increases were transient and all resolved within about 2 weeks.
Overall, more subjects receiving RAL reported musculoskeletal/connective tissue disorders vs. those receiving DTG, with fewer subjects receiving DTG (n=2) experiencing Grade 3 or 4 events vs. those receiving RAL (n=7). Subject 2809 on DTG had myositis with a mild increase in creatinine and Subject 627 also on DTG had rhabdomyolysis. The subject with myositis (Subject 2809) was hospitalized for mild symptoms, and although the investigator described the changes in creatinine as acute renal failure, the corresponding laboratories were not consistent with a conventional diagnosis of acute renal failure. A detailed narrative for this subject is provided in APPENDIX 6.

The case of rhabdomyolysis (Subject 627, DTG 50 mg once daily) was considered secondary to pneumonia, and this subject remained on study without recurrence. This is a 76 year-old White male with Baseline HIV-1 RNA viral load of 56053 c/mL and CD4 cell count of 99 cells/µL, who performed his Day 1 study visit on 03 October. On 22 March, the subject performed study visit Week 24. Labs collected at that date resulted: HIV RNA 76 copies/mL, CD4 232 cells per µm³, CPK 150 U/L (Baseline 2655 U/L; G3), AST 19 U/L, ALT 22 U/L, Creatinine 1.02 mg/dL (Baseline 0.99), and creatinine clearance 99 ml/m/1.73 m² (Baseline 110). On 29 March, the subject was admitted to the hospital with shortness of breath, cough, and fever and was diagnosed with pneumonia. Diagnostic tests reported for the admission included a chest X-ray with diffuse interstitial infiltrates, WBC count of 16 K/mm³ (14 K/mm³ of neutrophils), a creatinine of 1.42 mg/dL (1.09xULN), and arterial blood gases showing pH of 7.29, pCO2 of 72 mmHg, and pO2 of 72 mmHg. The subject was treated with albuterol and azithromycin and improved enough to be discharged on 02 April.

The subject was re-admitted on 11 April with complaints of pain in his lower extremities and stiffness and pain in his neck. He was admitted because of concern of worsening of his pneumonia and pain. He was started on vancomycin and cefepime, underwent a lumbar puncture, and cultures were taken. Lumbar puncture showed no white cells and cultures were negative for growth after 48 hours. All antibiotics were discontinued after 12 hours as CT scan showed the pneumonia but it was determined to be stable and improving. Final diagnosis was rhabdomyolysis. Infectious Disease was consulted and they suggested a possible interaction between Avelox (moxifloxacin) and tenofovir as a potential cause for this. Subject was aggressively hydrated and the symptoms resolved.

The investigator did not agree with a possible interaction being the cause for the subject’s symptoms, but thought it more likely due to the pneumonia and dehydration considering the symptoms were resolved with hydration and the short duration of the symptoms. Subject has previously taken Avelox while on tenofovir and had no issues at that time.

The subject had a higher CPK recorded at Baseline than during his illness and there was no evidence of renal compromise during the episode of ‘rhabdomyolysis’. There is no evidence of DTG being causally related as this was continued throughout and subsequent to the events, which appear more likely related to pneumonia and dehydration.
3.1.3.3. Studies in ART-Experienced (INI-Resistant) Adults

The incidence of events in the Musculoskeletal and Connective Tissue Disorders SOC in the DTG 50 mg BID ART-experienced (INI-resistant) population was lower than in the ART-naïve population despite the higher dose (Data Source: ISO Table 2.16). There were no reports of myositis and the incidence of myalgia was also lower than in the ART-naïve population.

There were no serious events in the subset of musculoskeletal adverse events of special interest in this population, and there was only one report of a withdrawal of study drug (Subject 41 in ING112574). Subject 41 is a 50 year old African American, male. At Screening, this subject was noted to have a CPK of 3,333 U/L (Grade 3). He denied any symptoms (myalgias, chest pain and fever) at the time and was noted to have a physically strenuous job as a mail carrier, and as the lab abnormality was not exclusionary, he was allowed to enter the study. A workup including CPK fractionation and electrophoresis was consistent with an increased MM fraction of CPK and evidence for Macro CK Type 1. The subject had a robust virological and immunologic response, but by Week 12 was noted to have a significant elevation in CPK and transaminases. IP was stopped due to the markedly elevated CPK. Lopinovir/ritonavir monotherapy was started at that time and has continued to the current date. The subject continued to deny any symptoms related to the CPK elevation (no myalgias, weakness, fever, chest pain, etc). An EMG was performed at this time, which was unremarkable (ruled out myopathy). The subject declined a muscle biopsy at the time as he was feeling well and did not want to lose time off work and was withdrawn from the study.

Table 67 Summary of Maximum Post Baseline-Emergent Creatine Phosphokinase Toxicities – ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th></th>
<th>ING112961 Cohort I</th>
<th>ING112574 Cohort II</th>
<th>TOTAL DTG 50 mg BID N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1 to 4</td>
<td>3 (11)</td>
<td>5 (21)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Grades 2 to 4</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Grades 3 to 4</td>
<td>0</td>
<td>0</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (7)</td>
<td>4 (17)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.168

3.1.3.4. Other Completed and Ongoing Studies in Adults

ING114915: There were no SAEs reported in the Musculoskeletal SOC and only one post-Baseline-emergent Grade 3 elevation of CPK in the DTG group and one Grade 3 and one Grade 4 elevation in the DRV/RTV group (Data Source: ING114915 Table 4).
**ING116070:** Two subjects reported AEs in the Musculoskeletal and Connective Tissues SOC, both Grade 1, non-drug-related back pain that occurred on the same day the subjects had a lumbar puncture (Data Source: ING116070 Week 2 Synoptic CSR Listing 11). One subject (Subject 22) had a Grade 4 CPK elevation at Week 12 in addition to a Grade 3 elevation at Week 4. The subject had minimally elevated CPK values at Screening, Day 1, and Week 2, and normal at Week 8 (Data source: ING116070 Week 2 Synoptic CSR Listing 22). There were no clinical symptoms reported and the investigator attributed these CPK elevations to strenuous exercise done by the subject.

**ING115502:** There was one SAE of severe compression of the L1 vertebra reported (Subject NDL-001-002), which was considered possibly related to underlying osteoporosis.

### 3.2. Haematology

There were no clinically significant trends in post-Baseline-emergent haematology abnormalities across all study populations.

#### 3.2.1. Studies in ART-Naïve Adults

There were no clinically significant trends in post-Baseline-emergent haematology abnormalities across the studies (Table 68).

**Table 68  Summary of Maximum Post Baseline-Emergent Haematology Toxicities – ART-Naïve Population**

<table>
<thead>
<tr>
<th></th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG 50 mg Once DAILY + 2 NRTI N=155 n (%)</td>
<td>DTG 50 mg Once DAILY + 2 NRTI N=50 n (%)</td>
<td>RAL 400 mg BID + 2 NRTI N=411 n (%)</td>
<td>DTG 50 mg + ABC/3TC Once DAILY N=414 n (%)</td>
</tr>
<tr>
<td>All haematology parameters</td>
<td>28 (18)</td>
<td>79 (19)</td>
<td>70 (17)</td>
<td>70 (17)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>16 (10)</td>
<td>49 (12)</td>
<td>47 (11)</td>
<td>49 (12)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>8 (5)</td>
<td>20 (5)</td>
<td>15 (4)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (2)</td>
<td>7 (2)</td>
<td>6 (1)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (&lt;1)</td>
<td>3 (&lt;1%)</td>
<td>4 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.172

The most commonly reported post Baseline-emergent haematology abnormality was decreased absolute neutrophil count, which occurred at similar rates, at all Grades, in all treatment groups (Table 69). Risk factors for neutropenia include the use of concurrent medication labelled for haematological toxicities, concurrent blood disorders, the presence of neutropenia at Baseline and subjects being of AA/AH.
Table 69  Summary of Maximum Post Baseline-Emergent Haematology Toxicities Neutrophil Counts – ART-Naïve Population

<table>
<thead>
<tr>
<th>Total absolute neutrophil count (G/L)</th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG 600 mg</td>
<td>EFV 600 mg</td>
<td>RAL 400 mg</td>
<td>DTG 50 mg + ABC/3TC C Once Daily</td>
</tr>
<tr>
<td></td>
<td>Once Daily + 2 NRTI N=155 n (%)</td>
<td>Once Daily + 2 NRTI N=50 n (%)</td>
<td>Once Daily + 2 NRTI N=411 n (%)</td>
<td>50 mg Once Daily + 2 NRTI N=414 n (%)</td>
</tr>
<tr>
<td>All Neutrophil Toxicities</td>
<td>22 (14)</td>
<td>10 (20)</td>
<td>56 (14)</td>
<td>48 (12)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>12 (8)</td>
<td>7 (14)</td>
<td>33 (8)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (5)</td>
<td>2 (4)</td>
<td>15 (4)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>5 (1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (&lt;1)</td>
<td>1 (2)</td>
<td>3 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.172

Rates for decreased haemoglobin, platelet, and white blood cell counts were low and comparable at all Grades between treatment groups (Data Source: ISO Table 2.172). Haemoglobin concentrations generally increased over time on all regimens (ISO Table 2.163), suggesting positive effects of ART.

3.2.2. Studies in ART-Experienced (INI-Naïve) Adults

There were no clinically significant trends or differences between the treatment arms in post Baseline-emergent, haematology abnormalities (Table 70). The incidence of Grade 2 to 4 haematology toxicities was low for all parameters across both treatment arms. The most commonly reported post Baseline-emergent haematology abnormality was decreased absolute neutrophil count, which occurred at similar rates, at all Grades, in all treatment groups with few Grade 3 or Grade 4 decreases.
### Table 70  
**Summary of Maximum Post Baseline-Emergent Haematology Toxicities – ART-Experienced (INI-Naïve) Population**

<table>
<thead>
<tr>
<th></th>
<th>ING111762</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>DTG 50 mg Once Daily + BR</strong></td>
<td><strong>RAL 400 mg BID + BR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=357</td>
<td>N=362</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All haematology parameters (Grade 1-4)</td>
<td>94 (26)</td>
<td>94 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>51 (14)</td>
<td>52 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>26 (7)</td>
<td>27 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>12 (3)</td>
<td>9 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>5 (1)</td>
<td>6 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute Neutrophil Count (Grade 1-4)</td>
<td>45 (13)</td>
<td>44 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>22 (6)</td>
<td>25 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>11 (3)</td>
<td>10 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>8 (2)</td>
<td>6 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>4 (1)</td>
<td>3 (&lt;1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 8.25

Similar to the ART-naïve population, haemoglobin concentrations generally increased over time on either regimen (Data Source: ING111762 Week 24 CSR Table 8.22), suggesting positive effects from ART.

### 3.2.3. Studies in ART-Experienced (INI-Resistant) Adults

There were no clinically significant trends in post-Baseline-emergent, haematology abnormalities across studies ING112961 and ING112574 (Table 71).

### Table 71  
**Summary of Maximum Post Baseline-Emergent Haematology Toxicities in ART-Experienced (INI-Resistant) Population**

<table>
<thead>
<tr>
<th></th>
<th>ING112961</th>
<th>ING112574</th>
<th>TOTAL DTG 50 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort I</td>
<td>Cohort II</td>
<td>DTG 50 mg BID + BR</td>
</tr>
<tr>
<td></td>
<td>DTG 50 mg</td>
<td>DTG 50 mg</td>
<td>N=183 n (%)</td>
</tr>
<tr>
<td></td>
<td>Once Daily</td>
<td>BID</td>
<td>N=24 n (%)</td>
</tr>
<tr>
<td></td>
<td>N=27 n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All haematology parameters</td>
<td>7(26)</td>
<td>6(25)</td>
<td>29(16)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>7(26)</td>
<td>3(13)</td>
<td>16(9)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>2(8)</td>
<td>10(5)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>2(1)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>1(4)</td>
<td>1(&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.173
As for the ART-naïve and ART-experienced (INI-naïve) populations, haemoglobin concentrations generally increased over time on any regimen (Data Source: ISO Table 2.173), suggesting positive effects from ART.

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

4.1. Vital Signs

There were no clinically significant patterns of changes in vital signs (weight, heart rate, systolic and diastolic blood pressure) across the Phase I, II, and III studies (Data Source: ISO Figure 2.52, Figure 2.53, Figure 2.54, Figure 2.55, Figure 2.56, Figure 2.57, Figure 2.58, Figure 2.59, Figure 2.508, Figure 2.509, and Figure 2.510).

4.2. Electrocardiograms

4.2.1. Studies in ART-Naïve Adults

No subjects had a QTcF >500 msec, and few subjects had change from Baseline in QTcF or QTcB ≥60 msec. Additionally on review of data from ING112276 and limited data from ING113086 and ING114467, few clinically significant ECG abnormalities were reported, and no trends were observed in these abnormalities.
## Table 72  Summary of Maximum Post Baseline-Emergent ECG Findings - ART-Naïve Population

<table>
<thead>
<tr>
<th></th>
<th>ING112276</th>
<th>ING113086</th>
<th>ING114467</th>
<th>Total</th>
<th>DTG Once Daily N=980</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>DTG</strong></td>
<td>Once Daily + 2 NRTI N=155</td>
<td>EFV 600 mg Once Daily + 2 NRTI N=50</td>
<td>DTG 50 mg Once Daily + 2 NRTI N=411</td>
<td>RAL 400 mg BID + 2 NRTI N=411</td>
<td>DTG 50 mg + ABC/3T C Once Daily N=414</td>
</tr>
<tr>
<td><strong>ING112276</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>ECG findings</td>
<td>154</td>
<td>49</td>
<td>42</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Normal</td>
<td>94 (61)</td>
<td>33 (67)</td>
<td>25 (60%)</td>
<td>33 (73)</td>
<td>27 (75)</td>
</tr>
<tr>
<td>Abnormal – Not clinically significant</td>
<td>59 (38)</td>
<td>16 (33)</td>
<td>16 (38)</td>
<td>9 (20)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Abnormal – Clinically significant</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>3 (8)</td>
</tr>
<tr>
<td><strong>QTcB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum post-Baseline, n</td>
<td>154</td>
<td>49</td>
<td>42</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>≤450 msec</td>
<td>145 (94)</td>
<td>38 (78)</td>
<td>41 (98)</td>
<td>43 (96)</td>
<td>34 (94)</td>
</tr>
<tr>
<td>&gt;450 to ≤500 msec</td>
<td>8 (5)</td>
<td>10 (20)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>&gt;500 msec</td>
<td>1 (&lt;1)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum post-Baseline Change, n</td>
<td>154</td>
<td>49</td>
<td>35</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>≤30 msec</td>
<td>132 (86)</td>
<td>32 (65)</td>
<td>33 (94)</td>
<td>38 (88)</td>
<td>22 (85)</td>
</tr>
<tr>
<td>&gt;30 to ≤60 msec</td>
<td>18 (12)</td>
<td>14 (29)</td>
<td>2 (6)</td>
<td>5 (12)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>&gt;60 msec</td>
<td>4 (3)</td>
<td>3 (6)</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>QTcF Interval</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum post-Baseline, n</td>
<td>154</td>
<td>49</td>
<td>42</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>≤450 msec</td>
<td>153 (&gt;99)</td>
<td>45 (92)</td>
<td>42 (100)</td>
<td>45 (100)</td>
<td>35 (97)</td>
</tr>
<tr>
<td>&gt;450 to ≤500 msec</td>
<td>1 (&lt;1)</td>
<td>4 (8)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>&gt;500 msec</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum post-Baseline Change, n</td>
<td>154</td>
<td>49</td>
<td>35</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>≤30 msec</td>
<td>135 (88)</td>
<td>40 (82)</td>
<td>33 (94%)</td>
<td>38 (88)</td>
<td>24 (92)</td>
</tr>
<tr>
<td>&gt;30 to ≤60 msec</td>
<td>15 (10)</td>
<td>7 (14)</td>
<td>0</td>
<td>5 (12)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>&gt;60 msec</td>
<td>4 (3)</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.219, Table 2.223 and Table 2.240
4.2.2. Studies in ART-Experienced (INI-Naïve) Adults

Most subjects in the both arms had QTcB and QTcF values $\leq 450$ msec throughout the study. One subject receiving DTG and 2 subjects receiving RAL had QTcB or QTcF values $>500$ msec. Few subjects had change from Baseline in QTcF or QTcB $>60$ msec. Few clinically significant ECG abnormalities were reported, and no trends were observed in these abnormalities (Data Source: ING111762 CSR Section 8.5).

Table 73 Summary of Maximum Post Baseline Emergent ECG Findings – ART-Experienced (INI-Naïve) Population

<table>
<thead>
<tr>
<th>ECG findings</th>
<th>ING111762 DTG 50 mg once daily + BR N=357</th>
<th>RAL 400 mg BID + BR N=362</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any time post-Baseline, n</td>
<td>174 (58)</td>
<td>170 (57)</td>
</tr>
<tr>
<td>Normal</td>
<td>111 (64)</td>
<td>116 (68)</td>
</tr>
<tr>
<td>Abnormal – Not clinically significant</td>
<td>50 (29)</td>
<td>41 (24)</td>
</tr>
<tr>
<td>Abnormal – Clinically significant</td>
<td>13 (7)</td>
<td>13 (8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QTcB Interval</th>
<th>DTG 50 mg once daily + BR N=357</th>
<th>RAL 400 mg BID + BR N=362</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum post-Baseline, n</td>
<td>176 (58)</td>
<td>169 (57)</td>
</tr>
<tr>
<td>$\leq 450$ msec</td>
<td>154 (88)</td>
<td>149 (88)</td>
</tr>
<tr>
<td>$&gt;450$ to $\leq 500$ msec</td>
<td>21 (12)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>$&gt;500$ msec</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Maximum post-Baseline Change, n</td>
<td>170 (58)</td>
<td>161 (57)</td>
</tr>
<tr>
<td>$\leq 30$ msec</td>
<td>151 (89)</td>
<td>146 (91)</td>
</tr>
<tr>
<td>$&gt;30$ to $\leq 60$ msec</td>
<td>15 (9)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>$&gt;60$ msec</td>
<td>4 (2)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QTcF Interval</th>
<th>DTG 50 mg once daily + BR N=357</th>
<th>RAL 400 mg BID + BR N=362</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum post-Baseline, n</td>
<td>176 (58)</td>
<td>169 (57)</td>
</tr>
<tr>
<td>$\leq 450$ msec</td>
<td>164 (93)</td>
<td>158 (93)</td>
</tr>
<tr>
<td>$&gt;450$ to $\leq 500$ msec</td>
<td>11 (6)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>$&gt;500$ msec</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Maximum post-Baseline Change, n</td>
<td>170 (58)</td>
<td>161 (57)</td>
</tr>
<tr>
<td>$\leq 30$ msec</td>
<td>152 (89)</td>
<td>146 (91)</td>
</tr>
<tr>
<td>$&gt;30$ to $\leq 60$ msec</td>
<td>14 (8)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>$&gt;60$ msec</td>
<td>4 (2)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

Data Source: ING111762 Week 24 CSR Table 8.35, Table 8.37 and Table 8.39

4.2.3. Studies in ART-Experienced (INI-Resistant) Adults

No subjects receiving DTG 50 mg BID had a QTcF $>500$ msec, and few subjects had QTcF or QTcB change from Baseline $\geq 60$ msec. Week 24 ECG results were available for 115 subjects in ING112574, and a small percentage had abnormal, clinically significant changes. No trends were noted in these abnormalities (Data Source: ING112574 CSR, Section 7.5).
Table 74  Summary of Maximum Post Baseline-Emergent ECG Findings - ART-Experienced (INI-Resistant) Population

<table>
<thead>
<tr>
<th>ECG findings</th>
<th>ING112961 Cohort I</th>
<th>ING112574 Cohort II</th>
<th>TOTAL DTG 50 mg BID + BR N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any time post-Baseline, n</td>
<td>27</td>
<td>24</td>
<td>115</td>
</tr>
<tr>
<td>Normal</td>
<td>14 (52)</td>
<td>8 (33)</td>
<td>74 (35)</td>
</tr>
<tr>
<td>Abnormal – Not clinically significant</td>
<td>13 (48)</td>
<td>15 (63)</td>
<td>28 (24)</td>
</tr>
<tr>
<td>Abnormal – Clinically significant</td>
<td>0</td>
<td>1 (4)</td>
<td>13 (11)</td>
</tr>
</tbody>
</table>

**QTcB Interval**

<table>
<thead>
<tr>
<th>Maximum post-Baseline, n</th>
<th>ING112961 Cohort I</th>
<th>ING112574 Cohort II</th>
<th>TOTAL DTG 50 mg BID + BR N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤450 msec</td>
<td>24 (89)</td>
<td>18 (75)</td>
<td>98 (46)</td>
</tr>
<tr>
<td>&gt;450 to ≤500 msec</td>
<td>2 (7)</td>
<td>6 (25)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>&gt;500 msec</td>
<td>1 (4)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Maximum post-BaselineChange, n</td>
<td>27</td>
<td>24</td>
<td>112</td>
</tr>
<tr>
<td>≤30 msec</td>
<td>24 (89)</td>
<td>18 (75)</td>
<td>98 (47)</td>
</tr>
<tr>
<td>&gt;30 to ≤60 msec</td>
<td>2 (7)</td>
<td>6 (25)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>&gt;60 msec</td>
<td>1 (4)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

**QTcF Interval**

<table>
<thead>
<tr>
<th>Maximum post-Baseline, n</th>
<th>ING112961 Cohort I</th>
<th>ING112574 Cohort II</th>
<th>TOTAL DTG 50 mg BID + BR N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤450 msec</td>
<td>24 (89)</td>
<td>21 (88)</td>
<td>107 (93)</td>
</tr>
<tr>
<td>&gt;450 to ≤500 msec</td>
<td>2 (7)</td>
<td>3 (13)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>&gt;500 msec</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum post-BaselineChange, n</td>
<td>27</td>
<td>24</td>
<td>112</td>
</tr>
<tr>
<td>≤30 msec</td>
<td>24 (89)</td>
<td>21 (88)</td>
<td>101 (90)</td>
</tr>
<tr>
<td>&gt;30 to ≤60 msec</td>
<td>2 (7)</td>
<td>3 (13)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>&gt;60 msec</td>
<td>1 (4)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.220, Table 2.224 and Table 2.241

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

5.1.1. Gender, Age, Race

In general, the safety profile for DTG was comparable across gender, age, and race. Across the clinical program, the overall numbers of subjects from special groups (i.e., women, African American/African heritage, age ≥50) was lower in comparison to the rest of the population, but had adequate representation to address the safety in these groups. Minor exceptions for gender were noted, such as a higher incidence of some GI AEs in female subjects receiving DTG, and differences in laboratory abnormalities in men and women, including more anaemia in women and more ALT and CPK increases in men. A greater proportion of subjects aged ≥50 years versus subjects <50 years had Grade 2
hyperglycemia, which was likely related to higher proportion of older subjects with diabetes mellitus as a concomitant medical condition. Minor exceptions were also noted for race, with more AA/AH subjects experiencing neutropenia, which is likely related to lower neutrophil counts in this racial group [Levine, 2006]. These differences were not considered severe or treatment-limiting, or associated with DTG use. In general, similar trends were seen on comparator treatments. Therefore, the safety profile for DTG was comparable based on gender, age, and race.

Additionally, DTG PK variability was low within subjects and across patient populations. DTG PK was similar between healthy and HIV-infected subjects and PK variability was low to moderate with between-subject variability (CVb%) of area under the concentration-time curve (AUC) and Cmax estimated at 30 to 40% in HIV-infected subjects (m2.7.2, Section 3.1.2). There was no apparent subgroup of PK outliers with high PK exposure attributable to intrinsic factors. The effect of demographic factors on the exposure of DTG was evaluated in population PK analyses using pooled PK data obtained in Phase II/III studies. Body size, age, gender, and smoking were statistically significant covariates in the model, but changes in PK parameters were <30% and not considered clinically significant. Race (Caucasian, Not-Caucasian and Japanese ancestry) or ethnicity (Hispanic/Latino or Not-Hispanic/Latino) had no significant effect on DTG PK parameters. Thus, no DTG dose adjustment is necessary based on demographic factors. Phase I studies in healthy or non-HIV-infected subjects showed that metabolic enzyme polymorphism, moderate hepatic impairment, and severe renal impairment had no clinically significant impact on DTG PK exposure (m2.7.2, Section 3.3). Further details on hepatic and renal impairment are presented below.

### 5.1.2. Hepatitis B and/or C Virus Co-Infection

Seven subjects were identified across the program who were HBV co-infected and had clinically significant flares of liver chemistries and/or HBV IRIS: 2 subjects in ING113086 (DTG:1, RAL:1), 1 subject in ING112574, and 4 subjects in ING111762. Of the cases identified on DTG, 5/7 were not on HBV active therapy at the time of liver chemistry elevation and 5/7 had HBV active therapy discontinued at the start of DTG therapy. All subjects had HIV virologic and immunologic responses to DTG. Subjects who were treatment-naïve were not eligible for re-start of study drugs due to wide availability of other therapeutic options. Subjects who were treatment-experienced could be considered for restart of DTG, after careful review of each case with the ViiV Healthcare Safety and Labelling Committee. Three subjects (1 in ING112574, 2 in ING111762) restarted or continued DTG after or in conjunction with the start of HBV active therapy (e.g., TDF/FTC or entecavir). For all 3 of these cases, liver chemistries have remained within normal limits after restart or continuation of DTG. Therefore, if subjects are not receiving HBV active therapy at the start of potent HIV therapy, there is an increased risk for HBV IRIS or flare in the setting of HIV viral decline and immunologic improvement. The improved efficacy noted for DTG for the entire population in ING111762 may be contributing to higher rates of HBV-related IRIS in the hepatitis co-infected population in this study.

For hepatitis C virus co-infected subjects, the risk for significant liver chemistry increases in the setting of HIV virologic and immunologic responses does not appear as profound
as that identified for HBV, but HCV IRIS may also contribute to the findings across the clinical program. Across all studies and patient populations, comparable rates of liver chemistry elevations were noted in HCV co-infected subjects across treatment groups.

Across all patient populations, safety data supports the administration of DTG in HIV-infected patients co-infected with hepatitis B and/or hepatitis C virus, with awareness of the need for appropriate HBV therapy and the possibility of HBV/HCV flares or IRIS after the start of DTG therapy. The sponsor plans to include recommended measures to manage the risk of HBV/HCV IRIS in the Warnings and Precautions Section in the proposed labelling for DTG.

5.1.2.1. Pharmacokinetic Analysis

Based on population PK analyses in ART-naïve and ART-experienced subjects, HCV co-infection has no significant effect on DTG PK exposure (m2.7.2, Section 3.3.1 and Section 3.3.2). There were limited PK data for subjects with HBV co-infection; therefore, HBV co-infection was not evaluated in the population PK analysis. In ING111762, DTG average concentration at time 0 (C0_avg) appeared to be higher in HBV co-infected subjects (m2.7.2, Section 2.3.8). This is likely due to lack of use of metabolic inducers based on review of the background therapy in these subjects. Nonetheless, DTG C0_avg observed in HBV co-infected subjects were similar to those observed in the in ART-naïve subjects in ING113086 (m2.7.2, Section 2.3.5). There are no demonstrated or suspected drug interactions between DTG and commonly/newly approved drugs for the treatment of HBV or HCV (m2.7.2, Section 3.4).

5.1.3. Hepatic Impairment

ING113097 was a Phase I, open-label, parallel-group, two-part, adaptive study to evaluate the pharmacokinetics and safety of single 50 mg doses of DTG in HIV-negative subjects with moderate hepatic impairment, compared to healthy control subjects matched for gender, age, and body mass index.

DTG pharmacokinetic parameters were similar between subjects with moderate hepatic impairment and matched healthy controls. Thus, subjects with mild and moderate hepatic impairment do not require a dose adjustment. Additional detail on DTG PK data is provided in m2.7.2, Section 2.1.2.2.

Although hepatitis B and hepatitis C virus co-infected subjects were allowed to enrol in the Phase III trials, there are no additional clinical data available in HIV-infected subjects with moderate to severe hepatic impairment (Child-Pugh Grade B and C, respectively), as patients meeting these criteria for hepatic impairment definitions were excluded from participating in the Phase IIb/III clinical trials.

5.1.4. Renal Impairment

ING113125 was a Phase I, open-label, parallel-group study to evaluate the pharmacokinetics and safety of a single 50 mg dose of DTG in HIV-negative subjects with severe renal impairment (CrCl <30 mL/min, not on dialysis), compared to healthy control subjects matched for gender, age, and body mass index.
Severe renal impairment had a relatively moderate effect on DTG PK, reducing Cmax and AUC by around 23-40%, which is not considered clinically significant. In addition, there was overlap in exposure between the two groups, and 2 of 8 subjects with renal impairment had higher exposures than their matched controls. Similar results would be expected with the use of other methods for assessment of renal function.

Therefore, no dose adjustment is needed in INI-naïve subjects with mild to severe renal impairment (CrCl of at least 30 mL/min, not on renal replacement therapy).

Additional detail on DTG PK data in Study ING113125 is provided in m2.7.2, Section 2.1.2.3.

5.2. Extrinsic Factors

This section is intended to summarize safety data pertinent to individualizing therapy or patient management based on extrinsic factors. Extrinsic factors are defined as those associated with the patient environment, including the effect of food.

Effect of Food

Co-administration of DTG (Phase III formulation) with food in study ING113674 demonstrated increased plasma DTG exposures with increasing fat and calorie content. Plasma DTG AUC over the dosing interval (AUC0-τ) increased by 33%, 41%, and 66% when DTG was administered with low fat, moderate fat and high fat food, respectively. The increased exposure with food, which is similar when DTG is dosed 50 mg BID, is not considered clinically significant based on the accumulated safety data in Phase IIb and III studies, which permitted DTG dosing without restriction to food or food content. In ING112574 (the Phase III pivotal study examining the safety and efficacy of DTG 50 mg BID in ART-experienced, INI-resistant subjects, in which dosing without regards to food was permitted), a similar safety and tolerability to that observed in the pivotal ART-naïve studies (ING113086 and ING1144676) where DTG is dosed 50 mg once daily was observed. Further, in ING112574, there was no relationship between DTG exposure (despite a wide range of DTG exposures, including DTG dosed BID with food and DTG dosed BID with atazanavir, which also boosts DTG concentrations) and the most prevalent adverse events, supporting the safety and tolerability of DTG with exposures observed in the Phase IIb/III programme. On the basis of data from these studies, it is recommended that DTG can be administered with or without food.

5.3. Drug Interactions

This section provides a brief summary of known drug interactions with DTG that would impact on patient safety. Results of drug interaction studies are discussed in greater detail in m2.7.2 and in the individual study reports. Overall, there are limited safety implications resulting from theoretical or actual drug:drug interactions with DTG compared to other antiretroviral agents, including EFV and those requiring co-administration with a PK enhancer.
5.3.1. **Effect of DTG on Other Drugs**

Based on *in vitro* and *in vivo* data, DTG had low propensity to cause drug interactions except for drugs that are OCT2 substrates with narrow therapeutic windows (m2.7.2, Section 1.3.4, Section 3.4).

5.3.1.1. **Dofetilide**

Co-administration of DTG with dofetilide has the potential to increase dofetilide plasma concentration and result in potential life-threatening toxicity caused by high dofetilide concentration, and as such, is contraindicated. For this reason, co-administration has not been studied and was prohibited in all clinical studies.

5.3.1.2. **Metformin**

Co-administration of DTG also has the potential to increase metformin plasma concentration via inhibition of the OCT2 transporter, however co-administration has not been studied. The effect of DTG on metformin concentrations would be expected to be similar to that of cimetidine, another OCT2 inhibitor, which cause an approximate 50% increase in metformin AUC [Somogyi, 1987]. Therefore, metformin should be titrated against its effect on blood glucose and should be started at a low dose (regardless of whether co-administered with DTG or not), with gradual dose escalation up to a maximum of 2,550 mg in adults; the purpose of metformin titration is both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycaemic control of the patient [Glucophage, 2008]. Metformin does not cause hypoglycaemia under normal conditions of use. Although theoretically increases in metformin concentration could increase the risk of lactic acidosis, it would be expected that any effect of DTG on metformin concentration would be reflected by a lower dose being required to achieve the desired therapeutic effect, rather than a clinically significant increase in exposure. Thus recommendations are proposed for prescribing physicians to take the predicted interaction into consideration when choosing initial dosing and titration steps and initiating therapy in subjects already taking metformin.

5.3.2. **Effect of Other Drugs on DTG**

DTG is eliminated mainly through metabolism by UGT1A1. DTG is also a substrate of uridine diphosphate glucuronosyltransferase isozyme (UGT) 1A3, UGT1A9, cytochrome P450 isozyme 3A4 (CYP3A4), P-glycoprotein (Pgp), and breast cancer resistance protein (BCRP); therefore drugs that induce these enzyme/transporters may theoretically decrease DTG plasma concentration and reduce the therapeutic effect of DTG and drugs that inhibits these enzymes/transporters may increase DTG plasma concentration resulting in undesirable side effects. Based on clinical data, only drugs that are strong inhibitors of UGT1A1, e.g. atazanavir or atazanavir/ritonavir, significantly increased DTG exposure (m2.7.2, Section 3.4). Inhibitors of CYP3A4, Pgp, and other transporters did not or is not expected to increase DTG exposure significantly (m2.7.2 Section 3.4).
5.3.2.1. Atazanavir (ATV) and Atazanavir/ritonavir (ATV/RTV)

A drug interaction study with the UGT1A1 inhibitor, ATV, did not result in a clinically meaningful increase in the plasma concentrations of DTG. Administration of DTG 30 mg once daily with ATV 300 mg once daily or ATV/RTV 300 mg/100 mg once daily in study ING118541 increased plasma exposures of the drug. Plasma DTG AUC (0-t), Cmax and trough concentration at the end of the dosing interval (Cτ) increased by 62% and 91%, 34% and 50%, and by 121% and 180%, respectively. An upper limit of exposure that has been associated with an increase incidence of AEs has not been identified. A wide range of exposures was observed with 50 mg BID dosing in ING112574, however, PK/PD analyses did not identify an association between plasma exposure and any safety parameter (m2.7.2, Section 2.3.7). Thus, no dose adjustment is needed when DTG is administered with either ATV or ATV/RTV based on safety results to date for subjects with comparable or higher exposures in ING112574.

5.4. Use in Pregnancy and Lactation

No studies have been conducted with DTG in pregnant women, and pregnant women were excluded from the DTG clinical studies. Subjects who became pregnant (intrauterine) were required to discontinue from the studies.

Pregnancy outcomes from female subjects who became pregnant during the conduct of the Phase I to IIIb clinical studies and the compassionate use program conducted with DTG to date, are presented in Appendix Table 8 (studies in ART-naïve adult subjects), Appendix Table 9 [studies in ART-experienced (INI-naïve) subjects], Appendix Table 10 (completed pharmacology studies), and Appendix Table 11 (other ongoing studies).

As of the submission cut-off date, there were 27 pregnancies reported across the DTG clinical studies and compassionate use program. Twenty-five of the pregnancies were reported in the ART-naïve population (14 received DTG, 6 RAL, and 5 Atripla), one was in the ART-experienced (INI-naïve) population (subject was on RAL), and one was reported in a completed Phase I, healthy volunteer study. There were no pregnancies reported in the ART-experienced (INI-resistant) population.

Of the 27 pregnancies reported; 6 resulted in delivery of a normal healthy baby, 8 had an elective termination, one was ectopic (Atripla) and 3 (one each for DTG, RAL and Atripla) resulted in spontaneous abortions (all between 5 and 12 weeks gestation). In 4 reports, the pregnancy was ongoing, and in 5 reports, the outcome of the pregnancy was unknown.

5.5. Clinical Development Program in Paediatric Subjects

5.5.1. Non-Clinical Studies

Independent in vitro studies demonstrated that two HIV integrase inhibitors (p8 [SCITEP] and p10 [L-708,906]) interfered with DNA cleavage activity of recombinase activating gene (RAG) 1/2 recombinases [Melek, 2002].
If HIV integrase inhibitors interfere with RAG1/2 functioning, there is a potential to affect the development of a fully functional lymphocyte repertoire in developing neonates and infants. Clinically, affected patients would theoretically exhibit an Ommen-like syndrome characterized by failure to thrive, erythroderma, hepatosplenomegaly, eosinophilia, and increased susceptibility to infection.

To address the potential effects of DTG on RAG1/2, immunotoxicity endpoints [T cell-dependent antibody response (TDAR), immunophenotyping, and T cell receptor V beta usage] were added to the definitive rat juvenile toxicity study. There were no treatment-related effects on immunologic competence as measured by TDAR, and no effects on lymphocyte subset counts (T cells, both CD4 and CD8 subsets, and B cells) and CD4 or CD8 T cell receptor Vβ usage in peripheral blood. Histopathology of immunologic organs (spleen, thymus, lymph nodes) and haematology evaluation revealed no effects. The NOAEL for immunotoxicity endpoints was 75 mg/kg/day. These results provided a robust nonclinical assessment of potential developmental immunotoxicologic effects and suggest no unusual drug specific risk of developmental immunotoxicity in juvenile animals.

No new target organ toxicities were observed in the definitive juvenile rat toxicology study. The NOAEL for DTG in juvenile rats is considered to be 2 mg/kg/day (see m2.6.6 Toxicology Written Summary).

No safety signals specific to paediatric subjects have been identified from preclinical studies with DTG to date.

Collectively these data suggest that the risk of immunosuppression with DTG in developing neonates and infants is negligible.

These findings support dosing of DTG in paediatric subjects at ~1 mg/kg once daily up to a maximum dose of 50 mg.

These data are presented in further detail in m2.4 (Nonclinical Overview).

5.5.2. Clinical Trial ING112578 (P1093)

5.5.2.1. Overall Exposure in Paediatric Subjects

All paediatric 12 to 18 year old subjects were exposed to DTG for >24 weeks. The mean exposure was 309 days (range 200 to 414 days).
**Table 75  Summary of Exposure to Study Drug - Study P1093**

<table>
<thead>
<tr>
<th>Exposure (weeks), n</th>
<th>DTG N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0 days</td>
<td>10</td>
</tr>
<tr>
<td>&gt;4 weeks</td>
<td>10</td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td>10</td>
</tr>
<tr>
<td>&gt;24 weeks</td>
<td>10</td>
</tr>
<tr>
<td>&gt;48 weeks</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure (days)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
</tr>
<tr>
<td>Mean</td>
<td>309</td>
</tr>
<tr>
<td>SD</td>
<td>83</td>
</tr>
<tr>
<td>Min</td>
<td>200</td>
</tr>
<tr>
<td>Max.</td>
<td>414</td>
</tr>
</tbody>
</table>

Data Source: ING112578 (P1093) Week 24 CSR Table 15 and Table 16

**5.5.2.2. Demographic and Baseline Characteristics**

The median age of subjects enrolled in the study was 13.5 years. Seven of 10 subjects (70%) were female and 6/10 (60%) were of Black or AA/AH.

Four subjects were classified as CDC category C at Baseline (Data Source: ING112578 (P1093) Week 24 CSR Table 37).

The median Baseline HIV-1 RNA was 4.5 10^6 c/mL, median Baseline CD4+ cell count was 543 cells/mm³ (Data Source: ING112578 (P1093) Week 24 CSR Table 8).

**5.5.2.3. Adverse events**

Limited safety data is available for the paediatric population and is described from ten adolescent (12 to <18 years of age) subjects receiving at least 24 weeks of DTG once daily in combination with an investigator-selected, optimized background regimen in ING112578 (P1093). Nine subjects received a DTG 50 mg once daily dose, and one paediatric subject received DTG 35 mg once daily (~1 mg/kg dosing).

DTG demonstrated no safety events during the dose finding period (Stage I) that led to rejection or modification of any dose. Nine of the 10 adolescent subjects reported a clinical AE, the majority of which were Grade 1 (Table 76). AEs reported in more than one subject included cough, lymphadenopathy, and sinus congestion. All AEs were reported as Grade 1 or 2 (mild or moderate) in intensity and many were related to common childhood illnesses (e.g., impetigo, ear congestion, etc) or pre-existing secondary Baseline diagnoses.

No AEs were deemed related to study drug by the reporting investigators. No SAEs (including fatalities), pregnancies or withdrawals due to AEs have been reported to date.
Table 76  Summary of All Adverse Events for Cohort I, Stage 1 Worst Grade for each subject (Incidence greater than 1 subject) – Study ING112578 (P1093)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 n (%)</td>
<td>2 n (%)</td>
<td></td>
</tr>
<tr>
<td>Number of subjects with one or more AEs</td>
<td>8 (80)</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2 (20)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>2 (20)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>2 (20)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data Source: ING112578 (P1093) Week 24 CSR Table 22

5.5.2.3.1.  Adverse Events of Special Interest (AESI)

AESI for DTG are described in Section 2.1.5. One subject reported rash pustular, which was not considered reasonably attributable to DTG by the reporting investigator. No cases of HSR have been reported for this study to date.

Diarrhoea and headache were developed by one subject each, otherwise no other AESI were reported for this cohort. Specifically, no cases of pancreatitis rhabdomylosis, myositis or myalgias, suicidal ideation or behaviours or IRIS were reported. And no events suggestive of GI ulcerative lesion, hepatobiliary disorders or TdP were reported (Data Source: ING112578 (P1093) Week 24 CSR Table 23).

5.5.2.4.  Clinical Chemistry

Clinical chemistry abnormalities were reported by 9/10 (90%) subjects; none were serious, deemed clinically significant or considered related to DTG by the investigator, and no trends were evident (Table 77).

Minimal absolute changes from Baseline for clinical chemistries were observed, but none were considered clinically significant. No subjects met liver stopping criteria, nor did any subjects have ALT elevations ≥3X ULN. One Grade 3 asymptomatic elevated lipase was reported at Day 344 (Week 48), which was not considered related to DTG. One subject had a Grade 1 increase in CPK.
Similar to observations in adult subjects (see Section 3.1.2 on Renal Function), adolescent subjects had small increases in creatinine that appeared at Week 2 and remained stable to Week 24, when an increase in the mean, but not the range, was observed (Table 78). One subject had a treatment-emergent change in urine dipstick protein analysis, from negative at Baseline to trace amounts present at Week 24 (see ING112578 (P1093) Week 24 CSR Section 7.3.1).

Table 78 Mean Change from Baseline in Serum Creatinine (mg/dL) - Study ING112578 (P1093)

<table>
<thead>
<tr>
<th>Cohort I, Stage 1</th>
<th>Actual Relative Time</th>
<th>N</th>
<th>Baseline Mean</th>
<th>Mean Change from Baseline (min, max)</th>
<th>Median Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>Baseline</td>
<td>10</td>
<td>0.58</td>
<td>0.05 (-0.10, 0.15)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Week 2</td>
<td>10</td>
<td>0.58</td>
<td>0.08 (-0.10, 0.27)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>10</td>
<td>0.58</td>
<td>0.08 (-0.06, 0.33)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Week 12</td>
<td>9</td>
<td>0.59</td>
<td>0.15 (-0.07, 0.35)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>10</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data Source: ING112578 (P1093) Week 24 CSR Table 35

5.5.2.5. Haematology

No haematology abnormalities were reported.
5.5.2.6. Vital Signs and Electrocardiograms

ECGs were not routinely collected, however no changes in diastolic or systolic blood pressure, respiratory or pulse rates, or temperature were noted.

5.6. Integrated Clinical Pharmacology Analysis in Adults

Data is presented in this safety summary using three “dosing periods”, in which treatment is combined regardless of dose and duration: Placebo, DTG alone, and DTG with combination drug. As such, subjects who may have been exposed to both PBO and DTG could have AEs in both dosing periods.

5.6.1. Overall Exposure in Integrated Clinical Pharmacology Studies

From the Integrated Clinical Pharmacology Studies Analysis, a total of 526 subjects received at least one dose of DTG; 220 healthy subjects received single doses of DTG from 2 mg to 250 mg; and 306 healthy subjects and HIV-infected subjects have received repeat, once daily (10 mg to 50 mg) or BID (50 mg) doses of DTG for up to 19 and 14 days, respectively (Data Source: CPM Table 1).

5.6.2. Frequently Reported AEs

Overall, there were relatively fewer AEs reported from the clinical pharmacology studies than the Phase IIb/III studies. The most frequently reported AEs from the clinical pharmacology studies were similar to observations from the Phase IIb/III studies in HIV-infected adults (Table 79). All 11 subjects with ocular icterus were in the atazanavir drug interaction study (ING111854) and receiving ATV at the time. None of the subjects experienced this event while on DTG alone.
Table 79  Summary of Common Adverse Events by Frequency in at least 2% in any treatment group – Clinical Pharmacology Studies

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS DTG Alonea</td>
</tr>
<tr>
<td></td>
<td>N=445</td>
</tr>
<tr>
<td>Any event</td>
<td>125 (28)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Ocular icterus</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

Data Source: CPM Table 2

A. HS DTG Alone includes dosing periods where healthy subjects received DTG alone.
B. ALL DTG includes dosing periods where healthy subjects and HIV-infected subjects received DTG either alone or with at least one other protocol defined medicinal product either sequentially and/or in combination.

5.6.3. Adverse Events by Maximum Intensity

In the Integrated Clinical Pharmacology Studies analysis there were slightly more Grade 1 events in those healthy subjects and HIV-infected subjects taking DTG and other protocol-defined medicinal products (either sequentially or in combination), compared to either healthy subjects taking DTG alone or subjects receiving placebo alone during dosing periods.  A low incidence of Grade 3 to 4 events was observed across dosing periods (Data Source: CPM 10): <1% of healthy subjects who received DTG alone; 1% of all subjects who took DTG (includes healthy subjects and HIV-infected subjects who received DTG alone or with at least one other protocol-defined medicinal product either sequentially and/or in combination); 1% of all subjects who took placebo.

5.6.4. Investigator-Assessed Drug-Related Adverse Events

Reporting rates for events considered reasonably attributable to DTG by investigators from the 26 Integrated Clinical Pharmacology studies were similar to those observed from the Phase IIb/III clinical trials.

Reports of ocular icterus all occurred in the atazanavir dosing periods of Study ING111854, and were considered related to ATV.
Table 80  Summary of All Treatment-Related Adverse Events by Frequency and SOC (in at least 2% in any treatment group) - Clinical Pharmacology Studies

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS DTG Alone</td>
</tr>
<tr>
<td></td>
<td>N=445</td>
</tr>
<tr>
<td>Any event</td>
<td>79 (18)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>0</td>
</tr>
<tr>
<td>Ocular icterus</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Source: CPM Table 3
a. HS DTG Alone includes dosing periods where healthy subjects received DTG alone.
b. ALL DTG includes dosing periods where healthy subjects and HIV-infected subjects received DTG either alone or with at least one other protocol defined medicinal product either sequentially and/or in combination.

5.6.5. Deaths

No deaths were reported in any of the completed clinical pharmacology studies.

5.6.6. Non-Fatal Serious Adverse Events

There were two SAEs reported from the clinical pharmacology studies (m2.7.4, Section 2.1.3.4). One subject had a manic episode which was considered unrelated to DTG in ING112941, and another subject in ING113099 had a suspected rifamycin hypersensitivity syndrome while receiving rifabutin and DTG (event was considered related to study drugs).
5.6.7. Adverse Events Leading to Withdrawal

Based on the clinical pharmacology integrated analysis, there were 12 subjects (12/559, 2%) who had AEs that led to discontinuation of study drug. There were no safety trends noted leading to discontinuation across the clinical pharmacology studies.

Study ING113096 was the only study that had more than two subjects who withdrew due to an AE. This was a drug interaction study with tipranavir/ritonavir, and 4/18 subjects developed ALT and AST elevations that resulted in the permanent discontinuation of investigational product and withdrawal from the study. These elevations occurred in subjects receiving TPV/RTV 500/200 mg or DTG 50 mg + TPV/RTV 500/200 mg. In all four subjects, the increase in ALT and AST began during dosing of TPV/RTV alone (Period 2), though 2 subjects were withdrawn after the ALT continued to increase early in Period 3 (DTG + TPV/RTV).

Two additional studies had two AEs leading to withdrawal: ING11207 (first-in-human study) had a subject in the 25 mg cohort experience a 3 beat nonsustained ventricular tachycardia, for which no other cause was identified, and a subject in the 5 mg cohort had an unrelated viral upper respiratory infection. ING113099, a rifabutin/rifampin drug interaction study had two subjects develop AEs leading to withdrawal. One due to an SAE of suspected rifamycin hypersensitivity and the other due to decreased lymphocytes while taking DTG and rifabutin.

Three studies each had one AEs leading to withdrawal, two of them unrelated to study drug. ING111405 (HIV PI drug interaction study) had an AE of high blood pressure, and ING112941 (PPI and high fat meal study) had a AE of Grade 2 manic reaction. In ING114819 (iohexol/renal function study), one subject withdrew after experiencing nausea, anxiety, weakness, loose bowels, and panic reaction. He admitted to both distributing and using a legal herbal substance with known opiate antagonist properties, but relationship to DTG could not be ruled out.

5.6.7.1. Clinical Laboratory Evaluations and Vital Signs

No trends were noted during the conduct of the Phase I/IIa studies to suggest DTG has a clinically significant effect on clinical chemistries (the exception of creatinine noted below), haematological parameters, or vital signs.

5.6.7.2. Liver Chemistries

No subject in the clinical pharmacology studies met criteria for drug induced liver injury (DILI) defined as ALT and/or AST >3 times ULN and total bilirubin >1.5 times the ULN.

Analysis of liver chemistries (alkaline phosphatase, ALT, AST, total and direct bilirubin) demonstrated no pattern of difference from placebo subjects and those receiving DTG (alone or with other drugs), with the exception of increased rates of increased bilirubin seen in the DTG and atazanavir drug interaction study during ATV administration (Data Source: CPM Table 7 and Table 7.1), and increased rates of liver enzyme elevations in
the DTG and TPV/RTV drug interaction study in subjects during TPV/RTV administration (see Section 5.6.7).

5.6.7.3. Renal Function

A small mean, reversible increase in creatinine of 0.11 mg/dL for subjects receiving DTG was observed; this was approximately a 10% increase (versus a zero increase in the placebo subjects). Occasional increases in both DTG and placebo subjects were observed for trace proteinuria, with few subjects on DTG increasing one level (from trace to 1+). There were no AEs of renal disorders reported in the integrated analysis of safety in clinical pharmacology studies.

In ING115697 (HCV PI drug-interaction study), one subject was withdrawn after developing a Grade 1 (1.68 mg/dL) elevation in serum creatinine on Day 6, Period 2 of receiving DTG and telaprevir. (This study was not included in the integrated safety analysis.)

ING114819 was a dedicated study to assess the effect of DTG on renal plasma flow and glomerular filtration rate (GFR). The results indicated that serum creatinine increased, and hence, calculated creatinine clearance decreased in subjects receiving DTG 50 mg once daily and twice daily. DTG at 50 mg once daily and 50 mg BID had no significant effect on GFR compared to placebo over 14 days based on iohexol clearance. In addition, neither treatment significantly changed para-aminohippurate (PAH) clearance (see m2.7.2 Section 2.1.5.3 for details).

5.6.7.4. Other Completed and Ongoing Clinical Pharmacology Studies

ING113125, ING115697, ING115465, ING116915, and ING114580 were ongoing at the time of the data cut-off date for the Integrated Clinical Pharmacology Studies Analysis, and thus were not included in that integrated safety analysis. Subsequently, these five studies enrolled an additional 82 subjects who received single-dose DTG and 57 subjects who received repeat-dose DTG. Final study reports are available, and details on these studies can be found in m2.7.2 and m5.3.3.1, m5.3.3.3 and m5.3.3.4.

No SAEs were reported in these studies. There have been five withdrawals due to AEs. One subject withdrew due to a panic reaction (unrelated to study drug) from ING116195. Four subjects withdrew from ING115697, a study of drug interactions with HCV protease inhibitors. Two subjects withdrew due to related AEs of increased ALT and increased Grade 1 serum creatinine, both subjects were taking DTG and telaprevir. Two other unrelated AEs leading to withdrawal were: dizziness (DTG only) and cellulitis (DTG and boceprevir). The remainder of the safety described in these studies is consistent that reported with prior Phase I studies and from HIV-infected subjects receiving DTG.

5.6.8. Cardiac Evaluation

ING111856 demonstrated that a single supra-therapeutic dose of DTG (250 mg) had no significant effect on cardiac repolarisation in a population of 42 healthy subjects, when
compare to moxifloxacin (400 mg; active control) or placebo (see Section 2.1.5.6.3). In addition, in the 26 completed clinical pharmacology studies, there were only singular reports of arrhythmia and supraventricular tachycardia in the subjects receiving DTG alone. No significant ECG findings were reported. No syncope was reported.

5.7. Overdose

For the purposes of this summary, an overdose was considered as any dose above the daily recommended dose (i.e., 50 mg once daily in INI-naïve adults; 50 mg BID in INI-resistant adults; and 1 mg/kg once daily with a maximum daily dose of 50 mg in INI-naïve paediatric patient).

There is currently limited experience with overdosing of DTG. Single daily doses up to 250 mg have been administered orally to healthy subjects in clinical pharmacology study ING111856; no unexpected adverse effects were reported for DTG during this study. The effects of higher doses are not known.

To assess for any potential overdosing of DTG in the Phase IIb/III clinical trials, a listing of comments from the IP dosing records was produced in order to identify overdose that may have arisen due to dosing errors (Data Source: ISO Listing 2.1, ISO Listing 2.31, ISO Listing 2.501). Only one subject, who was participating in ING112961 (Cohort II), was identified as taking a possible overdose as defined above. This subject took an evening DTG dose of 100 mg, which implied a total daily dose of 150 mg. This subject reported no AEs in the two weeks surrounding this event.

Across all clinical studies, there were no cases of overdose with DTG (or comparator) that led to the permanent discontinuation of investigational product and withdrawal of subjects from any study.

There is no known specific antidote for overdose with DTG. In the event of a suspected overdose, it is recommended that the patient be monitored and the appropriate supportive clinical care should be instituted, as dictated by the patient’s clinical status. Given that DTG is extensively protein-bound, it is unlikely that dialysis would be effective in eliminating DTG from the blood.

5.8. Drug Abuse

The INI class of compounds has no known drug abuse potential. The mechanism of action for this class does not involve receptors or neurotransmitters known to be involved in drug-dependence [m4.2.1.2, RH2007/00072/00].

In a secondary pharmacology evaluation, DTG did not significantly bind to any receptors or ion channels that would be considered relevant to neuropsychological stimulation (including monoamine oxidase A and B, cannabinoid CB1 or CB2, nicotinic cholinergic, dopamine D1 or D2L, dopamine transporter, GABA A or GABA B, glutamate NMDA, opiate, serotonin 5-HT1, 5-HT2, or 5-HT3) [m4.2.1.2, RH2007/00072/00].

No studies to investigate the potential for abuse or dependency with DTG have been performed given that: a) DTG is not centrally active, b) there is clear evidence that this
compound has low brain penetration, c) mechanistically, DTG does not interact with neurotransmitters/receptors involved in the drug-dependence mechanism, and d) preclinical and clinical data available are not indicative of a potential for drug abuse.

In summary, there are no data suggesting that DTG has the potential to imply illicit use, abuse, or dependency on DTG.

5.9. Withdrawal and Rebound

No studies to investigate the potential for withdrawal and rebound effects with DTG have been performed. This class of compounds has no known drug withdrawal or rebound potential.

In preclinical studies, no effects related to DTG administration on central and peripheral nervous systems were noted following dosing withdrawal. There is no clinical evidence to suggest withdrawal or rebound effects of DTG.

5.10. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There have been no studies to investigate the effect of DTG on driving performance or the ability to operate machinery.

This class of compounds has no known effects on one’s ability to drive or operate machinery or impairment of mental ability.

Adverse events were reported in controlled clinical studies that may influence a patient’s ability to drive or operate machinery, or that may impact upon mental ability (e.g., dizziness, headache, somnolence), however, the incidence of these adverse events in DTG-treated subjects were similar when compared with groups taking raltegravir- or efavirenz-containing regimens, with the exception of dizziness, which occurred less frequently in the overall group that received DTG compared with those who had received efavirenz.

Traffic accidents were reported as AEs for 4 of 980 (<1%) of the ART-naïve population taking DTG, and no traffic accidents were reported for the ART-experienced (both INST-naïve and INST-resistant) population taking DTG (Data Source: ISO Table 2.15, ISO Table 2.16, and ING111762 Week 24 CSR Table 8.2). There were also two traffic accidents reported for comparators, one for Atripla in ING114467 and one for RAL in ING111762.

Two of the DTG traffic accident AEs in the ART-naïve population were reported as SAEs. The road traffic accident reported for Subject 818 in ING112276 resulted in a fatal outcome (see APPENDIX 5). The subject’s wife commented that, prior to the accident, the subject had no problems with his health and that the accident was caused by the actions of the other motorist. The other case was reported for Subject 5146 in ING114467. This was non-fatal, and review all of the AEs reported for this subject did not highlight anything that may have impaired the subject’s ability to operate a motor vehicle; a case narrative for this SAE is included in APPENDIX 6.
One additional SAE was reported through to the [redacted] from ongoing study ING116529. This was also non-fatal, and review of the AEs reported for this subject also did not highlight anything that may have impaired his ability to operate a motor vehicle (a narrative for this case is included in APPENDIX 6).

Overall, given the pharmacology of DTG and available clinical evidence, there is no detrimental effect anticipated on the ability to drive or operate machinery, or on mental ability.

6. POST-MARKETING DATA

There is no post-marketing data on dolutegravir as it is not marketed in any country in the world. Thus, all safety data provided in this submission are from clinical studies conducted with DTG.

7. SAFETY CONCLUSIONS

Overall the safety profile for DTG, combined with the efficacy and virology profile, supports a favourable risk/benefit compared to other ARVs.

The safety profile for DTG 50 mg once daily in INI-naïve subjects was comparable to RAL and generally favourable compared to Atripla and EFV.

- In ING113086 (ART-naïve) and ING111762 [ART-experienced (INI-naïve)], the rate of clinical adverse events and drug-related adverse events was similar to RAL at 48 and 24 weeks, respectively.
- In ING114467 Week 48 data, the safety profile for DTG 50 mg plus ABC/3TC FDC was generally favourable compared to Atripla in ART-naïve, HIV-infected subjects.
  - The superiority of the DTG+ABC/3TC treatment response was due to a lower rate of adverse events leading to the permanent discontinuation of IP and withdrawal from the study, specifically from the psychiatric disorders, nervous system disorders, gastrointestinal disorders and general disorders and administration site conditions events SOCs.
  - Subjects in the Atripla treatment group were significantly more likely to develop dizziness, abnormal dreams, rash, anxiety and somnolence, whereas subjects in the DTG 50 mg plus ABC/3TC FDC treatment group were significantly more likely to develop insomnia.

DTG dosed 50 mg twice daily in highly ART-experienced (INI-resistant) subjects with advanced HIV disease resulted in a safety profile comparable to DTG 50 mg once daily in both ART-naïve and ART-experienced (INI-naïve) subjects, despite the advanced stage of disease and multiple concomitant medications.

- Although more SAEs were reported for ING112574 when compared to the INI-naïve studies, these were driven by more events from the infections and infestations SOC, as would be expected by the advanced nature of HIV disease in the ING112574...
study population. Very few SAEs were considered reasonably attributable to DTG in this study.

Hypersensitivity is an uncommon but recognized risk for ART containing DTG regardless of dose or treatment population.

Mild to moderate episodes of rash should be considered listed for DTG containing ART, regardless of dose or treatment population, in the Company RSI and Local Country Prescribing Information for DTG. Episodes occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks.

- Reporting rates for HSR and rash of any grade were comparable to RAL and less than observed for EFV/Atripla in ART-naïve and ART-experienced (INI-naïve) subjects.
- Cases of HSR reported for DTG (regardless of dose) and RAL were generally confounded by co-suspect medications that were consider to have contributed to the event.
- The nature and incidence of HSR or rash with ART regimens containing DTG 50 mg twice daily appears to be no different to such events observed with regimens containing containing DTG 50 mg once daily.
- No cases of SJS, TEN, or EM with DTG have been reported in the programme to date.
- There is no evidence for an increased risk for HSR or rash with either DTG 50 mg once daily in ART-naïve and ART-experienced (INI-naïve) subjects, or DTG 50 mg BID in ART-experienced (INI-resistant) subjects.

Cumulative data suggests a hepatic safety profile for DTG that is comparable to RAL or EFV.

- The ING113086 Week 48 data and ING111762 Week 24 data (less ING111762 HBV and/or HCV co-infected subjects) indicated that, overall, the incidence of post-Baseline-emergent liver chemistry toxicities was similar between DTG and RAL. From the ING114467 Week 48 data, the incidence of treatment-emergent liver chemistry toxicities for DTG+ABC/3TC was lower than observed for the Atripla comparator arm and lower when compared to both the DTG and RAL treatment groups in the ING113086 and ING111762 data.
- Analysis of the ING112574 safety data suggests no excess risk of hepatic toxicity for DTG in this advanced HIV population receiving multiple concomitant medications. The incidence of post-Baseline-emergent liver chemistry toxicities for DTG 50 mg BID in this study was comparable to DTG 50 mg once daily in ING113086 and ING111762.
- In most cases where liver abnormalities have been noted across the development program, either the co-administered antiretroviral treatment included drugs with
well-described bilirubin or liver enzyme elevations, and/or hepatitis virus co-infection was evident, and/or subjects had a medical history of alcohol abuse.

Safety and pharmacokinetic data supports the administration of DTG in HIV-infected patients co-infected with hepatitis B virus and/or hepatitis C virus.

- In HBV and/or HCV co-infected ART-naïve subjects, the occurrence of Grade 2 or higher ALT elevations was improved when compared to RAL or EFV.
- In ING111762, subjects with HBV co-infection receiving DTG were noted to have significant liver chemistry elevations in the setting of HIV virologic and immunologic responses to DTG and withdrawal (or lack of) HBV active therapy. The pattern of injury is likely consistent with IRIS and/or inadequate HBV therapy rather than direct liver injury due to DTG. Subjects with hepatitis C virus co-infection in ING111762 may be at greater risk of HCV IRIS with DTG due to improved HIV virologic responses versus RAL.
- In the ART-experienced (INI-resistant) population treated with DTG BID, the incidence of post Baseline-emergent Grade 2-4 ALT and AST toxicities in subjects with hepatitis virus infection was lower than the ART-naïve population and only marginally higher than for those without hepatitis virus infection.
- Clinical pharmacology drug interaction studies have demonstrated that commonly/newly approved drugs for the treatment of HBV or HCV had no effect on DTG PK.

Drug-related hepatitis is therefore an uncommon but recognized risk for ART containing DTG, regardless of dose or treatment population.

Overall, the renal profile of DTG is comparable to comparators in Phase III studies (i.e., RAL and EFV).

- Mild elevations of creatinine should be listed clinical chemistry elevations in the Company RSI and Local Country Prescribing Information for DTG, are related to a likely benign effect on creatinine secretion via blockade of the OCT2 receptor, do not progress on continued treatment with DTG, and revert towards Baseline after DTG discontinuation.
- Currently there is no evidence that DTG potentiates the nephrotoxicity observed with tenofovir.
- A low incidence of Grade 2 or higher creatinine toxicities were noted across the clinical program.
- No clinically significant median increases in urine albumin/creatinine values were noted in the Phase III clinical studies. Dipstick measurements of urinary albumin appeared unreliable, particularly in the EFV-controlled studies, and the more accurate measurement of albumin/creatinine ratio confirmed there was no difference in the effect of DTG on albumin excretion compared with EFV or RAL.

Preclinical evidence for GI toxicity with DTG (including vomiting, diarrhoea and gastric/colonic erosions), did not translate into significant findings for DTG in double blinded randomized clinical trials, where a similar rate and nature of GI events were
reported for DTG as observed for RAL and Atripla. Haemoglobin concentrations were generally stable or increased over time on all regimen, consistent with positive effects of ART.

Mild to moderate events indicative of general GI intolerance (i.e., diarrhoea, nausea, vomiting or abdominal pain) should be considered listed for DTG containing ART, regardless of dose or treatment population, in the Company RSI and Local Country Prescribing Information for DTG. Episodes occur early in treatment (nausea within the first one or two weeks and diarrhoea within the first six weeks), rarely requiring treatment interruptions or withdrawals and usually resolving within two to four weeks without recurrence.

- The nature and incidence of diarrhoea, nausea, vomiting or abdominal pain reported for subjects receiving DTG 50 mg BID were no worse than compared to events observed with DTG 50 mg once daily. Therefore, there does not appear to be an increased risk for GI events with this higher dose.

- There have been no signals to indicate an increased risk for the development of peptic ulcers or serious erosions (e.g., clinical symptoms or treatment-emergent decline in haemoglobin concentrations) with DTG.

DTG does not confer an increased risk for torsades de pointes.

- In a thorough QT study, DTG at supratherapeutic doses did not have an effect on cardiac conduction.

- AEs potentially indicative of TdP have rarely been observed across the entire clinical program, and no cases of TdP or ventricular tachycardia have been reported in subjects receiving DTG.

- ECG evaluations collected in Phase II and III studies show no evidence for QT prolongation with DTG.

The neuro-psychiatric profile for DTG was comparable to RAL and favourable to both Atripla and EFV. There was no evidence of increased risk for suicidal ideation and behaviours with DTG compared to RAL, Atripla, or EFV. There was no evidence of excess risk of psychiatric disorders for DTG 50 mg BID.

Episodes of mild to moderate insomnia should be considered listed for DTG containing ART, regardless of dose or treatment population, in the Company RSI and Local Country Prescribing Information for DTG. These tend to occur within the first three months of therapy, are self limiting, and generally resolve within one month without treatment interruptions or withdrawals. The frequency and nature of insomnia with DTG 50 mg BID in ART-experienced (INI-resistant) subjects appears to be similar to events with DTG 50 mg once daily in ART-naïve and ART-experienced (INI-naïve) subjects, with the exception of a possible earlier onset.

Mild to moderate episodes of headache should be considered listed for DTG containing ART, regardless of dose or treatment population, in the Company RSI and Local Country Prescribing Information for DTG. The majority of events occurred within the first four
weeks of treatment and were not treatment limiting, generally resolving within two to three weeks.

- The nervous system disorder profile for DTG appears to be comparable to RAL and favourable compared to Atripla.
- No dose-related effect of DTG 50 mg BID was observed on nervous system findings, including headache, in comparison to DTG 50 mg once daily dose.

Despite the rapid decline in HIV RNA observed on DTG, IRIS cases were generally infrequent on DTG, and the rates of IRIS on DTG were comparable to those observed on RAL and EFV.

- Based on medical adjudication of IRIS like events in ING111762, ART-experienced (INI-naïve) subjects with hepatitis B or C virus co-infection receiving DTG may be at greater risk for IRIS than those receiving RAL, due to improved HIV virologic and immunologic responses with DTG compared to RAL, and withdrawal (or lack of) HBV active therapy in HIV/HBV co-infected subjects. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B virus co-infected patients.
- For other medical conditions frequently implicated in IRIS events, there was a low rate of IRIS cases for both DTG and RAL.

The musculoskeletal profile for DTG was generally comparable to that observed for RAL and Atripla treatment groups in INI-naive subjects, and there was no evidence of excess risk of musculoskeletal disorders for DTG 50 mg BID in INI-resistant subjects.

Lipase elevations have been noted in ART-naïve subjects from the Phase IIb and Phase III studies and most have been transient. There is no indication that there is a higher rate of clinical pancreatitis on DTG vs. comparator.

Lipid profile for DTG is comparable with RAL, with both showing little change from Baseline. The combination of DTG+ABC/3TC was statistically favourable when compared to Atripla, with both regimen showing little change from Baseline. Changes in lipid parameters were generally small in both DTG and comparator groups in INI-naive populations, and did not appear to be adversely affected by the larger DTG 50 mg BID dose in the INI-resistant populations.

There were no clinically significant trends in post-Baseline-emergent haematology abnormalities.

There was no evidence for increased risk of neoplasms with either DTG 50 mg once daily in ART-naïve and ART-experienced (INI-naïve) subjects, or DTG 50 mg BID in ART-experienced (INI-resistant) subjects.

There was no evidence for increased risk for cardiovascular disorders with DTG, which had a cardiovascular profile comparable with RAL and EFV.
Based on animal data, dolutegravir is not anticipated to increase the risk of adverse developmental or reproductive outcomes in humans when used in accordance with dosing information in the product label.

No effect of gender, age, or race on safety profile of DTG have been observed (beyond what might be expected for each subgroup).

There are limited safety implications resulting from theoretical or actual drug:drug interactions with DTG compared to other antiretroviral agents, including EFV and those requiring co-administration with a PK enhancer:

- \textit{In vitro}, DTG inhibited the renal organic cation transporter (OCT2) and may increase plasma concentrations of drugs dependent on OCT2 for clearance (dofetilide and metformin). The co-administration of DTG and dofetilide is contraindicated. Careful monitoring is recommended when starting the combination of DTG with metformin, and metformin dose adjustments may be required.

No dose adjustment for DTG is needed in subjects with mild to moderate hepatic impairment (Child Pugh grade A or B) or in subjects with mild, moderate, or severe (CrCl <30 mL/min, not on dialysis) renal impairment.

Based on limited available data in children and adolescents (12 to less than 18 years of age and weighing at least 40 kg), there were no additional types of adverse reactions beyond those observed in the adult population.

There are no data suggesting that DTG has the potential for illicit use, abuse, or dependency, nor risks associated with withdrawal or rebound effect. Given the pharmacology of DTG and available clinical evidence, there is no detrimental effect anticipated on the ability to drive or operate machinery, or on mental ability.

There is currently limited experience with DTG overdose. Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.
8.REFERENCES


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Isentress Package Insert, revised April 2012.


9. APPENDICES
## 9.1. APPENDIX 1: Tabular Listing of Studies

### Appendix Table 1  Description of Clinical Efficacy and Safety Studies

<table>
<thead>
<tr>
<th>Protocol No./ Sponsor</th>
<th>No. Study Centres</th>
<th>Location(s)</th>
<th>Study Start; Enrolments Status and Date; Total Enrolment / Target Enrolment</th>
<th>Study Objectives</th>
<th>Study Design</th>
<th>Diagnosis; Key Inclusion Criteria</th>
<th>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</th>
<th>No. of Subjects by Group Entered/ Completed</th>
<th>Gender M/F; Mean Age (Range)</th>
<th>Primary Endpoint(S)</th>
<th>Study Reporting Status (Type of Report) / Location of Report</th>
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</thead>
</table>
| ING113674 ViiV Healthcare | 1 US          | 1 US        | Start 13 Apr 2010; Completed 06 Jul 2010; Part A: 24/24, Part B: 18/18  | To evaluate relative bioavailability study of three different tablet formulations of dolutegravir (DTG) 50 mg and effect of food on the selected formulation | Randomized, open-label, single dose, two part, three-period crossover | 18-65yrs, Healthy subjects, male / female | Part A: DTG 50 mg using current formulation; 25 mg; tablet; oral; single dose; fasting  
  DTG 50 mg using 25 mg/150 mg compression; 25 mg; tablet; oral; single dose; fasting  
  DTG 50 mg using 25 mg/200 mg compression; 25 mg; tablet; oral; single dose; fasting  
  Part B: DTG 50 mg using | Part A: 24 Enrolled, 21 Completed  
  Part B: 18 Enrolled, 18 Completed | | | | | | | | | | Plasma DTG AUC(0-∞), AUC(0-t), and Cmax | Completed Clinical Pharmacology Study Report (CPSR) 5.3.1.2 |
## Module 2.7.4 Summary of Clinical Safety

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<tr>
<th>Protocol No./ Sponsor</th>
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<th>Study Reporting Status (Type of Report) / Location of Report</th>
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<tr>
<td>ING114556</td>
<td>1 US</td>
<td>Start 21 Jun 2011; Completed 22 Aug 2011; 20/20</td>
<td>To evaluate the relative bioavailability and safety of a DTG granule formulation in healthy subjects</td>
<td>Randomized, open-label, single dose, five-period crossover</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>DTG 50 mg; tablet; oral; single dose; moderate fat meal</td>
<td>20 Enrolled, 20 Completed</td>
<td>10/10; 41.9yrs (21-61)</td>
<td>Plasma DTG AUC(0-∞), AUC(0-t), and Cmax</td>
<td>Completed CPSR 5.3.1.2</td>
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<tr>
<td>Protocol No./ Sponsor</td>
<td>No. Study Centres Location(s)</td>
<td>Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment</td>
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<td>purified water; oral; single dose</td>
<td>DTG 50 mg; granule with mineral water; oral; single dose</td>
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<td>DTG 50 mg; granule with baby formula; oral; single dose</td>
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<td>ING114581 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 06 Jun 2011; Completed 09 Aug 2011; 18/18</td>
<td>To evaluate relative bioavailability of DTG, abacavir (ABC) and lamivudine (3TC) of single dose administration of two experimental FDC tablet formulations</td>
<td>Open-label, single dose, randomized, 3-period, crossover study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>Treatment A: DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 1; tablet; oral; single dose  Treatment B: DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 2; tablet; oral; single dose  Treatment C: DTG 50 mg; (formulation code BC) plus EPZICOM; tablet; oral; single dose</td>
<td>18 Enrolled, 18 Completed</td>
<td>10/8; 29.8yrs (19-45)</td>
<td>Plasma DTG, ABC and 3TC AUC(0-∞), AUC(0-t), and Cmax</td>
<td>Completed CPSR 5.3.1.2</td>
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<td>ING111207 GSK</td>
<td>1 US</td>
<td>Start 13 Nov 2007; Completed 18 Feb 2008; 25/20</td>
<td>To assess safety, tolerability and PK of single doses of DTG</td>
<td>Double-Blind, Randomized, Placebo-Controlled</td>
<td>18-55yrs, Healthy subjects, male/ female</td>
<td>DTG 2 to 100 mg; oral suspension; single dose; fasted</td>
<td>25 Enrolled, 13 Completed</td>
<td>20/5; 31.8yrs (19-54)</td>
<td>DTG safety parameters AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and t½ following single dose</td>
<td>Completed CPSR 5.3.3.1</td>
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<td>Protocol No./ Sponsor</td>
<td>No. Study Centres Location(s)</td>
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<td>No. of Subjects by Group Entered/ Completed</td>
<td>Gender M/F; Mean Age (Range)</td>
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<td>ING111322 GSK</td>
<td>1 US</td>
<td>Start 27 Feb 2008; Completed 12 Jun 2008; Part 1: 32/32, Part 2: 12/12</td>
<td>Part 1: To assess safety, tolerability and Pharmacokinetics (PK) of repeat doses of DTG</td>
<td>Part 1: Double-Blind, Randomized, Placebo-Controlled</td>
<td>18-50yrs, Healthy subjects, male/female</td>
<td>Part 1: DTG 10 to 50 mg; oral suspension; once daily; 10 days; fasted</td>
<td>Part 1: 32* (includes 5 placebo Enrolled, 31 Completed</td>
<td>Part 1: 27/5; 31.7yrs (18-50)</td>
<td>Part 1: DTG safety parameters from predose values</td>
<td>Completed CPSR 5.3.3.1</td>
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<td>Part 2: To assess safety, tolerability and PK of single doses of DTG suspension and single doses of DTG tablets with or without food</td>
<td>Part 2: Randomized, 3-Period, Balanced, Crossover</td>
<td>DTG 10 mg x2 (20 mg); oral; single dose; fed</td>
<td>DTG 10 mg x2 (20 mg); tablet; oral; single dose; fed</td>
<td>Part 2: 12 Enrolled, 12 Completed</td>
<td>Part 2: 12/0; 30.8yrs (18-50)</td>
<td>DTG PK parameters following single dose administration on Day 1: AUC(0-∞) and AUC(0-24), Cmax, tmax, C24, t1/2, tlag, and CL/F; and (AUC(0-t), C0, Cl, Cmin, Cmax, tmax, t1/2, and CL/F on Day 10</td>
<td>DTG PK parameters following single dose administration on Day 1: AUC(0-∞) and AUC(0-24), Cmax, tmax, C24, t1/2, tlag, and CL/F; and (AUC(0-t), C0, Cl, Cmin, Cmax, tmax, t1/2, and CL/F on Day 10</td>
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<tr>
<td>ING111853</td>
<td>1 US</td>
<td>Start 17 Feb</td>
<td>To investigate the</td>
<td>Open-label,</td>
<td>DTG 20 mg; oral</td>
<td>6 Enrolled, 6</td>
<td>6/0; Percent</td>
<td>Completed</td>
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<th>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</th>
<th>No. of Subjects by Group Entered/Completed</th>
<th>Gender M/F; Mean Age (Range)</th>
<th>Primary Endpoint(S)</th>
<th>Study Reporting Status (Type of Report) / Location of Report</th>
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<tr>
<td>GSK</td>
<td>2009; Completed 21 Apr 2009; 6/6</td>
<td>recovery, excretion, and PK of 14C-DTG</td>
<td>single dose study</td>
<td>Healthy subjects, male</td>
<td>suspension; single dose; fasted</td>
<td>AUC(0-t), AUC(0-∞), Cmax, tmax, λz, tlag, and t½ of total drug-related material (radiocarbon) in blood and plasma following oral suspension [14C]-DTG dosing AUC(0-t), AUC(0-∞), Cmax, tmax, λz, tlag, CL/F, Vz/F, and t½ of DTG in plasma following oral suspension [14C]-DTG dosing</td>
<td>Completed 37.5yrs (32-46)</td>
<td>recovery of total radiocarbon in urine and faeces.</td>
<td>CPSR 5.3.3.1</td>
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## Module 2.7.4 Summary of Clinical Safety

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<th>No. of Subjects by Group Entered/ Completed</th>
<th>Gender M/F; Mean Age (Range)</th>
<th>Primary Endpoint(S)</th>
<th>Study Reporting Status (Type of Report) / Location of Report</th>
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<tbody>
<tr>
<td>ING115465</td>
<td>1 US</td>
<td>Start 30 Aug 2011; Completed 16 Apr 2012; 11/8</td>
<td>To describe DTG exposure in cervicovaginal fluid, cervical and vaginal tissue</td>
<td>Open-label, repeat dose study</td>
<td>18-35yrs, Healthy subjects, female</td>
<td>DTG 50 mg; tablet; oral; once daily; 5-7 days</td>
<td>11 Enrolled, 8 Completed</td>
<td>ITT-E: 0/8; *21yrs (18-27) *Median age</td>
<td>AUC(0-24), AUClast, AUClinf, Clast, Cmax, Tmax, and t½ for blood plasma (BP), cervicovaginal fluid (CVF), cervical tissue (CT), and vaginal tissue (VT) after dosing of DTG 50-mg tablet on the first dosing day (Day 1) and at steady-state after 5-7 days of treatment Accumulation</td>
<td>Completed CPSR 5.3.3.1</td>
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<th>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</th>
<th>No. of Subjects by Group Entered/ Completed</th>
<th>Gender M/F; Mean Age (Range)</th>
<th>Primary Endpoint(S)</th>
<th>Study Reporting Status (Type of Report) / Location of Report</th>
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<tr>
<td>ING116195</td>
<td>1 US</td>
<td>Start 14 Dec 2011; Completed 22 May 2012; 14/12</td>
<td>To describe DTG exposure in semen and rectal tissue</td>
<td>Open-label, repeat dose study</td>
<td>18-49yrs, Healthy subjects, male</td>
<td>DTG 50 mg; tablet; oral; once daily; 8 days</td>
<td>14 Enrolled, 12 Completed</td>
<td>ITT-E: 12/0; *25.5yrs (21-44) *Median age</td>
<td>AUC(0-24), AUClast, AUCinf, Clast, Cmax, tmax for blood plasma (BP), seminal fluid (SF), rectal mucosal fluid (RF), and rectal mucosal tissue (RT) after dosing of DTG 50 mg tablet on the first dosing day (Day1; PK) and at a steady-state 7 and 8 days later</td>
<td>Completed CPSR 5.3.3.1</td>
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<tr>
<td>ING113125 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 28 Jun 2011; Completed 20 April 2012; 16/16</td>
<td>To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with severe renal impairment</td>
<td>Single dose, open-label, parallel group, two-part study</td>
<td>18-70yrs, Severe renal impairment subjects and matched, healthy control subjects with normal renal function, male / female</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>Renal: 8 Enrolled, 8 Completed Healthy: 8 Enrolled, 8 Completed</td>
<td>Renal: 5/3; 56.8yrs (47-65) Healthy: 5/3; 56.1yrs (43-68)</td>
<td>Plasma DTG tlag, tmax, Cmax, AUC(0-t), AUC(0-∞), %AUCex, t½, CL/F and Vz/F</td>
<td>Completed CPSR 5.3.3.3</td>
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<tr>
<td>ING113097 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 19 Nov 2010; Completed 04 Jun 2011; 16/16</td>
<td>To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with mild or moderate hepatic impairment based on Child-Pugh category</td>
<td>Single dose, open-label, parallel group, two-part, adaptive study</td>
<td>18-70yrs, Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function, male / female</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>Hepatic Impaired: 8 Enrolled, 8 Completed Healthy Controls: 8 Enrolled, 8 Completed</td>
<td>Hepatic Impaired: 5/3; 55.5yrs (50-61) Healthy Controls: 5/3; 57.0yrs (42-67)</td>
<td>Plasma DTG AUC(0-τ), AUC(0-∞), Cmax, C24, apparent t½, apparent clearance (CL/F), and Vz/F</td>
<td>Completed CPSR 5.3.3.3</td>
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<tr>
<td>ING115381 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 20 Apr 2011; Completed 27 May 2011; 10/10</td>
<td>To assess safety, tolerability and PK of single doses of DTG in healthy Japanese subjects</td>
<td>Open label, single dose study</td>
<td>20-55yrs, Healthy Japanese subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>10 Enrolled, 10 Completed</td>
<td>6/4; 33.4yrs (22-52)</td>
<td>Plasma DTG following single dose administration: AUC(0-τ), AUC(0-∞), Cmax, and C24</td>
<td>Completed CPSR 5.3.3.3</td>
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<td><strong>Extrinsic Factor PK Study Reports</strong></td>
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<td>ING113099 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 13 May 2011; Completed 28 Nov 2011; 27/24</td>
<td>To assess the potential for a drug interaction between DTG and rifampin (RIF) and between DTG and</td>
<td>Randomized, open-label, two-period, single-sequence, two cohort</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily; 7 days. DTG 50 mg; tablet; oral; BID; 7</td>
<td>Arm 1: 12 Enrolled, 11 Completed Arm 2:</td>
<td>ITT-E: 19/7; 44.7yrs (26-59)</td>
<td>Plasma DTG Cτ, Cmax, and AUC(0-τ), and AUC(0-24) for comparison between once</td>
<td>Completed CPSR 5.3.3.4</td>
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<td>rifabutin (RIFABUT) study</td>
<td>days then DTG 50 mg; tablet; oral; BID + RIF 600 mg; capsule; oral; once daily; 14 days DTG 50 mg; tablet; oral; once daily for 7 days then DTG 50 mg; tablet; oral BID+ RIFABUT 300 mg; capsule; oral; once daily; 14 days</td>
<td>14 Enrolled, 9 Completed</td>
<td>daily and twice daily regimens only</td>
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<tr>
<td>ING115696 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 01 Sep 2011; Completed 17 Oct 2011; 12/12</td>
<td>To investigate the effects of prednisone on the steady-state PK of DTG</td>
<td>Open-label, repeat dose, two-period, single-sequence</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days</td>
<td>DTG 50 mg; tablet; oral; once daily; Days 1-10 + prednisone; tablet; oral; once daily (60 mg Days 1-5; 50 mg Day 6; 40 mg Day 7; 30 mg Day 8; 20 mg Day 9; 10 mg Day 10)</td>
<td>12 Enrolled, 12 Completed</td>
<td>5/7; 28.5yrs (23-38)</td>
<td>DTG PK parameters on Day 5 and Day 10: AUC(0-τ), Cmax, C0, Cτ, Cmin, CL/F, and t½</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
<td>ING115697 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 13 Mar 2012; Completed 23 May 2012; 32/32</td>
<td>To assess the potential for a drug interaction between DTG and telaprevir (TLV) and between DTG and bocepravir (BCV)</td>
<td>Randomized, open-label, two-period, single-sequence, two cohort study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days</td>
<td>DTG 50 mg; tablet; oral; once daily; Days 1-10 + TLV 750 mg; tablet; oral; q8h; 10 days</td>
<td>DTG + BCV 16 Enrolled, 13 Completed</td>
<td>DTG + TLV 16 Enrolled, 15 Completed</td>
<td>Plasma steady-state DTG AUC(0-τ), Cmax, Cmin, Cτ, following administration of DTG 50 mg once daily (q24h) for 5 days and following co-administration with BCV 800 mg q8h for 10 days or TVR</td>
<td>Completed CPSR 5.3.3.4</td>
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<td>Protocol No./Sponsor</td>
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<td>750 mg q8h for 10 days</td>
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<tr>
<td>ING115698 Viiv Healthcare</td>
<td>1 Canada</td>
<td>Start 02 Dec 2011; Completed 30 Dec 2011; 11/12</td>
<td>To assess the potential for a drug interaction between DTG and methadone</td>
<td>Open-label, repeat dose, two-period, single-sequence</td>
<td>18-65yrs, Healthy subjects enrolled in a methadone maintenance program, male / female</td>
<td>Stable methadone dose; oral solution; once daily; 3 days</td>
<td>Stable methadone dose; oral solution + DTG 50 mg; tablet; oral; BID; 5 days</td>
<td>11 Enrolled, 10 Completed</td>
<td>6/5; 34.5yrs (24-44)</td>
<td>Steady-state total and R-Methadone PK parameters: AUC(0-τ), Cmax, and Cτ</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
<td>ING111405 GSK</td>
<td>1 US</td>
<td>Start 09 Oct 2008; Completed 12 Dec 2008; 31/30</td>
<td>To assess the potential for a drug interaction between DTG and lopinavir (LPV)/ritonavir (RTV) and between DTG and darunavir (DRV)/RTV</td>
<td>Randomized, open-label, two-period, single-sequence, two cohort study</td>
<td>18-50yrs, Healthy subjects, male / female</td>
<td>DTG 30 mg; tablet; oral; once daily; 5 days</td>
<td>DTG 30 mg; tablet; oral; once daily + LPV/RTV 400/100 mg; tablet; oral; q12h; 14 days</td>
<td>31 Enrolled, 30 Completed</td>
<td>31/0; 29.4yrs (18-50)</td>
<td>Plasma DTG steady-state AUC(0-τ), Cmax, Cr, Cmin, CL/F, t1/2 and t1/2 following administration of DTG 30 mg q24h for 5 days and following co-administration with LPV/RTV 400/100 mg q12h or DRV/RTV 600/100 mg q12h for 14 days</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
<td>ING111602 GSK</td>
<td>1 US</td>
<td>Start 07 Jan 2009;</td>
<td>To assess the potential for a drug interaction between DTG and lopinavir (LPV)/ritonavir (RTV) and between DTG and darunavir (DRV)/RTV</td>
<td>Open-label, single dose,</td>
<td>18-65yrs, Healthy</td>
<td>DTG 50 mg; tablet; oral; single</td>
<td>16 Enrolled, 16</td>
<td>16/0; 30.8yrs</td>
<td>Single dose plasma DTG</td>
<td>Completed CPSR</td>
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<tr>
<td>ING111603 GSK</td>
<td>1 US</td>
<td></td>
<td>Completed 05 Mar 2009; 16/16</td>
<td>drug interaction between DTG and multivitamin and between DTG and Maalox</td>
<td>randomized, four-period crossover study</td>
<td>subjects, male/female</td>
<td>dose DTG 50 mg; tablet; oral; single dose + multivitamin; tablet; oral; single dose DTG 50 mg; tablet; oral; single dose + Maalox Advanced Maximum Strength 20mL suspension; single dose DTG 50 mg; tablet; oral; single dose 2 hrs prior to Maalox Advanced Maximum Strength 20mL; suspension; single dose DTG 50 mg; tablet; oral; single dose</td>
<td>Completed</td>
<td>(18-53)</td>
<td></td>
<td>AUC(0-∞), Cmax, and C24 CPSR 5.3.3.4</td>
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**Completed 05 Mar 2009; 16/16**

**MTG 50 mg; tablet; oral; single dose + multivitamin; tablet; oral; single dose MTG 50 mg; tablet; oral; single dose + Maalox Advanced Maximum Strength 20mL suspension; single dose MTG 50 mg; tablet; oral; single dose 2 hrs prior to Maalox Advanced Maximum Strength 20mL; suspension; single dose MTG 50 mg; tablet; oral; single dose**

**Completed (18-53)**

**AUC(0-∞), Cmax, and C24 CPSR 5.3.3.4**
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<td>DTG 50 mg; tablet; oral; once daily + ETR 200 mg; tablet; oral; q12h; 14 days</td>
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<td>CL/F, t½ following administration of DTG 50 mg q24h for 5 days and following co-administration with ETR 200 mg q12h for 14 days</td>
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<td>ING111604 GSK</td>
<td>1 US</td>
<td>Start 11 Aug 2008; Completed 01 Oct 2008; 16/16</td>
<td>To assess the potential for a drug interaction between DTG and tenofovir (TDF)</td>
<td>Open-label, repeat-dose, single-sequence, three-period study</td>
<td>female</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days</td>
<td>TDF 300 mg; tablet; oral; once daily; 7 days</td>
<td>16 Enrolled, 15 Completed</td>
<td>15/1; 38.6yrs (20-58)</td>
<td>Plasma DTG steady-state AUC[0-τ], Cmax and Cτ following administration of DTG 50 mg q24h for 5 days and following co-administration with TDF 300 mg q24h for 5 days</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
<td>ING111854 GSK</td>
<td>1 US</td>
<td>Start 07 Apr 2009; Completed 09 Jun 2009; 24/24</td>
<td>To assess the potential for a drug interaction between DTG and atazanavir (ATV) and between DTG</td>
<td>Randomized, open-label, repeat dose, two-period, single-sequence,</td>
<td>18-65yrs, Healthy subjects, male/ female</td>
<td>Period 1: DTG 30 mg; tablet; oral; once daily; 5 days; fed</td>
<td>Period 2: DTG 30 mg; tablet; oral; once daily; 5 days</td>
<td>24 Enrolled, 24 Completed</td>
<td>21/3; 37.2yrs (18-61)</td>
<td>Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
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|                     |                               | and ATV/RTV                                                                | two-cohort study | DTG 30 mg; tablet; oral; once daily + ATV/RTV 300/100 mg; capsule; once daily; 14 days  
DTG 30 mg; tablet; oral; once daily + ATV 400 mg; capsule; oral; once daily; 14 days | administration of DTG 30 mg q24h for 5 days and following co-administration with ATV/RTV 300/100 mg q24h or ATV 400 mg q24h for 14 days |
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<th>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</th>
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<td>ING111855 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 13 Dec 2011; Completed 28 Mar 2012; 16/16</td>
<td>To assess the potential for a drug interaction between DTG and oral contraceptives (ethinyl estradiol [EE] /norgestimate [NGM])</td>
<td>Randomized, two-period, double-blind study</td>
<td>18-40yrs, Healthy subjects, female</td>
<td>DTG 50 mg or placebo; oral; tablet; once daily days 1-11 and DTG 50 mg or placebo; tablet; oral; once daily days 12-21 EE / NGM; tablet; oral; once daily days 1-21</td>
<td>16 Enrolled, 15 Completed</td>
<td>0/16; 31.1yrs (20-40)</td>
<td>AUC[0-τ] of Norelgestromin and EE after Ortho-Cyclen alone and after Ortho-Cyclen with DTG</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
<td>ING112934 GSK</td>
<td>1 US</td>
<td>Start 02 Apr 2009; Completed 20 May 2009; 17/18</td>
<td>To assess the potential for a drug interaction between DTG, ETR, and LPV/RTV or DRV/RTV</td>
<td>Randomized, open-label, repeat dose, three-period, single-sequence, two-cohort adaptive study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + ETR/LPV/RTV 200/400/100 mg; tablet; oral; q12h; 14 days DTG 50 mg; tablet; oral; once daily + ETR (tablet) DRV (tablet) /RTV (capsule)</td>
<td>17 Enrolled, 17 Completed</td>
<td>17/0; 37.6yrs (20 -61)</td>
<td>Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cr, and Cmin following administration of DTG 50 mg q24h for 5 days, and following co-administration of DTG 50 mg q24h (and 50 mg q12h if appropriate) with ETR/LPV/RTV 200/400/100 mg</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
<td>ING112941 GSK</td>
<td>1 US</td>
<td>Start 23 Jul 2009; Completed 28 Sep 2009; Part 1: 14/14, Part 2: 10/10</td>
<td>To evaluate the effect of a high fat meal and omeprazole on DTG PK and to evaluate the safety and PK of a 250 mg dose of DTG</td>
<td>Part 1: Randomized, open-label, two sequence, three treatment crossover Part 2: Randomized, double-blind, single dose PK study</td>
<td>18-65yrs, healthy subjects, male / female</td>
<td>200/600/100 mg; oral; once daily; 14 days</td>
<td>Part 1: 14 Enrolled, 12 Completed Part 2: 10 Enrolled (includes 2 placebo), 10 Completed</td>
<td>Part 1: 12/2; 40.6yrs (23-55) Part 2: 9/1; 38.4yrs (21-54)</td>
<td>Plasma DTG following a single dose of 50 mg under fasted conditions with and without OMP 40 mg: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, tlag Plasma DTG following a single dose of 50 mg under fasted conditions and with a high-fat meal: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and tlag</td>
<td>Completed CPSR 5.3.3.4</td>
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<td>ING113068 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 09 Sep 2010; Completed 04 Nov 2010; Part A: 12/12, Part B: 15/15</td>
<td>To investigate the effects of fosamprenavir (FPV)/ RTV on the steady-state PK of DTG and to evaluate relative bioavailability of tablets with varying particle size</td>
<td>Part A: Open-label, repeat dose, two-period, single-sequence&lt;br&gt;Part B: Open-label, single dose, randomized, three-period, cross over study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>Part A: DTG 50 mg; tablet; oral; once daily; 5 days&lt;br&gt;DTG 50 mg; tablet; oral; once daily + FPV 700 mg; tablet / RTV 100 mg; capsule; oral; q12h; 10 days&lt;br&gt;Part B:</td>
<td>Part A: 12 Enrolled 12, Completed&lt;br&gt;Part B: 15 Enrolled, 15 Completed</td>
<td>Part A: 10/2; 33.4yrs (24-55)&lt;br&gt;Part B: 4/11; 34.7yrs (20-60)</td>
<td>Plasma DTG following a single dose of 250 mg under fasted conditions: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and tlag&lt;br&gt;Safety and tolerability parameters following a single dose of DTG 250 mg</td>
<td>Completed CPSR 5.3.3.4</td>
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<td>DTG 50 mg using 25 mg tablets with micronized drug substance; oral; single dose</td>
<td>DTG 50 mg using 25 mg tablets with unmicronized drug substance; oral; single dose</td>
<td>DTG 50 mg using 25 mg tablets with intermediate particle size drug substance; oral; single dose</td>
<td>q12h for 10 days Part B: Plasma DTG AUC(0-∞), AUC(0-t), and Cmax following a single dose of DTG 50 mg</td>
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<td>ING113096 GSK</td>
<td>1 US</td>
<td>Start 15 Feb 2010; Completed 05 Apr 2010; 18/18</td>
<td>To assess the safety, tolerability and PK of repeat dose co-administration of DTG alone, tipranavir (TPV)/RTV alone, and DTG in combination with TPV/RTV</td>
<td>Randomized, open-label, repeat dose, three-period single-sequence, study</td>
<td>18-55yrs, Healthy subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days</td>
<td>TPV / RTV 500/200 mg; capsule; oral; BID; 7 days DTG 50 mg; tablet; oral; once daily and TPV / RTV 500/200 mg; capsule; oral; BID; 5 days</td>
<td>18 Enrolled, 13 Completed</td>
<td>14/4; 29.3yrs (19-45)</td>
<td>Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg once daily for 5 days and following co-administration with TPV/RTV 500/200 mg BID for 5 days</td>
<td>Completed CPSR 5.3.3.4</td>
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<tr>
<td>ING114005 Viiv Healthcare</td>
<td>1 US</td>
<td>Start 16 Mar 2010; Completed 26 May 2010; 12/12</td>
<td>To evaluate PK of DTG 100 mg versus 50 mg and the effect of efavirenz (EFV) on the PK, safety and tolerability of DTG 50 mg</td>
<td>Open label, repeat dose, three period single-sequence</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>DTG 100 mg; tablet; oral; single dose DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily in AM + EFV 600 mg; tablet; oral; once daily in PM; 14 days</td>
<td>DTG 50 mg; tablet; oral; once daily and TPV / RTV 500/200 mg; capsule; oral; BID; 5 days</td>
<td>12 Enrolled, 12 Completed</td>
<td>12/0; 38.7yrs (20-65)</td>
<td>Plasma DTG AUC(0-24), Cmax, and C24, and dose-normalized AUC(0-24), Cmax, and C24 following single dose administration of 100 mg and 50 mg</td>
<td>Completed CPSR 5.3.3.4</td>
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<td>S.7.4</td>
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<td>steady-state AUC(0-τ), Cmax, C0, Ct, and Cmin following administration of DTG 50 mg q24h for 5 days and following co-administration with EFV 600 mg q24h for 14 days</td>
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### Module 2.7.4 Summary of Clinical Safety

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<tbody>
<tr>
<td>LAI116181 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 07 Nov 2011; Completed 20 Feb 2012; Cohort 1: 16/16, Cohort 2: 12/12</td>
<td>To assess the potential for a drug interaction between DTG and rilpivirine (RPV)</td>
<td>Open label, repeat dose, single-sequence, 3-period study</td>
<td>18-55yrs Healthy subjects, male / female</td>
<td>Cohort 1: Treatment A = DTG 50 mg; tablet; oral; q24h; 5 days Treatment B = RPV 25 mg; tablet; oral; q24h; 11 days Treatment C = RPV 25 mg; tablet; oral; q24h + DTG 50 mg; tablet; oral; q24h; 5 days Cohort 2: Treatment D = GSK1265744 30 mg; tablet; oral; q24h;12 days Treatment B = RPV 25 mg; tablet; oral; q24h; 12 days Treatment E =</td>
<td>Cohort 1: 16 Enrolled, 16 Completed Cohort 2: 12 Enrolled, 11 Completed</td>
<td>24/4; 31.4yrs (18-50)</td>
<td>Plasma DTG AUC(0-τ), Cmax, and Cr, following 50 mg q24h administration with and without RPV 25 mg q24h Plasma GSK1265744 steady-state AUC(0-τ), Cmax, tmax, and Cr following GSK1265744 30 mg q24h administration with and without RPV 25 mg q24h Plasma RPV steady-state AUC(0-τ), Cmax, tmax, and Cr following RPV 25 mg</td>
<td>Completed CPSR 5.3.4.4</td>
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<tr>
<td>ING111856 GSK</td>
<td>1 US</td>
<td>Start 28 Sep 2009; Completed 29 Dec 2009; 42/42</td>
<td>To evaluate the effect of DTG on cardiac conduction as assessed by 12-lead electrocardiogram compared to placebo and moxifloxacin (Thorough QTc study of DTG)</td>
<td>Randomized, partial-blind, single dose, three-period, cross-over study</td>
<td>18-55yrs, Healthy subjects, male / female</td>
<td>RPV 25 mg; tablet; oral; q24h + GSK1265744 30 mg; tablet; oral; q24h; 12 days</td>
<td>q24h administration with and without DTG 50 mg q24h or GSK1265744 30 mg q24h</td>
<td>q24h</td>
<td>CPSR 5.3.4.1</td>
<td></td>
</tr>
<tr>
<td>ING114819 ViiV Healthcare</td>
<td>1 US</td>
<td>Start 05 Oct 2010; Completed 03 Dec 2010; 38/36</td>
<td>To evaluate the effect of DTG on glomerular filtration rate as measured by iohexol and to evaluate creatinine clearance, extraglomerular</td>
<td>Open-label, randomized, three-arm, parallel, placebo-controlled</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily; 14 days DTG 50 mg; tablet; oral; q12h; 14 days Placebo; tablet; oral; once daily;</td>
<td>GFR as measured by iohexol plasma clearance at Days -1, 7, and 14</td>
<td>Completed CPSR 5.3.4.1</td>
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<tr>
<td>ING111521 GSK</td>
<td>14 US</td>
<td>Start 25 Jun 2008; Completed 26 Aug 2008; 35/30</td>
<td>Creatinine excretion, and renal plasma flow</td>
<td></td>
<td>14 days</td>
<td>Omnipaque 300 (647 mg/ml of iohexol) 5 ml; solution; IV</td>
<td>35 Enrolled (including 7 placebo) 35, Completed 35/0; 38.4yrs (20-55)</td>
<td>Change from baseline in plasma HIV-1 RNA to Day 11 DTG following dose on Day 1: AUC(0-∞), AUC(0-24), Cmax, tmax, C24, t½, tlag, and CL/F; and following last repeat dose on</td>
<td>Completed CPSR 5.3.4.2</td>
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- **Patient PD and PK/PD Study Reports**

  - **ING111521 GSK**
    - **Study Objectives**: To assess the safety, tolerability and efficacy of repeat dose DTG
    - **Study Design**: Dose-ranging, 10-day, repeat dose, placebo-controlled monotherapy study
    - **Diagnosis; Key Inclusion Criteria**: 18-65yrs, HIV-infected subjects, male/female
    - **Treatment Details**: DTG 2, 10, 50 mg tablet; oral; once daily; 10 days; fasted
    - **No. of Subjects by Group Entered/ Completed**: 35 Enrolled (including 7 placebo) 35, Completed
    - **Gender M/F; Mean Age (Range)**: 35/0; 38.4yrs (20-55)
    - **Primary Endpoint(S)**: Change from baseline in plasma HIV-1 RNA to Day 11 DTG following dose on Day 1: AUC(0-∞), AUC(0-24), Cmax, tmax, C24, t½, tlag, and CL/F; and following last repeat dose on
    - **Study Reporting Status (Type of Report) / Location of Report**: Completed CPSR 5.3.4.2
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<tr>
<td>ING116070 ViiV Healthcare</td>
<td>3 US</td>
<td>Start 24 Jan 2012; Ongoing; 14/14</td>
<td>To determine plasma (total and unbound) DTG concentration and evaluate the relationship between DTG concentration in plasma and CSF</td>
<td>Phase IIIb single-arm, open-label, multicenter study</td>
<td>≥18yrs, HIV-infected, ART-naïve subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily + ABC/3TC 600/300 mg; tablet; oral; once daily; 96 weeks</td>
<td>14 Enrolled, 13 Ongoing</td>
<td>ITT-E: 13/0; 40.2yrs (28-52)</td>
<td>Proportion of subjects with plasma HIV-1 RNA &lt;50 c/mL over time; Absolute values and change from Baseline in plasma HIV-1 RNA over time; Absolute values and changes from Baseline in CD4+ and CD8+ T cell counts overtime Incidence of disease</td>
<td>Completed Week 2 Synoptic Clinical Study Report (CSR) 5.3.4.2</td>
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<tr>
<td>ING112276</td>
<td>34 centres: 6 France, 4 Germany, 3 Russia, 4 Italy, 5 Spain, 12 US</td>
<td>Start 30 Jul 2009; Ongoing; 205/200</td>
<td>To select a once daily oral dose of DTG administered with either ABC/3TC or TDF/ emtricitabine (FTC) and to evaluate antiviral activity, safety and PK over time</td>
<td>Phase IIb, Randomized, multicentre, parallel group, dose-ranging</td>
<td>≥18yrs, HIV-infected, ART-naive subjects, male / female</td>
<td>DTG 10 mg; tablet; oral + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; tablet; oral; once daily; 96 weeks</td>
<td>DTG 10 mg: 53 Randomized, 47 Completed DTG 25 mg: 51 Randomized, 45 Completed DTG 50 mg: 51 Randomized, 46 Completed EFV 600 mg: 50 Randomized, 39 Completed DTG 50 mg</td>
<td>177/28; 37.2yrs (20-79)</td>
<td>Proportion of subjects with HIV-1 RNA &lt;50 c/mL (c/mL) through Week 16 using the Time to Loss of Virological Response (TLOVR) algorithm. Dose selection will be based primarily on antiviral activity and tolerability in conjunction with immunologic, safety and PK measures will also be considered</td>
<td>Completed: (Week 16 Synoptic CSR) (Week 24 Full CSR) (Week 48 Abbreviate d CSR) (Week 96 Full CSR)</td>
<td>5.3.5.1</td>
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### Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication
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<tr>
<td>ING113086 ViiV Healthcare</td>
<td>100 centres: 27 Spain 19 US, 12 France, 11 Russia, 10 Germany, 7 Canada, 7 Italy, 4 Australia, 3 UK</td>
<td>Start 19 Oct 2010; Ongoing; 822/788</td>
<td>To assess safety and efficacy of DTG 50 mg once daily to RAL 400 mg BID both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy</td>
<td>Phase III, multicentre randomized, double blind, double-dummy, active-controlled, parallel group, fully-powered non-inferiority study</td>
<td>≥18yrs, HIV-infected, ART-naïve subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily or RAL 400 mg; tablet; oral; once daily + ABC/3TC 600 mg/300 mg or TDF/ FTC 300 mg/200 mg; tablet; oral; once daily; 96 weeks</td>
<td>DTG: 411 Randomized, 359 Ongoing. RAL: 411 Randomized, 345 Ongoing</td>
<td>703/119; 37.0yrs (18-75)</td>
<td>The proportion of subjects with HIV-1 RNA &lt;50 c/mL through Week 48 using a Missing, Switch or Discontinuation = Failure (MSDF) algorithm</td>
<td>Completed: Week 48 Full CSR 5.3.5.1</td>
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<tr>
<td>ING114467 ViiV Healthcare</td>
<td>136 centres: 4 Australia, 4 Belgium, 10 Canada, 1 Denmark, 6 France, 10 Germany,</td>
<td>Start 01 Feb 2011; Ongoing; 833/800</td>
<td>To assess safety and efficacy of DTG plus ABC/3TC fixed-dose combination therapy administered once</td>
<td>Phase III, randomized, double-blind, double-dummy, active-controlled,</td>
<td>≥18yrs, HIV-infected, ART-naïve subjects, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily + ABC/3TC 600 mg/300 mg; tablet; oral; once daily; 96 weeks</td>
<td>DTG: 414 Randomized, 363 Ongoing. EFV/TDF/FTC:</td>
<td>703/130; 36.4yrs (18-85)</td>
<td>The proportion of subjects with plasma HIV-1 RNA &lt;50 c/mL through Week 48 using MSDF as codified by</td>
<td>Completed: Week 48 Full CSR 5.3.5.1</td>
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<tr>
<td>Protocol No./Sponsor</td>
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<td>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</td>
<td>No. of Subjects by Group Entered/Completed</td>
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<tr>
<td>ING111762 ViiV Healthcare</td>
<td>185 centres: 4 Belgium, 12 France, 4 Greece, 1 Hungary, 7 Italy, 2 Netherlands, 3 Romania, 24 Spain, 4 UK, 6 Canada, 72 USA, 6 Argentina, 2 Australia, 9 Brazil, 5 Chile, 4 Mexico, 12 Russia, 3 South Africa, 5 Taiwan</td>
<td>Start 26 Oct 2010; Ongoing; 719/688</td>
<td>To evaluate safety and efficacy of DTG 50 mg once daily vs. raltegravir (RAL) 400 mg BID, both administered with an investigator-selected background regimen</td>
<td>Phase 3, multicentre randomized, double-blind, active-controlled, parallel group, non-inferiority study</td>
<td>≥18yrs, HIV-infected, ART-experienced subjects, integrase inhibitor naive regimen, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily or RAL 400 mg; tablet; oral; BID + Investigator-selected background regimen; 48 weeks</td>
<td>DTG 354 Randomized 305 Ongoing 1 Completed RAL 361 Randomized 189 Ongoing 111 Completed</td>
<td>485/230; 42.5yrs (18-73)</td>
<td>Completed: Week 24 Full CSR 5.3.5.1</td>
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<tr>
<td>ING112961</td>
<td>16 centres:</td>
<td>Start 31 Aug</td>
<td>To assess the</td>
<td>≥18yrs, Cohort I: Cohort I: Cohort I:</td>
<td>The proportion of subjects with HIV-1 RNA &lt;50 c/mL through Week 48 using MDF algorithm as codified by the FDA’s ‘snapshot algorithm. The proportion of subjects with plasma HIV-1 RNA &lt;50 c/mL will also be assessed at Week 24</td>
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<tr>
<td>ViiV Healthcare</td>
<td>7 France, 1 Italy, 1 Spain, 6 US 1 Canada</td>
<td>2009; Ongoing; Cohort I: 27/30, Cohort II: 24/50</td>
<td>antiviral activity of DTG containing regimen</td>
<td>multicentre, open-label, single-arm, sequential cohort, pilot study</td>
<td>HIV-infected, ART-experienced subjects, raltegravir resistance, male / female</td>
<td>DTG 50 mg; tablet; oral; once daily; 96 weeks</td>
<td>27 Randomized, 12 Ongoing</td>
<td>25/2; 46.7yrs (19-61)</td>
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<td>(Week 24 Cohort I Full CSR)</td>
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<td></td>
<td>Cohort II: DTG 50 mg; tablet; oral; BID; 48 weeks</td>
<td>183/175</td>
<td>141/42; 47.0yrs (19-67)</td>
<td>Mean change from baseline in plasma HIV-1 RNA (log_{10} c/mL) at Day 8</td>
<td>Completed: Week 24 Full CSR 5.3.5.2</td>
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<tr>
<td>ING112574 ViiV Healthcare</td>
<td>78 centres: 1 Belgium, 3 Canada, 15 France, 6 Italy, 4 Portugal, 8 Spain, 41 US</td>
<td>Start 6 May 2011; Ongoing; 183/175</td>
<td>To assess the antiviral activity of DTG administered with failing background therapy to Day 8 and thereafter with optimized background ART</td>
<td>Phase III, multicentre, single-arm, open-label study</td>
<td>≥18yrs, HIV-infected, ART-experienced subjects, integrase inhibitor regimen, male / female</td>
<td>DTG 50 mg; tablet; oral; BID; 24 weeks</td>
<td>183 Randomized, 155 Ongoing</td>
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<td>(Week 96 Cohort I/ Week 48 Cohort II Abbreviated CSR) 5.3.5.2</td>
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<th>Study Design</th>
<th>Diagnosis; Key Inclusion Criteria</th>
<th>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</th>
<th>No. of Subjects by Group Entered/ Completed</th>
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<th>Primary Endpoint(S)</th>
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<tr>
<td>ING112578</td>
<td>1 US</td>
<td>Start 16 March 2011; Ongoing; 22/168</td>
<td>To select a DTG dose for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG adult dose selected from the Phase IIb clinical trial in ART-naive adult subjects (ING112276), to evaluate safety, tolerability, and steady-state PK of DTG in combination with other ARTs</td>
<td>Phase II/III, multicenter, open-label, non-comparative intensive PK study</td>
<td>≥6wks-&lt;18yrs, HIV-1 infected subjects, male / female</td>
<td>DTG once-a-day doses with target dose of ~1 mg/kg and with 4 weight bands, and maximum dose of 50 mg; 48 weeks</td>
<td>Cohort 1 (Stage 1): 10 Enrolled, 10 Ongoing; Cohort 1 (Stage 2): 12 Enrolled, 12 Ongoing</td>
<td>Cohort 1: (Stage 1) 3/7; 14.0yrs (12–17) Cohort 1: (Stage 2): no data available</td>
<td>Toxicity through week 24 All AEs or lab toxicities of Grade 3 or higher severity Judged to be at least possibly attributable to the study medication Termination from treatment due to a suspected adverse drug reaction (SADR) Death PK: AUC(0-24)</td>
<td>Completed: Week 24 Full CSR (10 subjects [Stage 1] from Cohort 1 through 24 weeks)</td>
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### Reports of Analyses of Data from More Than One Study

| ING116265 | NA | NA | To evaluate the effects of UGT | Meta-analysis of Healthy adult | DTG 50 mg; tablet; oral; once | 89 subjects included in | 78/11; 36.9yrs | NA | Completed: Meta- |

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Module 2.7.4 Summary of Clinical Safety
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<th>Study Reporting Status (Type of Report) / Location of Report</th>
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<tr>
<td>Healthcare</td>
<td>65 centres: 32 US, 3 Puerto Rico, 6 France, 3 Germany, 5 Italy, 5 Spain, 3 Switzerland, 3 Romania, 5 Russia</td>
<td>Start 31 Oct 2011; Ongoing; 483/468</td>
<td>To demonstrate the non-inferior antiviral activity of DTG compared to DRV/RTV</td>
<td>and CYP polymorphisms on the PK of DTG</td>
<td>PGx and PK data from 9 Phase II studies</td>
<td>subjects daily; 5 days</td>
<td>the analysis (19-64)</td>
<td>analysis Report 5.3.5.3</td>
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<tr>
<td><strong>Other Clinical Studies</strong></td>
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<tr>
<td>ING114915 ViiV Healthcare</td>
<td>65 centres: 32 US, 3 Puerto Rico, 6 France, 3 Germany, 5 Italy, 5 Spain, 3 Switzerland, 3 Romania, 5 Russia</td>
<td>Start 31 Oct 2011; Ongoing; 483/468</td>
<td>To demonstrate the non-inferior antiviral activity of DTG compared to DRV/RTV</td>
<td>and CYP polymorphisms on the PK of DTG</td>
<td>PGx and PK data from 9 Phase II studies</td>
<td>subjects daily; 5 days</td>
<td>the analysis (19-64)</td>
<td>analysis Report 5.3.5.3</td>
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<tr>
<td>ING114916 ViiV Healthcare</td>
<td>Centres in US, Canada</td>
<td>Planned Start 2011; Ongoing; 0/1000</td>
<td>To provide access to patients who have documented RAL or ELV resistance, who have limited treatment options and who require DTG to construct a viable ARV regimen for therapy</td>
<td>and CYP polymorphisms on the PK of DTG</td>
<td>PGx and PK data from 9 Phase II studies</td>
<td>subjects daily; 5 days</td>
<td>the analysis (19-64)</td>
<td>analysis Report 5.3.5.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING115502 Independent</td>
<td>37 centres: 6 US, 4 Australia, 3</td>
<td>Start 27 Jun 2011; Ongoing; 50 Enrolled; 50 Ongoing</td>
<td>To provide a mechanism to supply DTG on an as needed basis to drug-experienced patients</td>
<td>and CYP polymorphisms on the PK of DTG</td>
<td>PGx and PK data from 9 Phase II studies</td>
<td>subjects daily; 5 days</td>
<td>the analysis (19-64)</td>
<td>analysis Report 5.3.5.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Module 2.7.4 Summary of Clinical Safety

<table>
<thead>
<tr>
<th>Protocol No./ Sponsor</th>
<th>No. Study Centres/ Location(s)</th>
<th>Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment</th>
<th>Study Objectives</th>
<th>Study Design</th>
<th>Diagnosis; Key Inclusion Criteria</th>
<th>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</th>
<th>No. of Subjects by Group Entered/ Completed</th>
<th>Gender M/F; Mean Age (Range)</th>
<th>Primary Endpoint(S)</th>
<th>Study Reporting Status (Type of Report) / Location of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians/ Investigators (ViiV supported)</td>
<td>Brazil, 2 Canada, 11 France, 3 Italy, 1 Netherlands, 3 Spain, 4 UK</td>
<td>50/50</td>
<td>individual named patient basis for treatment of individuals with integrase resistance who have no available treatment alternatives and/or limited treatment options</td>
<td>subjects, male / female</td>
<td>≥18yrs, HIV-infected, ART-experience d subjects, integrase inhibitor regimen, male / female</td>
<td>DTG 50 mg; tablet; oral; BID or Placebo; tablet oral; BID + current failing regimen; 7 days</td>
<td>4 Randomized; 4 Ongoing</td>
<td>No data available</td>
<td>The mean change from baseline in plasma HIV-1 RNA (log₁₀ c/mL) at Day 8, using a last observation carried forward with discontinuation equals baseline</td>
<td>Completed: Brief Study Summary 5.3.5.4</td>
</tr>
<tr>
<td>ING116529 ViiV Healthcare</td>
<td>26 US</td>
<td>Start 18 Apr 2012; Ongoing; 4/30</td>
<td>To quantify the antiviral activity of DTG compared to placebo (PCB) when administered with failing background therapy for 7 days</td>
<td>Phase III, randomized, multicentre, placebo-controlled, double-blind followed by an open label phase</td>
<td>≥18yrs, ART-experienced subjects, integrase inhibitor regimen, male / female</td>
<td>DTG 50 mg; tablet; oral; BID or Placebo; tablet oral; BID + current failing regimen; 7 days</td>
<td>4 Randomized; 4 Ongoing</td>
<td>No data available</td>
<td>Plasma DTG, ABC and 3TC AUC(0-∞), AUC(0-t), and Cmax</td>
<td>Completed: Brief Study Summary 5.3.5.4</td>
</tr>
<tr>
<td>ING114580 ViiV Healthcare</td>
<td>1 US</td>
<td>Planned Start; Ongoing; 0/66</td>
<td>To evaluate the bioequivalence between a single FDC tablet formulation of DTG 50 mg, ABC 600 mg and 3TC</td>
<td>Phase I, randomized, two part, open-label, crossover, single center study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>Part A: Treatment A = DTG 50 mg/ABC 600 mg/3TC 300 mg; FDC tablet; oral; single dose; fasted</td>
<td>0/0</td>
<td>No data available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Module 2.7.4 Summary of Clinical Safety**

<table>
<thead>
<tr>
<th>Protocol No./ Sponsor</th>
<th>No. Study Centres Location(s)</th>
<th>Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment</th>
<th>Study Objectives</th>
<th>Study Design</th>
<th>Diagnosis; Key Inclusion Criteria</th>
<th>Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)</th>
<th>No. of Subjects by Group Entered/ Completed</th>
<th>Gender M/F; Mean Age (Range)</th>
<th>Primary Endpoint(S)</th>
<th>Study Reporting Status (Type of Report) / Location of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus EPZICOM</td>
<td></td>
<td></td>
<td>Treatment B = DTG 50 mg + plus EPZICOM; tablet; oral; single dose; fasted</td>
<td>Part B: Treatment C = DTG 50 mg/ABC 600 mg/3TC 300 mg; FDC tablet; oral; single dose; high fat meal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# 9.2. APPENDIX 2: Tabular Description of Extent of Exposure

## Appendix Table 2  Summary of Extent of Exposure by Study and Overall in Phase IIb and Phase III Clinical Trials

<table>
<thead>
<tr>
<th>Exposure (weeks), n (%)</th>
<th>ART-Naive</th>
<th>ART-Experienced (INI-Naive)</th>
<th>ART-Experienced (INI-Resistant)</th>
<th>Total DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TOTAL Study ING111762</td>
<td>ING112961</td>
<td>ING112574</td>
</tr>
<tr>
<td></td>
<td>ING112276</td>
<td>ING113086</td>
<td>ING114467</td>
<td>TOTAL DTG</td>
</tr>
<tr>
<td>Exposure (months)</td>
<td>N=155 n (%)</td>
<td>N=50 n (%)</td>
<td>N=411 n (%)</td>
<td>N=414 n (%)</td>
</tr>
<tr>
<td>n&lt;12</td>
<td>155 (3)</td>
<td>4 (10)</td>
<td>11 (3)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>12 to &lt;24</td>
<td>41 (26)</td>
<td>13 (26)</td>
<td>371 (90)</td>
<td>359 (87)</td>
</tr>
<tr>
<td>24 to &lt;48</td>
<td>106 (68)</td>
<td>32 (64)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Exposure (days)</td>
<td>Median (Range)</td>
<td>155 (1-716)</td>
<td>672 (5-700)</td>
<td>317 (90)</td>
</tr>
<tr>
<td>Duration of dosing in Subject-years</td>
<td>272.4</td>
<td>82</td>
<td>508.3</td>
<td>497</td>
</tr>
</tbody>
</table>

Data Source: ISO Table 2.501, Table 2.502 and Table 2.503

Table summarises exposure during the randomized phase for ING112276, ING113086, ING114467 and ING111762; exposure during the open label phase prior to any switch from once daily to BID in ING112961; and exposure during the open label phase for ING112574.

a. Sum across subjects of treatment start date – treatment stop date +1 divided by 365.25. When the IP stop date was missing, the duration was calculated up to the date of last visit.
or the recorded date of withdrawal/completion, whichever was earlier.
b. Only includes exposure to DTG once daily for subjects who switched to BID post Week 96
## Appendix Table 3  Summary of Exposure to Study Drug in ING112276

<table>
<thead>
<tr>
<th>Exposure (weeks), n (%)</th>
<th>DTG 10 mg Once Daily N=53</th>
<th>DTG 25 mg Once Daily N=51</th>
<th>DTG 50 mg Once Daily N=51</th>
<th>Total DTG Once Daily N=155</th>
<th>EFV 600 mg Once Daily + 2 NRTI N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>53</td>
<td>51</td>
<td>51</td>
<td>155</td>
<td>50</td>
</tr>
<tr>
<td>&lt;12 weeks</td>
<td>0</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>12 to &lt;24 weeks</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>24 to &lt;48 weeks</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>48 to &lt;96 weeks</td>
<td>11 (21)</td>
<td>15 (29)</td>
<td>15 (29)</td>
<td>41 (26)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>≥96 weeks</td>
<td>40 (75)</td>
<td>33 (65)</td>
<td>33 (65)</td>
<td>106 (68)</td>
<td>32 (64)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure (days)</th>
<th>Median (Range)</th>
<th>Median (Range)</th>
<th>Median (Range)</th>
<th>Median (Range)</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>53</td>
<td>51</td>
<td>51</td>
<td>155</td>
<td>50</td>
</tr>
<tr>
<td>673 (86-714)</td>
<td>672 (1-716)</td>
<td>672 (1-702)</td>
<td>672 (1, 716)</td>
<td>672.5 (5, 700)</td>
<td></td>
</tr>
</tbody>
</table>

| Duration of dosing in Subject-years a | 95.2 | 88.7 | 88.6 | 272.4 | 82 |

Data Source: ISO Table 2.6

Table summarises exposure during the randomized phase, prior to switch.
9.3. **APPENDIX 3: Definition of an Adverse Event**

An AE was any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE could, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IP administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication (overdose per se was not reported as an AE/SAE).

“Lack of efficacy” or “failure of expected pharmacological action” per se was not reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy were reported if they fulfilled the definition of an AE or SAE.

Events that did not meet the definition of an AE included:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that led to the procedure was an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that did not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.
### 9.4. APPENDIX 4: Tabular Listings of Deaths

**Appendix Table 4  Listing of Deaths Reported from Studies in ART-Naïve Adults**

<table>
<thead>
<tr>
<th>Trial/Source</th>
<th>Centre</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Duration of exposure (days)</th>
<th>Diagnosis</th>
<th>Cause of Death</th>
<th>Time to Onset (days)</th>
<th>Other Medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING112276</td>
<td>67274</td>
<td>818</td>
<td>M</td>
<td>81</td>
<td>DTG/ABC/3TC</td>
<td>10 Q24 600/300 Q24</td>
<td>637</td>
<td>Multiple injuries Road traffic accident</td>
<td>Multiple injuries Road traffic accident</td>
<td>636</td>
<td>Not specified</td>
</tr>
<tr>
<td>ING112276</td>
<td>65765</td>
<td>0055</td>
<td>M</td>
<td>005</td>
<td>DTG/TDF/FTC</td>
<td>50 Q24 300/200 Q24</td>
<td>935</td>
<td>Myocardial infarction</td>
<td>Myocardial infarction</td>
<td>934</td>
<td>Smoker Dyslipidemia, history of MI in previous year</td>
</tr>
<tr>
<td>ING113086</td>
<td>81017</td>
<td>3264</td>
<td>M</td>
<td>326</td>
<td>DTG/TDF/FTC</td>
<td>50 Q24 300/200 Q24</td>
<td>13</td>
<td>Homicide</td>
<td>Homicide</td>
<td>12</td>
<td>Dermatitis, Hepatitis B, Meningitis cryptococcal</td>
</tr>
<tr>
<td>ING113086</td>
<td>83776</td>
<td>3528</td>
<td>M</td>
<td>352</td>
<td>RAL/TDF/FTC</td>
<td>400 Q12 300/200 Q24</td>
<td>116</td>
<td>Completed suicide</td>
<td>Completed suicide</td>
<td>115</td>
<td>Not specified</td>
</tr>
<tr>
<td>ING114467</td>
<td>88626</td>
<td>6765</td>
<td>F</td>
<td>676</td>
<td>EFV/FTC/TDF</td>
<td>600/200/300 Q24</td>
<td>88</td>
<td>Disseminated intravascular coagulation Pneumonia aspiration Respiratory distress</td>
<td>Disseminated intravascular coagulation Pneumonia aspiration Respiratory distress</td>
<td>81</td>
<td>Emphysema</td>
</tr>
<tr>
<td>ING114467</td>
<td>81268</td>
<td>5315</td>
<td>M</td>
<td>531</td>
<td>EFV/FTC/TDF</td>
<td>600/200/300 Q24</td>
<td>262</td>
<td>Septic shock Renal failure Systemic candida Vascular pseudoaneurysm Respiratory failure</td>
<td>Renal failure Respiratory failure</td>
<td>262</td>
<td>Alcohol abuse Aspergilloma aspergillosis</td>
</tr>
</tbody>
</table>
## Module 2.7.4 Summary of Clinical Safety

### Appendix Table 5  Listing of Deaths Reported from Studies in ART-Experienced (INI-Naïve) Adults

<table>
<thead>
<tr>
<th>Trial/ Source</th>
<th>Centre ID</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Treatmenta</th>
<th>Dose (mg)</th>
<th>Duration of exposure (days)</th>
<th>Diagnosis</th>
<th>Cause of Death</th>
<th>Time to Onset (days)</th>
<th>Other Medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING111762</td>
<td>84854</td>
<td>9012</td>
<td></td>
<td>M</td>
<td>RAL LPV/RTV</td>
<td>400 Q12</td>
<td>104</td>
<td>Epistaxis</td>
<td>Acute hepatic and renal failure</td>
<td>104</td>
<td>Not specified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200/50 Q12</td>
<td></td>
<td>Coagulation factor deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute hepatic failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infection unknown origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING111762</td>
<td>81135</td>
<td>0571</td>
<td></td>
<td>M</td>
<td>RAL MVC TDF</td>
<td>400 Q12</td>
<td>220</td>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
<td>219</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

Data Source: Safety database (OCEANS), which is maintained separately from the clinical trials database. There may, therefore, be descriptive differences of little or no clinical significance between the data presented in this table and the tables and appendices which are produced from the clinical trials database. The OCEANS and clinical trials’ databases are cross-checked to ensure compatibility of subject identifiers, study treatment at the time of event, outcome, causality, and the clinical nature of SAEs experienced. Discrepancies may arise between subject age presented elsewhere in this summary and in this table since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

a. RAL = raltegravir, LPV/RTV = lopinavir/ritonavir, MVC=maraviroc, TDF=tenofovir, Q12 = twice daily.
## Appendix Table 6  Listing of Deaths Reported from Studies in ART-Experienced (INI-Resistant) Adults

<table>
<thead>
<tr>
<th>Trial/ Source</th>
<th>Centre</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Treatmenta</th>
<th>Dose (mg)</th>
<th>Duration of exposure (days)</th>
<th>Diagnosis</th>
<th>Cause of Death</th>
<th>Time to Onset (days)</th>
<th>Other Medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir 50 mg once daily</td>
<td>ING112961</td>
<td>65765</td>
<td>1111</td>
<td>M</td>
<td>DTG DRV ETR T20 TDF/FTC</td>
<td>50 Q24</td>
<td>45</td>
<td>Left frontal mass suspicious of meningioma</td>
<td>Brain mass</td>
<td>44</td>
<td>Not specified</td>
</tr>
<tr>
<td></td>
<td>ING112961</td>
<td>68188</td>
<td>1680</td>
<td>M</td>
<td>DTG DRV MVC TDF/FTC</td>
<td>50 Q24</td>
<td>144</td>
<td>Febrile bone marrow aplasia Immunoblastic lymphoma</td>
<td>Febrile bone marrow aplasia Immunoblastic lymphoma</td>
<td>143</td>
<td>Not specified</td>
</tr>
<tr>
<td>Dolutegravir 50 mg twice daily</td>
<td>ING112961</td>
<td>65791</td>
<td>2463</td>
<td>M</td>
<td>DTG ETV DRV RTV</td>
<td>50 Q12 600 Q12 100 Q12 200 Q12</td>
<td>233</td>
<td>Completed Suicide</td>
<td>Completed Suicide</td>
<td>232</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>ING112574</td>
<td>089452</td>
<td>1203</td>
<td>F</td>
<td>DTG MVC T20 TDF/FTC</td>
<td>50 mg Q12</td>
<td>109</td>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Progressive multifocal leukoencephalopathy</td>
<td>141 (33 days after last dose)</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

Data Source: Safety database (OCEANS), which is maintained separately from the clinical trials database. There may, therefore, be descriptive differences of little or no clinical significance between the data presented in this table and the tables and appendices which are produced from the clinical trials database. The OCEANS and clinical trials’ databases are cross-checked to ensure compatibility of subject identifiers, study treatment at the time of event, outcome, causality, and the clinical nature of SAEs experienced. Discrepancies may arise between subject age presented elsewhere in this summary and in this table since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

a. DRV = darunavir, DTG = dolutegravir, ETR = etravirine, RTV = ritonavir, T20 = enfuvirtide, MVC = maraviroc, TDF/FTC = tenofovir disoproxil fumarate /emtricitabine, Q24 = once daily, Q12 = twice daily
## Appendix Table 7  Listing of Deaths Reported from Other Ongoing Studies in Adults

<table>
<thead>
<tr>
<th>Trial/Source</th>
<th>Centre</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Duration of exposure (days)</th>
<th>Diagnosis</th>
<th>Cause of Death</th>
<th>Time to Onset</th>
<th>Other Medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING115502 (named patient program)</td>
<td>BRA-001-001</td>
<td>F</td>
<td>DTG DRV RTV ETR MVC AZT/3TC</td>
<td>50Q12</td>
<td>12</td>
<td>Pulmonary haemorrhage Cytomegalovirus chorioretinitis</td>
<td>Pulmonary haemorrhage Cytomegalovirus chorioretinitis</td>
<td>12</td>
<td>Kaposi's sarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING115502 (named patient program)</td>
<td>USA-005-001</td>
<td>M</td>
<td>DTG DRV RTV AZT</td>
<td>50Q12</td>
<td>134</td>
<td>Non-hodgkin’s lymphoma, hypotension, adrenal insufficiency</td>
<td>Non-hodgkin’s lymphoma</td>
<td>134</td>
<td>Not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING115502 (named patient program)</td>
<td>FRA-022-001</td>
<td>M</td>
<td>DTG DRV RTV TDF/FTC</td>
<td>50Q12</td>
<td>Not specified</td>
<td>Sepsis Septic shock associated with myocardial infarction and cardiorespiratory arrest</td>
<td>Sepsis Septic shock</td>
<td>Not specified</td>
<td>Encephalitis, Kaposi’s sarcoma, meningioma, pancytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ING116529</td>
<td>099400</td>
<td>000241</td>
<td>M</td>
<td>Blinded therapy</td>
<td>DTG DRV RTV</td>
<td>50Q12</td>
<td>7</td>
<td>Cardiac death</td>
<td>Cardiac death</td>
<td>34 days</td>
<td>Hypertension Left ventricular hypertrophy History of stroke</td>
</tr>
</tbody>
</table>

Data Source: Safety database (OCEANS), which is maintained separately from the clinical trials database. There may, therefore, be descriptive differences of little or no clinical significance between the data presented in this table and the tables and appendices, which are produced from the clinical trials database. The OCEANS and clinical trials’ databases are cross-checked to ensure compatibility of subject identifiers, study treatment at the time of event, outcome, causality, and the clinical nature of SAEs experienced. Discrepancies may arise between subject age presented elsewhere in this summary and in this table since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

a. DTG=dolutegravir, DRV = darunavir, RTV = ritonavir, ETR = etravirine, MVC= maraviroc, AZT/3TC= zidovudine+lamivudine  Q12 = twice daily
9.5. **APPENDIX 5: Case Narratives of Deaths**

The Data Source for the Case Narratives included in this section is the Sponsor’s global safety database (OCEANS), which was searched on 01 November for fatal SAE cases initially received by the Global Safety and Pharmacovigilance department for this development programme, up to 26 October. Since OCEANS is maintained separately from the clinical trials database for these studies, the data presented here will likely be more up to date than presented in the individual study CSRs.

It is important to note that, as these studies are still ongoing, these cases are still subject to change. Additionally, discrepancies may also arise between subject age presented from OCEANS data compared to age presented from the clinical trial database, since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

### 9.5.1. Studies in ART-Naïve Adults

#### 9.5.1.1. ING112276

<table>
<thead>
<tr>
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<tr>
<td>Investigator Number:</td>
<td>067274</td>
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<tr>
<td>Subject Number:</td>
<td>000818</td>
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<td>Treatment Number:</td>
<td>2009</td>
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<tr>
<td>Case Id:</td>
<td>Z0010977A</td>
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<tr>
<td>Suspect Drugs:</td>
<td>Dolutegravir</td>
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<tr>
<td>Serious Events:</td>
<td>Multiple injuries, Road traffic accident</td>
</tr>
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</table>

This -year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 15 October.

This subject was randomised to receive dolutegravir 10 mg once daily.

Concomitant medications included Kivexa.

On 13 July, 636 days after the start of investigational product, the subject died due to automobile accident and multiple injuries. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the multiple injuries and automobile accident may have been caused by investigational product.

**Investigator Text:**

On the 08Aug wife of the patient called the Investigator and informed that the patient died on 13Jul due to the car accident. During the event patient was driving. According to the patient's wife before car accident the patient did not any problems with

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*c*: 2 years later

* 新薬承認情報提供時に置き換え
his health. The another car moved into the opposite carriageway and crashed in the car of the patient. Patient died in the car due to multiple trauma and ongoing internal bleeding.
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Module 2.7.4 Summary of Clinical Safety

Protocol Id: ING112276
Investigator Number: 065765
Subject Number: 000055
Treatment Number: 3033
Case Id: Z0010624C
Suspect Drugs: Dolutegravir
Serious Events: Myocardial infarction

This 52-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 28 September 2017.

Treatment with dose-blinded dolutegravir was completed on 12 August 2018 (the subject was unblinded to the 50 mg once daily dolutegravir dose), and the subject received open label dolutegravir 50 mg once daily from 13 August 2018. He was also taking Truvada.

Medical conditions at the time of the event included coronary artery disease and hyperlipidemia. The subject had previously developed myocardial infarction during this study (approximately Week 93) and an episode of anxiety (accompanied by shortness of breath and chest pain, at approximately Week 118), which are documented in case reports Z0010624A and Z0010624B – the narratives for which are included in Section 8.3)

The subject was also a smoker. Subject was adopted; no family information was available regarding relevant risk factors and family history of medical conditions.

On 19 April 2021, 934 days after the start of dolutegravir (approximately Week 133), the subject developed grade 4 myocardial infarction and died. The subject was found dead at the home, and a presumptive diagnosis of myocardial infarction was made since no autopsy was performed. The subject’s partner stated that the subject was in his usual state of health and had no symptoms or complaints the week of the event. The investigator considered that there was no reasonable possibility that the myocardial infarction may have been caused by dolutegravir.

Information received from the medical monitor on 23 April 2021: The subject had been admitted on 14 July 2017 due to chest pain. This episode was reported as an MI without ST elevation (onset on 14 July 2017; recovered on 16 July 2017; Grade 4; Relationship = Yes). The subject CK-MB, CK, and Troponin were elevated at that time when the subject ECG was unremarkable. Coronary angiography showed mid RCA stenosis (100%) and distal left main stenosis (30%).

This subject has also previously been noted to have issues with alcohol use/abuse. He had significant psychosocial stressors (job and health insurance loss) and symptoms consistent with anxiety but did not have prior suicide attempts, suicidal ideation or evidence for a suicide attempt prior to his death. The subject had been in touch with site coordinator earlier in the week he died and seemed to be doing fine. On 19-Apr-d* the
subject was found face down on kitchen floor. When medical assistance arrived, he was pronounced dead. The diagnosis of MI was assumed. The police was also called and their report stated that there was no foul play and no suspicion of suicide.

Investigator text:

It is believed that subject had a MI that resulted in death.

9.5.1.2. ING113086

Protocol Id: ING113086
Investigator Number: 081017
Subject Number: 003264
Treatment Number: 3091
Case Id: Z0007516A
Suspect Drugs: Dolutegravir
Serious Events: Homicide

This 22 year old male subject received IP from 15 DEC 2019. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included Truvada.

The subject's past medical history included cryptococcal meningitis. Medical conditions at the time of the event included dermatitis and hepatitis B. Concomitant medications included Bactrim and azithromycin.

On 27 DEC 2019, 12 days after the start of IP, the subject was a victim of homicide and was found deceased at home on 28 DEC 2019. Treatment with blinded trial medication was discontinued on 27 DEC 2019, the date the subject died. Cause of death is unknown. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the homicide may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 083776
Subject Number: 003528
Treatment Number: 3049
Case Id: Z0008790A
Suspect Drugs: Raltegravir
Serious Events: Completed suicide

This 22 year old male subject was randomized to receive oral RAL 400 mg twice daily 07 DEC 2019.

Concomitant medications included TDF/FTC.

*a*: The year 2019

* 新薬承認情報提供時に置き換え
On 01 APR b*, 115 days after the start of IP, the subject committed suicide by throwing himself under a train. Treatment with blinded trial medication was discontinued and the subject was withdrawn from the study. The investigator confirmed the date of death as 01 APR b*, and that an autopsy was performed but that no further information would be available. The investigator considered that there was no reasonable possibility that the suicide may have been caused by IP.

9.5.1.3. ING114467

Protocol Id: ING114467
Investigator Number: 088626
Subject Number: 006765
Treatment Number: 2484
Case Id: Z0010868A
Suspect Drugs: Atripla, Morphine
Serious Events: Disseminated intravascular coagulation, Pneumonia aspiration, Respiratory distress

This 28-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product at 1 tablet per day from 13 May a* to 08 August a*.

Medical conditions at the time of the event included emphysema. Concomitant medications included morphine, barium sulfate, iohexol and iopamidol.

On 02 August a*, 81 days after the start of investigational product, the subject developed grade 3 or severe respiratory distress secondary to narcotic administration. On 09 August a*, the subject developed grade 3 or severe intubation requirement secondary to aspiration pneumonia. On 11 August a*, the subject developed grade 3 or severe disseminated intravascular coagulopathy. The subject presented to the ER on 02 August a* with a several day history of abdominal pain and was hospitalised. The subject was given intravenous morphine for pain resulting in a respiratory depression, requiring intubation. CT of the abdomen and pelvis showed dilatation of the pancreatic duct. Laboratory test results dated 03 August a* included amylase of 1200 units/L (normal range 25-115). The subject was treated with salbutamol sulphate, enoxaparin, lactulose, pantoprazole, sodium chloride, D5 + NS + KCl, midazolam, piperacillin sodium, vancomycin, lorazepam, etomidate, naloxone, ondansetron hydrochloride and suxamethonium. Treatment with blinded trial medication-viiv was discontinued on 08 August a* and the subject was withdrawn from the study. The subject died on 12 August a* due to disseminated intravascular coagulopathy, secondary to aspiration pneumonia and respiratory distress secondary to narcotic administration. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the respiratory distress secondary to narcotic administration, intubation secondary to aspiration pneumonia and disseminated intravascular coagulopathy may have been

*a*: The year
*b*: Following year
caused by investigational product and that the respiratory distress secondary to narcotic administration was possibly due to the concomitant medication, morphine.

Follow up received from the Clinical team on 02 August a*:

The year old subject was randomised on 13 May a* with a CD4 count of 301 and a HIV RNA of 26,695. The subject had baseline concomitant medications that included proventil, megace and symbicort and had reported AEs of constipation and poor appetite.

As the subject developed abdominal pain on 01 August a*, the subject received Zosyn, vancomycin and was on ventilator support.

Follow up received from the Medical team on 26 August a*: The subject was doing well in the Single study. At day 1 - her CD4 cell count was 301 (47%; screening 323, 29%) and her viral load was 26695 c/mL. She was noted to have a low albumin at 2.2 mg/dL and elevated lipase at 78 U/L. Her platelets were also low at screening - 81,000/mm3 but were not evaluated at Day 1 due to severe platelet clumping. The subject had an adequate viral load response by week 8 (08 July) with a viral load of 70 cp/mL but the CD4 cell count was relatively stable - 305 (28%). At week 8, the platelets had improved to 110 000/mm3 (after reaching a peak of 131 000).

On 01 August a*, the subject presented to a local emergency room (ER) with complaints of abdominal pain for 1 week. She was given morphine 4 mg IV and developed respiratory distress, requiring intubation. She stayed in ER till 02 August a*, when she was admitted to the ICU. A CT scan of the brain on 02 August a* showed no haemorrhage or mass effect but did not show age related involutational change.

The subject's abdominal/pelvic CT from 02 August a* revealed left pleural effusion, atelectasis within the right lung base with abnormal appearance of the right lower lobe posteriorly (honeycombing, bronchiectasis or atelectasis), emphysematous changes within the lingual, right middle lobe, right renal cyst, dilatation of pancreatic abnormalities), leiomyomatous uterus, central canal stenosis (L2-L3,L3-L4). Small focus of air anterior to heart (significance unknown), fatty infiltration of liver considered. After consultation with surgery and repeat abdominal examinations, it was felt that she did not have free air in her peritoneum (which was suspected based on the abdominal CT).

The corresponding amylase on 01 August a* was 95 U/L (NR: 25-115), then 1088 U/L and 1200 on 03 August a*, 1143 and 1216 on 04 August a*, 537 on 06 August a*, 274, on 07 August a* 95 on 09 August a*. The study medications were stopped on 08 August a*. Lipase on 01 August a* was 287 and did not become elevated.

Admission laboratory data (as per admission note) on 01 August a*: Na 141, K 4.6, Cl 103, bicarbonate 38, BUN 14, creatinine 1.0, glucose 88, total protein 7.7, albumin 2.5, calcium 8.9, total bilirubin 0.3, AST 28, ALT 21, alkaline phos 112, amylase 92,

a*: The year
Module 2.7.4 Summary of Clinical Safety

CRP 34.5, lipase 287, troponin-I <0.04. Urinalysis: mild cloudy urine, nitrate negative, LE negative.

Prior to admission the subject's medical history included: chronically abnormal chest x-ray, pleural effusion, weight loss, chronic shortness of breath, functional decline, pulmonary embolus, moderate-sized pleural effusion, however there was no significant pleural fluid was found on ultrasound, chronic lobar parenchymal changes on CT scan of the chest and HIV.

The doctor noted that the subject was not receiving oxygen supplementation. The admission labs were consistent with alkalosis and in light of her respiratory disease, seems consistent with emphysema and chronic carbon dioxide retention, which abated with ventilation.

A CT scan of the chest on 02 August a*, showed no acute abnormality, periventricular white matter microangiopathic ischemic changes in cavernous segment, internal carotid artery and atherosclerotic calcification.

On 12 August a*, the subject died due to cardiopulmonary arrest. There were multiple potential causes for her decompensation (also likely due to small size), respiratory decompensation (also unlikely due to ease of ventilation). She did not have evidence for an acute intra-abdominal process and had a thorough work up. The abdominal wall haemorrhage likely contributed significantly to the underlying condition leading to hypotension and need for pressors.

Follow up information received via answer query report on 21 October a*:

The investigator confirmed that an autopsy was not performed and that they could not get a copy of the death certificate.

Follow up information received via answer query report on 21 March b*:

The investigator confirmed that the events that occurred were on 02 August a*, 81 days after the start of investigational product, the subject developed severe respiratory distress secondary to narcotic administration. On 09 August a*, the subject developed severe intubation secondary to aspiration pneumonia. On 11 August a*, the subject developed severe disseminated intravascular coagulopathy. The investigator removed the events deep vein thrombosis secondary to prolonged hospitalisation, abdominal wall hematoma secondary to surgical insertion of gastrostomy tube and treatment with morphine due to abdominal pain.

Investigator text:

Pt was brought in to the ER for abd pain x several days. She was given morphine IV for the pain but developed respiratory depression because of it, hence, she was intubated. Pt now in ICU. Pt is withdrawn from the study as of 08Aug a*, per PI's discretion. Pt's

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
condition worsened (this happened after the IP was stopped). Pt developed complications, the family did not want her to be resuscitated on her second code, she then expired on the 12th of August.

**Protocol Id:** ING114467  
**Investigator Number:** 081268  
**Subject Number:** 005315  
**Treatment Number:** 3032  
**Case Id:** Z0013364A  
**Suspect Drugs:** Atripla  
**Serious Events:** Renal failure, Respiratory failure, Septic shock, Systemic candida, Vascular pseudoaneurysm

This 55-year-old male subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 31 March.

Medical conditions at the time of the event included alcohol abuse, pulmonary aspergilloma and invasive aspergillosis. Concomitant medications included multivitamins, nicotine, ocular lubricants, thiamine, pantoprazole, paracetamol, cephalzinol sodium, diphenhydramine hydrochloride and haloperidol.

On 18 December a*, 262 days after the start of investigational product, the subject developed grade 4 septic shock, grade 4 renal failure and grade 4 candidemia. On 20 December a*, the subject developed grade 4 respiratory failure. On 21 December a*, the subject developed grade 4 pseudoaneurysm of lung vessel branch. The subject was hospitalised and the events were life-threatening. Subject had approximately 7 days of vomiting and diarrhoea prior to admission, denied dysuria and urinary frequency. Subject presented with severe weakness and shortness of breath. On admission the subjects mental status was lethargic and subject was difficult to understand. Results from blood cultures from 18 December a* showed Candidemia. On 21 December a*, subject had interventional radiology procedure; bronchial artery embolization resulting in greatly decreased bleeding to left upper lung. Several failed attempts to remove subject from ventilator occurred over the course of the hospitalization. On 04 January a*, subject had tracheotomy preformed. The subject was treated with vancomycin, paracetamol, liposomal amphotericin B, sodium citrate, ceftriaxone, fentanyl, lignocaine hydrochloride, lorazepam, noradrenaline acid tartrate, piperacillin sodium and Bactrim and the subject was withdrawn from the study. On 09 January a*, subject was discharged from the hospital and released to hospice. The subject died on 16 January b*, due to renal failure and respiratory failure. The investigator considered that there was no reasonable possibility that the septic shock, candidemia, pseudoaneurysm of lung vessel branch and respiratory failure may have been caused by investigational product. The investigator considered that there was a reasonable possibility that the renal failure may have been caused by investigational product.

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*a*: The year  
*b*: Following year

* 新薬承認情報提供時に置き換え
Follow-up information received on 19 December and 22 December a* from clinical study team:

This subject has had a very complicated medical course over the past few months, despite responding very well to therapy in the study. This □ year old male was enrolled in SINGLE on 31Mar a*, and at study entry, he had a HIV-1 RNA of 135,515 cp/mL and a CD4 cell count of 219 (21%) cells/mm³. By week 24 (13Sept), the HIV-1 RNA was <50 and CD4 cell count was 668(275%). Despite the robust immulogic recovery, he has had the following OIs in September and October. In September, he was diagnosed with candidal esophagitis, and in October, he was diagnosed with PCP and has been on Bactrim since late September. Of note, he had cystic lesions in his lung resulting from the PCP. In November, this subject was diagnosed with pyelonephritis and treated with Ciprofloxacin. Ultrasound examination of the kidneys confirmed pyelonephritis. The creatinine at that time is currently unknown. The last creatinine in study was performed in Sept a*, at which point it was stable (about 0.5 mg/dL). The Week 32 labs in November were haemolyised, so creatinine was not performed. Per your records, the subject had a stable creatinine in late Oct, prior to the pyelonephritis. For his current presentation - this subject is currently in the ICU and is on Levophed (norepinephrine). He had a pulmonary haemorrhage, which was preceded by hemoptysis as an outpatient, likely related to invasive aspergillosis.

Prior to admission:

"He has another problem for which I had him scheduled to see me this week: Probable fungal ball in lung cavity (presumptive aspergilloma). His sputum and BAL did not reveal fungal elements by stain or culture. Repeat culture from this admission is pending. Until recently, he was asymptomatic. In recent week, he has developed cough with some trace hemoptysis. Was planning on taking him off study and beginning voriconozole with different HIV RX." As discussed today, he presented to the local ER prior to implementation of this plan.

Subject had approximately 7 days of nausea, vomiting, and diarrhoea prior to admission. Denies dysuria or urinary frequency, but didn't have these symptoms when he had E. coli pyelonephritis in November. In November, he had CT findings of bladder wall thickening with partial obstruction of ureter. Awaiting urology consultation to evaluate. F/u UA with cytology okay. Per discussion today, renal ultrasound performed in the last couple of days (this admission), the subject did not have obstruction and no evidence of invasive fungal disease on renal ultrasound.

18DEC a* - Seen in local ER & transferred/admitted to Hospital MICU with shock.

Presented with hypotension, leukocytosis, metabolic acidosis (Anion Gap), and acute kidney failure. Afebrile. Given IV fluid and low dose pressor (levophed). FI02 given PNC (not intubated or ventilated). Given empiric antibiotics - IV vancomycin and piperacillin/tazobactam in MICU. Urine, stool, and blood cultures pending. C.diff PCR

a*: The year
Module 2.7.4 Summary of Clinical Safety

negative. HIV meds held. Bactrim prophylaxis continued. Had not been taking on regular basis in recent weeks.

The investigator contacted the subject's mother (with whom the subject lives) and she said that subject was taking IP up to 17DEC a* - last dose day before initial SAE 'hospitalization for shock'. Family will visit on Saturday & will bring pill bottles with them.

The anuric acute renal failure was present at time hospitalization on 18DEC a*. He is receiving dialysis; metabolics look better today.

The investigator could not exclude possibility that HIV meds have contributed to renal failure (sepsis acute renal injury/low GFR - elevated drug levels - etc). Therefore, it is possible that IP may have contributed to anuric acute renal failure (added injury to insult).

Interim history is remarkable for:

20DEC a* - Pulmonary haemorrhage requiring intubation, mechanical ventilation (FiO2 40), transfusion of RBC and PLT. Unsuccessful attempt a locating and coiling vessel responsible for bleeding. Note: he was having coughing and haemoptysis before he developed nausea, vomiting, and diarrhoea.

21DEC a* - Interventional radiology identified pseudoaneurysm and bleed in LUL. Branch of pulmonary artery with aneurysm coiled. Bleeding into LUL greatly decreased. Pseudoaneurysm probably caused by aspergillus.

20DEC a* - Candidemia. Yeast grew from blood culture drawn 18DEC a*. May explain initial sepsis syndrome.

Contribution of IP cannot be ruled out. All HIV therapy/study drugs has been stopped as of admission to the hospital on 18Dec. The subject continues on Levophed and continues in the ICU. The metabolic acidosis is improving, but the situation is still tenuous, as dialysis is still required and additional bleeding could occur in the lungs. Surgery would likely not an option for this subject due to his poor post-surgical survival rate.

Follow-up information received on 23 December a* from clinical study team:

At week two visit the subject had a Grade 3 value was AST/SGOT at 240. His Day 1 AST value was 153 (Grade 2), and the screening value was 142 (also a Grade 2). He also has a Grade 2 elevated ALT/ SGPT of 184. The Day 1 and screening values were grade 1 elevations at 135 and 111. Bilirubin remains within normal limits.

Alk phos has been grade 1 (low level) elevated since screening. Lipase was slightly elevated at Screening and Day 1 as well. His HBV and HCV screening labs were non-reactive.
The investigator comment to the prior investigational product administration laboratory test results "Alcohol use indiscretion likely played a major role. Subject's mother called me 5 d prior to visit and said that her son was drinking more alcohol and appeared intoxicated at the time. I talked to subject later during the call & he acknowledged that he had been drinking too much and assured me that he would adhere to the study requirement. He lives with his mother and she will be monitoring him. The con med of Keppra was started in Feb a* - it's possible that this med may be adding to problem. There have been no con med changes while he has been on Single study. I will call him to check on OTC acetaminophen use. I had talked to the subject during his study visit (when these labs were obtained) & he was not symptomatic."

Follow up information received on 06 January b* from medical monitor:

The subject was smoking 0.1 packs/day for 5 years.

The subject had abdominal pain. His diarrhoea was watery and non bloody. He had severe weakness, poor appetite and shortness of breath. He does not have any chest pain, headache, swelling of the legs and fever. At the hospital he was found to have creatinine of 6.3, BUN of 49 and AG of 16. He also had hyponatremia with sodium of 103 but the duration of hyponatremia is not clear from the records. He was transferred here for rise in creatinine and hypotension. An US done at the hospital showed increased echogenicity and no hydrounephrosis. He did not have any uap since the arrival. Since the admission here, he was given 6-7 litres of NS for volume repletion, one dose of vancomycin and he is also started on zosyn. His BP did not respond well to fluids and he was started on levophed. He is maintaining his sats and is not intubated. He did not have any history of NSAIDs intake or recent contrast exposure.

Impression from consultation nephrology attended on 19 December a*:

"Pt has severe volume depletion probably from diarrhoea. Many other medical problems including AIDS (we" treated with low viral load), aspergillus, pneumocystis c; and now anuric acute renal failure. Hx of possible urinary obstruction, but my review of the renal US does not show much obstruction. Foley catheter flushes well and there is no urine in bladder. Mental status seems lethargic and he is difficult to understand. Sentences are incomplete, but he is awake, moves a" extremities and can indicate discomfort. He is on pressors and also has hyponatremia -probably chronic (many days). He also has a profound metabolic acidosis (nl gap) probably from diarrhoea. Agree to give hypotonic NaHC03 to help replace."

Hospital course was as follows:

The subject was admitted to [deleted] Medical Centre, placed on Levophed and broad spectrum antibiotics, including vancomycin (per Dr. [deleted], not in available hospital records). Pulmonary haemorrhage requiring intubation, mechanical ventilation (Fi02 40), transfusion of RBC and PLT developed on 20 December a*. Unsuccessful attempt at locating and coiling vessel responsible for bleeding. Note: he was having coughing and
haemoptysis before he developed nausea, vomiting, and diarrhoea. On 21 December a*, interventional radiology identified pseudoaneurysm and bleed in LUL after lengthy evaluation (including significant contrast use). A branch of the pulmonary artery with an aneurysm coiled, and the bleeding into LUL greatly decreased. The pseudoaneurysm was probably caused by aspergillus. No recurrence of the pulmonary haemorrhage has been noted up to 03 January b*.

The subject also was noted to have 1 blood culture and 1 urine culture with Candida albicans growth and was subsequently placed on voriconazole for treatment of the Candida albicans fungemia/UTI and invasive pulmonary aspergillosis. Broad spectrum antibiotics were discontinued after isolation of the Candida in blood culture at the outside hospital (from 18 December culture).

With regards to the renal failure, an ultrasound was obtained on 22 December a* with the following results: 1) Increased echogenicity of the bilateral kidneys suggests HIV nephropathy and 2) thickened bladder wall more than expected with existing Foley catheter in place, which may suggest cystitis or inflammatory change. The subject was initially placed on CVVHDF (sometime between 20 December to 22 December) but was switched to haemodialysis when pressors were no longer required (date unknown). After dialysis, the creatinine dropped to 1.2 mg/dL and remained between 0.6-0.9 mg/dL until 02 January b* when creatinine was 3.4 mg/dL. Hospital notes on that day reference plans for HD on 02 January b*. Per review of creatinine and discussions with Dr. [deleted], subject was likely receiving CVVHD until ~30 December a*, as creatinine noted to be 0.7 mg/dL on that date. Electrolytes and acid-base disturbance were corrected with haemodialysis and treatment of underlying sepsis.

Current plans - per discussion on 03 January with Dr. [deleted], the subject was beginning to have spontaneous urine output, up to ~250 mL. Additionally, he was more alert with removal of sedation. As he had poor conditioning prior to admission and was intubated for an extended time with multiple failed attempts to extubate, the subject was to have a tracheotomy by 06 January b* to allow long term attempts to take him off the ventilator. Further plans from Dr. [deleted] include resuming HIV medications with raltegravir and possibly abacavir and renally adjusted lamivudine dosing. The study medication has not been unblinded at this time. Dr. [deleted] also felt that the acute illness/renal injury was likely related to the sepsis (secondary to candidemia).

Follow-up information from answered query received 23 January b*:

Investigator Text: We cannot exclude possibility that HIV meds contributed to renal failure (sepsis acute renal injury/low GFR-elevated drug levels/etc). Therefore, it is possible that IP may have contributed to anuric acute renal failure (added injury to insult).

Investigator Text:
Subject had approximately 7 days of vomiting and diarrhoea prior to admission, denied dysuria and urinary frequency. Subject presented with severe weakness and shortness of breath. Subject has history of AIDS pneumocystis pneumonia and a pulmonary aspergilloma. 18DEC a*-Admitted to hospital with septic shock. Mental status was lethargic and patient was difficult to understand. 20DEC a*-Pulmonary haemorrhage required intubation and mechanical ventilation. Results from blood cultures from 18DEC a* showed Candidemia. 21DEC a*-Subject had interventional radiology procedure; bronchial artery embolization resulting in greatly decreased bleeding to left upper lung. Several failed attempts to remove patient from ventilator occurred over the course of the hospitalization. On 04JAN a* patient had tracheotomy performed. 09JAN a*- Patient was discharged from the hospital and released to hospice. 16JAN a*- Patient died.

9.5.2. Studies in ART-Experienced (INI-Naïve) Adults

9.5.2.1. ING111762

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<td>084854</td>
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<td>Suspect Drugs:</td>
<td>Raltegravir</td>
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<tr>
<td>Serious Events:</td>
<td>Acute hepatic failure, Coagulation factor deficiency, Epistaxis, Infection, Renal failure acute</td>
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</tbody>
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This 55-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 06 SEP .

The subject was randomised to receive oral RAL 400 mg twice daily.

The subject had no known risk factors. Concomitant medications included Aluvia.

On 19 DEC a*, 104 days after the start of investigational product, the subject developed grade 2 or moderate infection unknown origin. On 31 DEC a*, the subject developed grade 4 acute hepatic failure, grade 2 or moderate acute renal failure, grade 2 or moderate epistaxis and grade 2 or moderate coagulation factor deficiency. The subject was hospitalised. The subject was treated with red blood cells, lactulose, vitamin k and plasma. Treatment with investigational product was discontinued in December a* (exact date unknown) and the subject was withdrawn from the study. The epistaxis and coagulation factor deficiency were resolved on 01 JAN b*. The subject died on 01 JAN b* due to acute hepatic failure and acute renal failure. The infection unknown.

a*: The year
b*: Following year
origin was unresolved at the time of the subject's death. The investigator considered that there was no reasonable possibility that the acute hepatic failure, infection unknown origin, acute renal failure, epistaxis and coagulation factor deficiency may have been caused by investigational product.

Diagnostic Results (31 Dec a*)

Bilirubin, 164 mol/L (0.0 - 21.0)
Aspartate Amino Transferase, 2950 uL (5.0 - 40.0)
Alanine Amino Transferase, 749 UL (5.0 - 40.0)
Alkaline phosphatase, 271 UL (40.0 - 120.0)
Gamma-glutamyltransferase, 196 UL (0.0 - 60.0)
Lactic dehydrogenase, 1995 UL (100.0 - 190.0)
Creatine, 678 mo/L (60.0 - 120.0)
Phosphate, 2.71 mmol/L (0.8 - 1.4)
C-reactive protein, 129.1 mg/L (0.0 - 10.0)
Prothrombin time, 33 secs (9.0 - 11.0)
Prothrombin time, greater than 120 secs (26.0 - 34.0)

Additional information received 06 JAN b* via medical monitor:

This was a 21 year-old African heritage male. He was screened to SAILING on 2 AUG a* and performed Day 1 visit on 6 SEP a*. Medical history was negative for both hepatobiliary disorders and infections and infestations other than HIV-1. AEs listed at the CRF prior to liver enzymes elevation included recent myalgia (11 NOV a* to 20 NOV a*), Flu (12 NOV a* to 20 NOV a*), and Malaise (20 NOV a* to ongoing). It was also documented that the subject has taken paracetamol/codeine (11 NOV a* to ?), Brufen (ibuprofen; 11 NOV a* to ?), Allergex (chlorpheniramine; 14 NOV a* to ?), paracetamol (14 NOV a* to 20 NOV a*) and Voltaren (diclofenac; 14 NOV a* to 20 NOV a*). Con ART listed was Aluvia (since 6 SEP a*).

When we started following this subject's liver enzymes the available results were the following:

02 AUG a*: AST 25 U/l (0-42), ALT 14 U/l (0-48), Alkaline phosphatase 95 U/l (20-125), total bilirubin 7 μmol/L (0-22)
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06 SEP a*: AST 34 U/l, ALT 19 U/l, Alkaline phosphatase 96 U/l, total bilirubin 6 μmol/L, Hep B surf AG non-reactive, Hep C Ab non-reactive

20 SEP a*: AST H@47 U/l, ALT 40 U/l, Alkaline phosphatase 79 U/l, total bilirubin 12 μmol/L

04 OCT a*: AST H@43 U/l, ALT 46 U/l, Alkaline phosphatase 89 U/l, total bilirubin 13 μmol/L

01 NOV a*: AST 20 U/l, ALT 15 U/l, Alkaline phosphatase 92 U/l, total bilirubin 8 μmol/L

29 NOV a*: AST G3 H@298U/l, ALT G3 H@308 U/l, Alkaline phosphatase 91 U/l, total bilirubin 15 μmol/L

The subject was contacted by the site on 02 DEC a*

He informed that he had been on and off Disprin for recurrent headaches, stopped drinking alcohol 5 months ago, had no change in diet and did not ingest mushrooms for a very long time, since they were not part of his daily diet. The subject also confirmed no use of herbal medications, and no study IP overdose. The subject was a gardener, but denied contact with chemicals. He had one sex partner, his girlfriend and are staying together.

The patient informed a history of diarrhoea from 28 NOV a* to 01 DEC a* which resolved without medication. As he was feeling tired on the 30 NOV a*, he sought attention with a Chemist (as stated telephonically on Friday) and bought the Disprin extra strength 500 mg to take prn p.o., Panamol tablets (Paracetamol) to take prn p.o., Multivitamins 1 daily p.o., Vit. BCO 1 daily p.o. (bought after the 29 NOV a*, a day after his follow up visit). He also informed that he felt a mild left sided chest pain on 02 DEC a* while running and had stopped. No cough, no abdominal pains. His physical at that date was unremarkable.

Follow up lab tests were performed on 14 DEC a* (AST = 134 U/L, ALT = 95 U/L, Alk Phosp = 61 U/L, and total bilirubin = 8 umol/L) and on 19 DEC a* (AST= 506 U/L, ALT= 365 U/L, Alk Phosp= 239 U/L, total bilirubin= 34 umol/L, and direct bilirubin of 17 umol/L). The last labs were still not compatible with liver stop criteria but were close to the stopping criteria for ALT elevation alone.

The site was contacted on 29 DEC a* regarding the liver enzyme elevations.

Dr [deleted] was following up on this when he got the information that the subject passed away.

Other pertinent lab information:

a*: The year
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Screening: HIV RNA RT PCR 263559, Absolute CD4 cell count 107.0, %CD4 12.0, creatinine 41.1 (69.8-117.6 umol/l), glucose 5.2 (3.9-5.5 mmol/l), sodium 138, potassium 3.4, lipase 12, WBC 3.9, Hgb @12.3, platelets 377000, absolute neutrophils 2.95, absolute lymphocytes 0.63.

D1: HIV RNA RT PCR 323469, Absolute CD4 cell count 109.0, %CD4 14.0, creatinine 48.4, glucose 5.8, sodium 134, potassium 3.8, lipase 12, WBC @2.9, Hgb @13.4, platelets 293000, absolute neutrophils 1.89, absolute lymphocytes @0.73.

WK2: creatinine 66.4, glucose 5.9, sodium 133, potassium 4.0, lipase 16, WBC 4.4, Hgb @12.2, platelets 340000, absolute neutrophils 3.50, absolute lymphocytes @0.75.

WK4: HIV RNA RT PCR 109, Absolute CD4 cell count 106.0, %CD4 10.0, creatinine 54.3, glucose 4.9, sodium 138, potassium 4.5, lipase 25, WBC @2.8, Hgb @10.9, platelets 276000, absolute neutrophils 1.92, absolute lymphocytes @0.68.

WK8: HIV RNA RT PCR less than 50, Absolute CD4 cell count 135.0, %CD4 11.0, creatinine 47.5, glucose 5.4, sodium 134, potassium 4.1, lipase 26, WBC @2.7, Hgb @12.5, platelets 343000, absolute neutrophils @1.58, absolute lymphocytes 0.92.

WK12: HIV RNA RT PCR less than 50, Absolute CD4 cell count 125.0, %CD4 19.0, creatinine 80.8, glucose 5.7, sodium 127, potassium 4.0, lipase 34 (retest 92), WBC @3.1, Hgb @9.8, platelets 274000, absolute neutrophils 2.32, absolute lymphocytes @0.47.

WK16 (19 DEC a*): HIV RNA RT PCR less than 50, Absolute CD4 cell count 27.0, %CD4 15.0, creatinine 101.5, glucose 6.9, sodium 128, potassium 4.5, lipase 69, WBC @1.8, Hgb @9.0, platelets 256000, absolute neutrophils @1.56, absolute lymphocytes @0.19.

On 19 DEC a*, the subject presented for his Week 16 visit and was noted to have an acute illness with a fever, rigors, arthralgias, and fatigue. On examination, the subject was noted to have an elevated temperature at 39.5 C. No other focal findings were noted on examination. CXR showed no infiltrates or evidence for other pathology. Dr. [deleted] was concerned that the subject may have pneumonia, so he administered ceftriaxone 2 grams IV daily for 5 days (19-24 DEC a*). Over the course of this treatment, the subject reported feeling subjectively better, including resolution of the fever. No documentation of vital signs was available. As the subject appeared significantly improved, Dr. [deleted] asked the subject to return in 1 week. The subject did not return for that visit on 29 DEC a*. Dr. [deleted] contacted Dr. [deleted] on 29 Dec to follow up on the Week 16 lab abnormalities.

On 31Dec, the subject was admitted to the hospital with the following summary:

The subject was admitted on 31 DEC a* presenting with confusion, jaundice and renal impairment. His physical exam was significant for a BP of 107/60 mmHg, pulse of 100
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bpm, apparent fever (temperature not documented), tachypnea, tachycardia 9:11 AM EST and possible terminal neck stiffness.

Diagnostic tests performed showed total bilirubin of 164 mol/L (7.8 x ULN; 83% due to conjugated bilirubin), AST of 2950 U/L (73.8 x ULN), ALT of 749 U/L (18.7 x ULN), ALP of 271 U/L (2.3 x ULN), GGT of 196 U/L (3.3 x ULN), Ammonia of 128 mol/L (21-71), Lactate Dehydrogenase of 1995 U/L (10.5 x ULN), PTT > 120.0 sec, and INR of 2.68.

Increased serum creatinine (678 mol/L; 5.7 x ULN), increased serum urea (36.0 mmol/L; 5.1 x ULN), hyponatremia (121 mmol/L), hyperkalemia (5.8 mmol/L), decreased carbon dioxide (6 mmol/L), decreased corrected calcium (1.77 mmol/L), decreased albumin (13 g/L), increased phosphorus (2.71 mmol/L), and increased CRP (129.1 mg/L) were also documented.

Hepatitis A, B, and C antibodies were reported as negative.

The subject was prescribed with a pRBC transfusion.

Deterioration of consciousness and epistaxis were noted and the subject was started on lactulose, Vit K and FFP.

The subject passed away 48 h after admission. The final diagnosis was not documented at the Discharge Summary.

In discussion with Dr. [deleted], he has no documentation of tuberculosis in his records or from the records he received from the government clinic that has been following this subject. He is not sure that the subject's report of TB in the hospital records is reliable due to the noted mental status changes for this subject. He discussed an autopsy with the family this week, and they refused.

Follow-up information received on 10 FEB b* via query response:

No treatment was given.

Follow-up subsequently retrieved from the liver CRFs included:

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the previous week. The subject consumed alcohol. The average number of units consumed per week was 6 units. The subject had no liver disease medical conditions, no drug related liver disease conditions and no other relevant medical conditions.

There were no diagnostic imaging tests. There were no liver biopsies performed.

b*: Following year
Participant was called to return to the clinic for follow-up as discussed via E-mail. Relatives informed us that he passed away on 01 JAN b*. Participant presented with pyrexia to touch, and seemed acute chronically ill. Jaundice and renal impairment queried. Complaints of painful feet. Participant was admitted to hospital on 30 DEC a* and passed away on 01 JAN b*. The reason for death is Acute Liver and Kidney failure.

This 61-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 22 JUN b* to 01 FEB b*.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject has no personal or family history of cancer. Concomitant medications included Truvada and maraviroc.

On 27 JAN b*, 219 days after the start of investigational product, the subject developed grade 4 metastatic adenocarcinoma of possible gastrointestinal origin and grade 4 increased alkaline phosphatase grade 4 of 942 U/L (normal range 20 to 125). The subject was hospitalised and the events were life-threatening. Laboratory test results showed alkaline phosphatase at 1760 U/L on 20 FEB b* (normal range 40 to 115); 2405 U/L on 09 MAR b* (normal range 20 to 125); 2855 U/L on 26 MAR b* (normal range 20 to 125), 2906 U/L on 26 MAR b* (normal range 45 to 129), 2390 U/L on 23 APR b* (normal range 45 to 129). The subject commenced chemotherapy with carboplatin and paclitaxel on 03 MAY b*. Repeat laboratory test showed results of 2004 U/L on 03 MAY b*, 1138 U/L on 08 MAY b*, 999 U/L on 24 MAY b* and 1012 U/L on 29 MAY b*. Treatment with blinded trial medication was discontinued on 01 FEB b* and the subject was withdrawn from the study. The subject made DNR on 18 JUL b* offered comfort measures only. The subject died on 31 JUL b* due to metastatic adenocarcinoma of possible gastrointestinal origin. The increased alkaline phosphatase grade 4 was unresolved at the time of death. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the metastatic adenocarcinoma of possible gastrointestinal
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origin and increased alkaline phosphatase grade 4 may have been caused by investigational product.

Additional information received on 27 APR b* via medical monitor:

This subject was found to have significant elevation of the alkaline phosphatase (AP) prompting initial discontinuation of the investigational drug and then discontinuation all ART; despite withdrawal of all drugs, the AP continued to rise.

He was initially entirely asymptomatic but in mid February he developed right sided rib pain; exam was unremarkable and chest x-ray with rib detail on 17 FEB b* revealed no abnormality save old granulomatous disease (calcified RUL granuloma) and normal cardiomedial structures except calcification of the aorta.

About the time he was discontinued from the study, he complained of early satiety and dyspepsia as well as left shoulder discomfort, relieved by ibuprofen. He declined shoulder x-ray or orthopedic evaluation (due to concerns about payments <he has no health insurance>) but an abdominal ultrasound was done on 28 FEB b* revealed probable fatty liver and possible biliary sludge but no other pancreatic/biliary issues.

Shortly thereafter the results of the initial evaluations of the elevated AP suggested primarily bone sources and he was referred to the Endocrine/Bone specialist. A Bone "SuperScan" on 16 MAR b* revealed diffusely increased bone tracer uptake throughout the axial, appendicular skeleton and skull suggestive of a boney metabolic abnormality. His PTH here was elevated at 115.6 although the one done by the study lab was normal earlier. Skull series on 26 MAR b* requested by the endocrine consultants revealed "diffuse heterogeneity of skull mineralization". He was referred for a bone biopsy.

About two weeks later he presented to the endocrine clinic complaining of severe constipation and continued early satiety; a KUB/upright CXR on 12 APR b* showed interval development of possible right perihilar airspace disease and patchy sclerosis throughout the osseous structures. His constipation apparently resolved with laxatives.

On 23 APR b* he presented to the endocrine clinic with shortness of breath (02 sat 83% post exercise) and was referred to the ER where spiral CT revealed no PE but "severe lymphadenopathy involving the mediastinum, perihilar, and upper abdomen (epigastric/periportal) nodes with focal edema/inflammation of stomach suggestive of gastritis. He was admitted and bransbronchial biopsy on 24 APR b* revealed malignant cells consistent with adenocarcinoma. He also complains of continued early satiety, constipation and now has diffuse musculoskeletal pain and 11 kg weight loss. Other significant labs during the admission: WBC 9.9, Hgb 11.2 - 9.7 and platelets 60K-48k (of note, hemogram in February was essentially normal); D-dimer 4804; renal function normal; Ca 8.6, Alb 3.6; AP 2258. Bone Survey on 26 APR b* suggested multiple blastic lesions throughout the skeleton.

b*: Following year
Follow up information received on 24 JUL b* via answered query report:

The normal ranges for alkaline phosphatase were different as 20 - 145 u/L was the Quest study lab reference range and 45 - 129 u/L were the local hospital lab reference range. The subject did not receive any corrective therapy for the increased alkaline phosphatase levels.

Follow up information received on 19 AUG b* via deletions report:

The concomitant medication RAL was deleted.

Diagnostics:

17 FEB b*: Chest x-ray: no abnormality except old calcified RUL granuloma.
Abdominal Ultrasound 28 FEB b*: probable fatty liver & biliary sludge. bone
Superscan 16 MAR b*: suggestive of boney metabolic abnormality. KUB/Upright
Chest x-ray, 12 APR b*: possible right perihilar airspace disease & patchy sclerosis throughout the osseous structures

23 APR b*: Spiral CT: severe lymphadenopathy. 24 APR b*: bransbronchial biopsy: malignant cells consistent with adenocarcinoma. 26 APR b*: Bone survey: suggested multiple blastic lesions throughout the skeleton. 30 APR b* Bone marrow biopsy and 02 MAY b*: colon biopsy: both suggestive of gastrointestinal (mainly gastric or colonic) or pancreatobiliary primary. 09 MAY b*: PET, Skull to mid thigh: The most likely primary adenocarcinoma site is the rectum, with widespread metastatic disease diffusely throughout the bones, lungs, hila/mediastinum, lower right cervical level 4 lymph nodes, left ventricular anteroapical myocardium and/or pericardium, possibly spleen. 13MAY b*: CT head: skull base metastasis.

Death Summary: metastatic adenocarcinoma remains suspected GI primary; diagnosed: carcinomatosus meningitis May b*; had stroke and pneumonia in June, possible pulmonary embolis and acute kidney injury early July b*; made DNR 18 JUL b* offered comfort measures only, died 31 JUL b*.

Investigator text:

All the above was in work-up of elevated alkaline phosphatase, of 942, at the week 32 visit on 27 JAN b*, leading to the current diagnosis. Additional lab tests were done per Quest study lab, outside the usual. Please see Quest results, as they are not a choice in the dropdown box in this form. Work-up continues to find the origin, now thought to possibly be rectal. There is no documentation of previous personal or family history of cancer. Started chemo therapy on 03 MAY b*. Restarted HIV ART on 08 MAY b*.

b*: Following year
9.5.3. Studies in ART-Experienced (INI-Resistant) Adults

9.5.3.1. ING112961

Protocol Id: ING112961
Investigator Number: 065785
Subject Number: 001111
Treatment Number: UNKNOWN
Case Id: Z0002677A
Suspect Drugs: Dolutegravir
Serious Events: Brain mass

This 81-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 03 November.

Concomitant medications included 0.9 % Normal Saline, potassium chloride and enoxaparin.

On 17 December a*, 44 days after the start of dolutegravir, the subject experienced lower extremity weakness and difficulty breathing. The subject was hospitalised. The event was considered disabling. A CT of head revealed a left frontal mass suspicious for meningioma. MRI showed a focal mass lesion involving the left frontal region. The subject was diagnosed with a grade 4 frontal central nervous mass. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The subject died on 26 March b*. Cause of death was reported as frontal central nervous mass. The investigator considered that there was no reasonable possibility that the cerebral frontal mass may have been caused by dolutegravir.

Follow-up information received from Clinical Study Team on 29 December a*:

The subject was admitted to hospital on 17 December a*, for altered mental status and syncope exhibiting slight confusion and memory lapses. The subject was negative for toxoplasmosis antibodies, but toxoplasmosis treatment and repeat MRI scan in three weeks were recommended. The subject was discharged in stable condition and transferred to a nursing facility on 23 December a* while awaiting follow-up with regard to brain lesion. The discharge diagnosis was consistent with a possible toxoplasmosis vs. lymphoma vs. meningioma.

Additional information received 10 February b*:

Concomitant medications included normal saline, potassium chloride, and enoxaparin (Lovenox). The subject had no relevant medical history.

a*: The year
b*: Following year
Follow-up information received 30 March b*:

It was reported that the subject died due to the event of brain mass on 26 March b*. It was not known whether an autopsy was performed or not.

Follow-up information received from clinical study team:

The subject was confirmed not to have undergone any tests in addition to the ones already reported. Initial hospital plans were to do further work up on the subject's cerebral mass, but all those plans were eventually placed on hold because of the severity of illness and the subject having shortly passed away. No final conclusions could be drawn from the analysis of the subject's medical records.

Investigator comment: the best assessment was that the subject who had very advanced AIDS and severely prolonged immunosupression due to the lack of effective treatment options developed possibly a brain lymphoma. The radiologist could not rule out the alternative diagnosis of meningioma, based on the appearance of the lesions on CT and MRI scans. The investigator thought that last possibility was less likely, considering the overall clinical picture. There were some initial notes on the subject's hospital chart raising the possibility that he may have had toxoplasmosis, but this was safely ruled out again by the overall clinical picture. No other diagnosis considerations are or were being considered. The lesions in radiographic studies were not consistent with PML.

Investigator Text:

The office received a message on 12/17/a* from answering service stated that patient was admitted into the hospital via 911EMS due to lower extremity weakness and difficulty breathing.

Protocol Id: ING112961
Investigator Number: 068188
Subject Number: 001680
Treatment Number: UNKNOWN
Case Id: Z0003348A, Z0003348B, Z0003348C
Suspect Drugs: Cyclophosphamide + doxorubicin + vincristine + prednisone, Dolutegravir
Serious Events: Febrile bone marrow aplasia, Febrile bone marrow aplasia, Immunoblastic lymphoma

This —-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 13 October b*.
On 11 January b*, 90 days after the start of dolutegravir, the subject developed grade 4 immunoblastic lymphoma. The event was clinically significant (or requiring intervention). Immunoblastic lymphoma was diagnosed by results of a gingival biopsy. The subject was treated with CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone) chemotherapy. Treatment with dolutegravir was continued. The subject died on 11 March b* due to immunoblastic lymphoma. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the immunoblastic lymphoma may have been caused by dolutegravir.

Investigator text:

immunoblastic lymphoma diagnosed after a biopsy (oral tumefaction) SAE per protocol

On 14 February b*, 124 days after the start of dolutegravir, the subject developed grade 4 febrile aplasia. The subject was hospitalised. Concomitant medications included (CHOP) chemotherapy (administered for lymphoma, diagnosed in December a* - not reported as a serious adverse event). Treatment with dolutegravir was continued. Diagnostic tests on 14 February b* revealed white blood cell count 1.020 x 10^9/l (normal range 4-10.5), haemoglobin 92g/l (normal range 130-175), platelet count 40 x 10^9/l (normal range 130-400). Blood cultures collected on 14 February b* resulted negative. The subject was treated with lenograstim. The event resolved on 15 February b*. The investigator considered that there was no reasonable possibility that the febrile aplasia may have been caused by dolutegravir and that the event was possibly due to the concomitant medication, cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP) chemotherapy, which was stopped as a result.

Investigator text:

the patient had 39.5C at home on the 13 Feb. and was hospitalized with aplasia on the 14 Feb. He was discharged on the 15 Feb.b* -

On 05 March b*, 143 days after the start of dolutegravir, the subject developed a new episode of grade 4 febrile aplasia. Diagnostic tests on 05 March b* revealed haemoglobin 95 g/l (normal range 130-175), platelet count 56 X10^9/l (normal range 150-400), white blood cell count 0.210 x 10^9/l (normal range 4-10.5). CSF analysis from the same date showed EBV DNA of 2700 copies/ml. Lumbar puncture was again performed on 08 March b* showing lymphocytes that corresponded mainly to CD3 lymphocytes, with no cells compatible with lymphoma. The results of an 09 March b* chest CT scan were consistent with pulmonary lymphoma On 11 March b*, haemoglobin 105 g/l (normal range 130-175), platelet count 33 X10^9/l (normal range 150-400), white blood cell count 0.040x 10^9/l (normal range 4-10.5). The subject was treated with acyclovir, Tazocilline, tobramycin, oxycodone hydrochloride, morphine, red cells bag, platelet concentrate, pegfilgrastim, ketoprofen, Bactrim, phytomenadione, midazolam hydrochloride, Tienam and frusemide. Treatment with dolutegravir was discontinued and the subject was withdrawn from the study. The subject died on 11 March b* due to febrile aplasia. An autopsy was not performed. The investigator
considered that there was no reasonable possibility that the febrile aplasia may have been caused by dolutegravir.

Investigator Text:

the patient had a febrile aplasia and died on the 11th of March b*
This 29-year-old male subject was enrolled in a ViiV-sponsored, open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day from 26 September to 16 May.

Medical conditions at the time of the event included depression. Concomitant medications included lexapro, Adderall, metoclopramide hydrochloride, montelukast sodium, esomeprazole, vardenafil, zolpidem tartrate, tesamorelin acetate, darunavir, ritonavir and etravirine.

On 16 May, 232 days after the start of dolutegravir, the subject committed suicide. The subject had lost his job and apartment. The subject died on 16 May due to completed suicide by drug intoxication and intoxication with ethylene glycol. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the subject committed suicide may have been caused by dolutegravir.

Follow-up information received on 21 August via email:

The subject had no known history of suicidal ideation or attempts. He never expressed any anxiety. The subject did not use drugs or ethanol. There was no known family history of psychiatric disorders and/or suicide attempts. The subject has never expressed any suicidal thoughts to the study staff prior to his death. He was concerned about housing, job etc, but he was working on his PhD. He was actively making plans to return to South Beach and to get another job. He was working part-time as a teacher of English to no-English speaking pupils. He had also just bought a new car. Not the usual activities for someone planning on suicide. There were the psychosocial stressors of losing his job and apartment.

Investigator text:

subject missed appointment and phone disconnected. Contacted emergency contact and was informed patient committed suicide on 16 May. Subject has lost his job and his apartment recently. had a history of depression. 08-01-b* per the death certificate and medical examiner's office the cause of death was ethylene glycol and drug intoxication.
This 31-year-old female subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir 50 mg twice daily from 20 July.

As of 20 July, the subject had <20 CD4+ cells/mm³ and a particularly high viral load of 23,390,390 c/mL plasma HIV-1 RNA.

As concomitant ART the subject received: enfuvirtide from prior to Screening until 27 July, maraviroc from prior to Screening until 7 November, atazanavir from 28 July to 31 August, stavudine and tipranavir/ritonavir from 14 November until 16 February.

On 17 August, 28 days after the start of dolutegravir, the subject developed grade 3 or severe CMV systemic infection. The subject was hospitalised. Associated sign/symptoms included fever and grade 2 rashes.

The subject had blood tests performed on the 17 August with evidence of CMV active replication: Agp65=14, CMV-DNA 7000 cp/ml. An ophthalmological evaluation preformed on the same date excluded a CMV retinitis. The subject did not have any relevant medical condition except the known HIV infection with <20CD4+ cells/mm³ and 9,687,850 c/mL HIV-1 RNA at this time point.

There was no organ dysfunction due to CMV localisation. The subject was treated with ganciclovir and prednisone. Treatment with dolutegravir was continued. The event resolved on 03 September. The investigator considered that there was no reasonable possibility that the CMV systemic infection may have been caused by dolutegravir.

Additional follow-up information received on 23 August:

* a*: The year
* b*: Following year
A 47-year-old female has a baseline CD4 of less than 20, and a baseline HIV RNA of 23,390,390 copies/mL (7.37 log 10). She has had minimal virologic response, with HIV RNA at Day 8 (7.26 log 10) or Week 4 (6.99 log 10).

Her CD4 remains less than 20 cells.

She has a reported systemic CMV infection with the following test results:

- **Ag p65 CMV = 14**
- **Blood CMV-DNA = 7000 copies/ml**

Con-meds include Augmentin and atarax, concomitant antiretroviral therapy maraviroc (Celsentri) 300 mg BID and atazanavir 400 mg BID as OBR along with DTG.

Deletion report was received on 28 October a*:

Treatment medication of ganciclovir was deleted.

Investigator text:

On the blood tests performed on the 17th Aug a* evidence of CMV active replication: Agp65=14, CMV-DNA 7000 cp/ml. An ophthalmologist evaluation performed on the same date excluded a CMV retinitis. Patient presented fever and associated a G2 skin rash. No organ dysfunction due to CMV localization.

The subject's past medical history included toxoplasma gondii encephalitis.

As of 10 October a* the subject’s CD4+ cells remained <20/mm³ with 4,021,232 c/mL HIV-1 RNA.

On 18 October a*, 90 days after the start of dolutegravir, the subject developed grade 2 or moderate seizure. The subject was hospitalised. MRI of the brain excluded active neurotoxoplasmosis. The cerebral lesion localized in the right frontal lesion was compatible with residual scarring of the previous neurotoxoplasmosis. EEG showed epileptogenic focus in the right frontal region. The subject was treated with levetiracetam, Cotrimoxazole and atovaquone. Treatment with dolutegravir was interrupted on 18 October a*, re-started on 25 October a* and permanently stopped on 05 November a*. The event resolved on 05 November a*. The investigator considered that there was no reasonable possibility that the seizure may have been caused by dolutegravir.

Follow-up information received via medical monitor on 24 October a*:

Subject had extensive past opportunistic infections that may explain these symptoms including cerebral toxoplasmosis, disseminated cryptococcosis, meningitis and...
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disseminated CMV infection. Current OI prophylaxis includes valganciclovir, sulfamethoxazole-trimethoprim. Current conditions included fever.

Follow-up information received from medical monitor on 27 October a*:

Subject was discharged on 27 October a* with diagnosis of 'seizure in HIV-infected patient with right cerebral ischemia'. Occurrence of new CNS opportunistic diseases have been excluded by MRI. The patient is doing well, she is receiving levetiracetam. It was not known when the ischemic cerebral event occurred; the imaging is not consistent with an acute ischemic episode and the previous MRI (negative for a frontal right ischemic area) was performed years ago.

Follow-up information received on 28 November a* via query response:

Investigator confirmed right cerebral ischemia is not considered to be an SAE.

Diagnostics:

MRI brain: Exclusion of active Neurotoxoplasmosis. The cerebral lesion localized in the right frontal lesion is compatible with residual scarring of the previous neurotoxoplasmosis. EEG: epileptogenic focus in the right frontal region.

Follow-up information received on 23 February b* via answered query report:

The investigator confirmed dolutegravir was discontinued on 05 November a* due to virological failure and suspected allergic rash but not due to the SAE.

Investigator text:

Probable seizure on the 18th October a*. Firstly admitted to "[Redacted]" Hospital in [Redacted] where she started levetiracetam, as seizure prophilaxis, and cotrimoxazole for suspected neurotoxoplasmosis. She was discharged on the 20th October and admitted to our Hospital in the same day.

Medical conditions at the time of the event included human immunodeficiency virus and severe immunosuppression secondary to uncontrolled HIV infection. Concomitant medications included stavudine and tipranavir (Aptivus).

The subject was withdrawn from the study 07 November a*.

On 06 December a*, 139 days after the start of dolutegravir and 31 days after the last dose, the subject developed grade 3 or severe reactivation of systemic cytomegalovirus. Associated symptoms included ipovisus at left eye. The subject was hospitalised. The subject was treated with foscarnet sodium for a total of 18 days with suppression of CMV agp65 and marked decrease of blood CMV DNA. The event resolved on 23 December a*. The investigator considered that there was no reasonable possibility that the reactivation of systemic cytomegalovirus may have been caused by dolutegravir.

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
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Diagnostic text:
CMV/DNA = 86419 copies/ml Agp65 = 220 nuclei

Investigator text:

Diagnosis of CMV systemic reactivation (symptoms; ipovisus at left eye). Patient was treated with Foscavir intravenous for a total of 18 days with suppression of CMV agp65 and marked decrease of blood CMV DNA

The subject's past medical history included severe immunosuppression related to uncontrolled HIV infection. Concomitant medications included Ascriptin.

On 08 December a*, 141 days after the start of dolutegravir and 33 days after the last dose, the subject developed grade 4 progressive multifocal leucoencephalopathy (PML). The subject had been admitted to the hospital with CMV reactivation and PML on 06 December a* with associated symptoms of ipovisus at left eye and mild fever. Brain CT scan showed large right frontal hypodensity and a smaller left frontal subcortical hypodensity. EEG revealed epileptiform alterations in the right cerebral hemisphere. Brain MR showed suspected progressive multifocal leucoencephalopathy in the right frontal-parietal region. The subject was treated with filgrastim, meropenem and valgancyclovir. The subject died on 16 February b* due to progressive multifocal leucoencephalopathy.

An autopsy was not performed. The investigator considered that there was no reasonable possibility that the progressive multifocal leucoencephalopathy may have been caused by dolutegravir.

Follow up information received on 10 January b*:

The primary reason for stopping dolutegravir were rash and itching, of course the concomitant presence of virological rebound made this decision easier.

Follow-up information received on 28 March b* via query response:

I confirm date of diagnosis 08 Dec a*

Follow-up information received 05 April b* via Answered Query Report:

The subject was not receiving any concomitant antiretroviral therapy at the time of this event. An autopsy was not performed.

Investigator text:

The patient was withdrawn from the study on the 07th November a*. She was admitted in our Hospital on 06th December a* for CMV reactivation and PML (symptoms ;

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
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The worsening of PML resulted in death on 16th February b*. -

On 16 November a*, 119 days after the start of dolutegravir and 11 days after the last dose, the subject developed grade 2 or moderate cytomegalovirus infection reactivation. The subject was hospitalised due to fever related to reactivation of CMV systemic infection. The subject was treated with Piperacillin + tazobactam, vancomycin hydrochloride, fluconazole, filgrastim, bromazepam, ganciclovir and potassium chloride. The event resolved on 03 December a*. The investigator considered that there was no reasonable possibility that the cytomegalovirus infection reactivation may have been caused by dolutegravir.

Follow-up information received 05 April b* via Answered Query Report:

Body temperature on admission and discharge was unknown as was admitted to a different hospital.

Investigator text:

Patient admitted to our hospital due to fever related to reactivation of CMV systemic infection.

9.5.4. Other Ongoing Studies in Adults

9.5.4.1. ING115502

Protocol Id: ING115502
Investigator Number: BRA-001
Subject Number: BRA-001-001
Treatment Number:
Case Id: B0783197A
Suspect Drugs: Combivir, Darunavir, Dolutegravir, Etravirine, Ganciclovir, Maraviroc, Paclitaxel, Ritonavir
Serious Events: Cytomegalovirus chorioretinitis, Pulmonary haemorrhage

This 29-year-old male subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received dolutegravir at 50 mg twice daily from 02Feb. -

Medical conditions at the time of the event included kaposi's sarcoma. Concomitant medications included paclitaxel.

On 14Feb a*, the subject developed Grade 1 or mild cytomegalovirus (CMV) retinitis. The subject was hospitalised. Ophthalmic examination and retinography confirmed CMV retinitis. The subject was treated with ganciclovir and treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator
considered that there was no reasonable possibility that the cytomegalovirus retinitis may have been caused by dolutegravir and that the event was possibly due to medical condition CD4 counts, disease under study and immune reconstitution inflammatory syndrome (IRIS).

The subject experienced another SAE of Grade 4 pulmonary bleeding on 08Mar a* and received an IV infusion of 90 mg of Taxol after 4 weeks of interruption of this drug. The subject complained of chest pain during the first hours and went to a nearby hospital. In the emergency room the subject presented with massive pulmonary bleeding. Attempts to reanimate failed. One hypothesis was a bleeding of the Kaposi sarcoma in the lungs after the chemotherapy section. In the past, the subject has presented with many episodes of necrosis of Kaposi sarcoma in the left leg after receiving chemotherapy. The subject also had anaemia and leucopenia during ganciclovir treatment and the subject's last platelet count was 150,000 μL. The subject died on 08Mar a*.

The investigator considered that there was no reasonable possibility that the pulmonary bleeding or the CMV may have been caused by dolutegravir and the event was possibly related to HIV disease, Kaposi sarcoma and CMV retinitis. The event was also due to the concomitant medications taxol, ganciclovir, darunavir, ritonavir, etravirine, maraviroc, zidovudine and lamivudine.

On 02 May a* the subject was withdrawn from the study.

Protocol Id: ING115502
Investigator Number: USA-005
Subject Number: USA-005-001
Treatment Number:
Case Id: B0807217A
Suspect Drugs: Dolutegravir
Serious Events: Adrenal insufficiency, Hypotension, Non-Hodgkin's lymphoma

This 39-year-old male subject was enrolled in an ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received dolutegravir (DTG) 50 mg BID from 19 January 2018 to 21 June 2018.

Medical conditions at the time of the event included HIV infection. Concomitant medications included amoxicillin clavulanate (Augmentin), levofloxacin (Levaquin), piperacillin (Zosyn), fluconazole, ceftriaxone, ampicillin+subbactam, meropenem, valacyclovir and tenofovir.

On 01 Jun 2018, 134 days after starting DTG and ibalizumab, the subject developed fever (103 degrees Celsius) and heart rate high (125 bpm). The subject was hospitalised. The subject had no recorded relevant risk factors. He had been seen in clinic on 31 May a* with fevers and headache attributed to a sinus infection, but it was clear even then this might be something other than a sinus infection. Two weeks later the work-up revealed the 'sinus infection' was actually lymphoma with brain masses. Test results and

a*: The year

* 新薬承認情報提供時に置き換え
examinations were normal, apart from aspartate aminotransferase 79 (normal range 5 – 37 U/L). The subject was diagnosed with Grade 2 or moderate fever and headache of unknown aetiology. Treatment with DTG and ibalizumab was continued. Adrenal insufficiency also diagnosed on 21Jun a*. Hypotension on 03Jul a*. The hypotension due to adrenal insufficiency was of a seriousness that required hospitalisation with ICU care (dopamine drip). Separate SAE form was pending for this event. The hypotension was not related to study medications but was due to NHL. The NHL was never treated despite the placement of a Hickman catheter, because it became clear the subject was too sick to tolerate systemic chemotherapy or brain irradiation. His adrenal insufficiency was initially treated from June 19th, with hydrocortisone and fludrocortisone. When subject was readmitted week of June 25, he was treated with dexamethasone. Despite appropriate corticosteroid therapy, the hypotension did not improve, required life support (dopamine) and eventually it was decided to stop all treatment and change to hospice/comfort care. Pt put on comfort care on around 01Jul a*. On 04Jul a* the subject was diagnosed non Hodgkin's lymphoma. The headache was an aspect of the non-hodgkin's lymphoma NHL (and not an sAE) which invaded liver and pituitary. The adrenal failure was secondary to cancer invading the brain.

The subject received oral dolutegravir 50 mg twice daily from 19 January a* to 21 June a*. Concomitant medications included ibalizumab. The subject was diagnosed with Non-Hodgkin's lymphoma on 04 June a*. The subject died due to this event on 07 July a*.

The investigator considered that there was no reasonable possibility that the fever and heart rate high may have been caused by DTG and ibalizumab and that the events were possibly due to AIDS-related malignancy and suspected sinus infections.

Follow-up information received 31 July a*:

The additional SAEs were hypotension and adrenal insufficiency, both remained unresolved and were not related to investigational products. Stop date of investigational product was updated and reported as 04Jul a*.

Protocol Id: ING115502
Investigator Number: FRA-022
Subject Number: FRA-022-001
Treatment Number: 
Case Id: B0841491A
Suspect Drugs: Dolutegravir
Serious Events: Sepsis, Septic shock

This -year-old male subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir (DTG) at 50 mg BID from an unspecified date.
Medical conditions at the time of the event included encephalitis, Kaposi, meningioma and pancytopenia. Concomitant medications included darunavir, ritonavir, Truvada and maraviroc.

On 25 August, the subject developed septicaemia and septic shock associated with myocardial infarction and cardiorespiratory arrest. The subject died on 31 August due to septic shock and septicemia. The investigator considered that there was no reasonable possibility that the septicaemia and septic shock may have been caused by dolutegravir.

9.5.4.2. ING116529

Protocol Id: ING116529
Investigator Number: 099400
Subject Number: 000241
Treatment Number: 2007
Case Id: Z0016574A
Suspect Drugs: Blinded trial medication-ViiV, Dolutegravir
Serious Events: Cardiac death

This -year-old male subject was enrolled in a ViiV-sponsored, double-blind study to demonstrate the antiviral activity of dolutegravir (DTG) 50 mg twice daily versus placebo both co-administered with a failing antiretroviral regimen over seven days, followed by an open label phase with all subjects receiving DTG 50 mg twice daily co-administered with an optimised background regimen (OBR) in HIV-1 infected, integrase inhibitor therapy-experienced and resistant, adults. The subject received blinded oral investigational product at 1 tablet twice per day from 28 June to 05 July, followed by open-label oral dolutegravir at 50 mg twice per day from 05 July to 31 July.

The subject's past medical history included stroke. Medical conditions at the time of the event included hypertension and left ventricular hypertrophy.

Concomitant ART included enfuvirtide and atazanavir/ritonavir from prior to Screening to 5 July. From 5 July the subject received etravirine and darunavir/ritonavir.

As of the 28 June, the subject had 230 CD4+ cells/mm³ and 3,823 c/mL plasma HIV-1 RNA.

By the 25 July, the subject had 335 CD4+ cells/mm³ and <50 c/mL plasma HIV-1 RNA.

On 01 August, 34 days after the start of investigational product and 27 days after the start of open-label dolutegravir, the subject died at home due to (grade 4) suspected...
cardiovascular death. Exact cause of death was unknown. The subject was withdrawn from the study. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the suspected cardiovascular death may have been caused by investigational product and dolutegravir.

Investigator text:

Subject died at home. No details of the death are known. Subject was seen the day prior for a routine visit with Podiatry and was said to have no complaints. Cause of death is currently presumed vascular in nature as the subject had long history of stroke. To date PI has not been able to contact family for details. we have been unable to get the death certificate, it is unknown if an autopsy was done. Exact cause of death, unknown.
9.6. APPENDIX 6: Case Narratives of Other SAEs and Pregnancies

The Data Source for the Case Narratives included in this section is the Sponsor’s global safety database (OCEANS), which is maintained separately from the clinical trials’ databases for these studies. OCEANS was searched on 01 November for SAE and pregnancy cases initially received by the Global Safety and Pharmacovigilance department for these studies up to 26 October. It is important to note that these studies were ongoing at the time of the OCEANS data search, and thus, these cases are still subject to change. Additionally, discrepancies may arise between subject age presented from OCEANS data compared to age presented from the clinical trials’ databases, since OCEANS reports the age of the subject at SAE onset, whereas the clinical trials’ databases records subject age at Screening.

9.6.1. ING112276 SAE and Pregnancy Case Narratives

9.6.1.1. Cases Reported up to 30 September

The narratives included in this section correspond to the SAEs and Pregnancy cases included in the ING112276 Week 96 CSR (with a data lock point of 30 September for safety data), which is included in m5.3.5.1. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.

Protocol Id: ING112276
Investigator Number: 065759
Subject Number: 000003
Treatment Number: 3049
Case Id: Z0010848A
Suspect Drugs: Dolutegravir
Serious Events: Phlebitis

This 3-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 07 October.

This subject was randomised to receive dolutegravir 25 mg once daily.

No relevant concomitant medications were provided.

On 15 June, 616 days after the start of dolutegravir, the subject developed grade 3 or severe phlebitis of the leg. The subject was hospitalised on 15 July. Treatment with dolutegravir was interrupted for an unknown period of time. The event resolved on 15 August, but details of treatment of the event are unknown. The investigator
considered that there was no reasonable possibility that the phlebitis leg may have been caused by dolutegravir.

Investigator text:

Patient's partner called site on 07-22-c* and stated patient has been in the hospital; since 07-15-c* due to phlebitis on the leg. No further information available at this time. 8/15/c* no further information at this time per source. -

c*: 2 years later
This 30-year-old female subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 04 November 2019.

On 03 February 2019, 91 days after the start of efavirenz, the subject developed grade 2 or moderate bronchitis. The subject was hospitalised. The subject was treated with aspirin, azithromycin, ipratropium bromide, nitroglycerin, sodium chloride, paracetamol, Robitussin AC, Vicodin, potassium chloride and Guaifenesin + dextromethorphan. Treatment with efavirenz was continued. The event resolved on 27 February 2019. The investigator considered that there was no reasonable possibility that the bronchitis may have been caused by efavirenz.

Investigator Text:

Patient went to [deleted] Hospital [deleted] ER and was admitted for Bronchitis from 02/10/b* to 02/13/b*. Records have been requested. Patient was then seen by his PCP as an ER follow up on 02-22-b* these records have been requested as well. Records received, con meds and AE updated.

This 30-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 14 September 2019.

This subject was randomised to receive dolutegravir 50 mg once daily.

No relevant medical history.

b*: Following year

* 新薬承認情報提供時に置き換え
On 01 December a*, 78 days after the start of dolutegravir, the subject developed severe shingles. The subject was hospitalised. Treatment with dolutegravir was continued. The subject was treated with acyclovir, ceftriaxone, vancomycin, and valacyclovir. Results of CT of the Head without contrast on 06-Dec-a* showed no acute intracranial pathology. Chest x-ray on 06-Dec-a* showed probable patchy infiltrates in left lower lobe. Lumbar puncture performed on 06-Dec-a*: CSF analysis did not show evidence of bacterial meningitis. The event resolved on 04 January b*. The investigator considered that there was no reasonable possibility that the shingles may have been caused by GSK1349572.

Investigator text:

Patient was admitted to local hospital for treatment of Shingles on 06-Dec-a*. PI notified of condition 07-Dec-a* patient was discharged from hospital on 08-Dec-a*. Completed treatment with valacyclovir on 17-Dec-a*, shingles are resolved -

Protocol Id: ING112276
Investigator Number: 065762
Subject Number: 000048
Treatment Number: 1011
Case Id: Z0002454A
Suspect Drugs: Efavirenz
Serious Events: Neurosyphilis

This 44-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 23 September .

Medical conditions at the time of the event included neurosyphilis. Concomitant medications included Epzicom and lignocaine hydrochloride.

On 30 October a*, 37 days after the start of efavirenz, the subject developed grade 3 neurological syphilis. The subject was hospitalised. He also experienced peripheral vision loss in the right eye on 05 November a*. The subject was treated with benzylpenicillin. MRI brain showed no intracranial abnormality to explain b/l optic disc swelling. Evidence of papilledema, right greater than left, however, no abnormal intracranial findings to explain the symptoms. He was discharged on 06 November a* with pic-line and pump to administer treatment until 19 November a*. Treatment with efavirenz was continued. The pic-line was removed on 19 November a*. The event resolved on 19 November a*. The investigator considered that there was no reasonable possibility that the neurological syphilis may have been caused by efavirenz.
Investigator text:

patient reported to E.R. on 30-oct-a* with loss of peripheral vision in right eye. Neurosyphilis was diagnosed and i.v. penicilin started every 4 hours. patient kept overnight and discharged on 06-nov-a* with pic-line and pump to administer treatment until 19-nov-a*. Pic-line removed 19-nov-a* and patient scheduled for follow up testing. pt reported event to site on 20-nov-a* at week 8 visit.
This 40-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 28 September.

The subject was randomized to receive dolutegravir 50 mg once daily.

Concomitant medications included midazolam hydrochloride, eptifibatide and prasugrel (Effient).

On 14 July, 654 days after the start of the investigational product, the subject developed grade 4 myocardial infarction without ST elevation. The subject was hospitalized and the event was life-threatening. The subject was treated with nitroglycerin, fentanyl, heparin midazolam hydrochloride, eptifibatide and prasugrel. Treatment with the investigational product was continued. The event resolved on an unspecified date. The investigator considered that there was a reasonable possibility that the myocardial infarction without ST elevation may have been caused by the investigational product. The investigator reported that it cannot be ruled out 100% that dolutegravir was not the cause of the SAE. The investigator indicated that it is "unlikely" but it cannot be ruled out as "not related" to IP.

Diagnostics: On 14 July creatine phosphokinase 1230 unit/L (normal range 61-224), creatine phosphokinase MB 163 ng/ml (normal range 0-3.6), troponin I 7.88 ng/ml (normal range 0-0.007). On 15 July creatine phosphokinase 918 unit/L, creatine phosphokinase MB 61.6 ng/ml, troponin 12.64 ng/ml. Subject had an electrocardiogram with no acute findings. Subject underwent left heart catheterization with ventriculography. Right coronary angiography. Mid RCA was 100% for stenosis. There was a TIMI grade 0 flow through the vessel. Distal left main was 30% stenosis.

Investigator Text:

Subject presented to the Emergency room on 14, July with chest pain. Subject had and an Electrocardigram with no acute findings. Subject underwent Left heart catheterization with ventriculography. Right coronary angiography. Mid RCA was 100% for stenosis. There was a TIMI grade 0 flow through the vessel. Distal left main was 30% stenosis. Currently the subject was a pack a day smoker for 30 years. Patient has a negative history for heart disease. Family history negative for heart disease. Patient was...
discharged home on 16, July c* in stable condition. See con med list for new medication.

Follow-up information received on 20 July c* from clinical:

Admission date 14 July c*, sex male. Impression Non-ST elevated myocardial infarction, HIV, tobacco use and borderline dyslipidemia. The subject had elevated cholesterol, which was diet controlled, when driving home from school yesterday he states he was not feeling well. He had chest tightness with associated dyspnoea, some mild nausea and he took two aspirins. The subjects discomfort continued throughout the evening and he did not have a restful sleep, he awoke at 7 a.m. and continued with chest discomfort, he took two more aspirins and went to school. The subject then went to the emergency room due to continued chest discomfort, his electrocardiogram showed no acute findings, he was in sinus rhythm with incomplete right bundle branch block, no acute ST -T wave changes. The chest discomfort eased with sublingual nitro-glycerine spray. Social history 30 years currently smoking a pack a day, negative family history for heart disease. Review of systems, Physical examination Blood pressure 112/60, and pulse 69, afebrile. Well developed, well nourished male in no acute distress. Neck- supple without jugular venous distension, carotid upstrokes 2+ bilaterally. Respiratory - effort non-laboured. Clear auscultation. Cardiovascular - Regular rate and rhythm. Normal S1, S2. No murmurs. Abdomen - without hepatosplenomegalaly. Extremities- pulse equal and active.

Laboratory values - haemoglobin 13.9, platelets185, sodium 137, potassium 3.5, chloride 100, CO2 27, BUN 5, creatinine 1.2, glucose 13 (units and normal ranges not provided). Chest X ray no acute findings. On 14 July c* AST 114 unit/L (normal range 8-42), AST 32 unit/L (normal range 0-65), albumin 3.8 gm/dl (3.4-5.0), A/G ratio 1.1 (normal range 1.1-2.2) creatinine ration 4.2 (normal range 12.0-20.0) and CK index 13.3%, on 15 July c*, anion GAP 6 mmol/L (normal range 7-16), CHOL 166 mg/dl, TRIG 118 mg/dl, ratio risk 2.0 (normal range less than 0.50), CHOL/HDL 8.30, HDL associated risk less than 1.82, HDL CHOL 20 mg/dl, LDL CHOL 122 mg/dl, CK index 6.7 %.

Cardiovascular catheterization comprehensive report on 14 July c*, procedures performed, left heart catheterization with ventriculography, right coronary angiography, coronary thrombectomy and intervention on proximal RCA, thrombectomy, stent, balloon angioplasty. Indications - Angina/MI; myocardial infarction with ST elevation (NSTEMI), CCS class IV, with onset 12-24 hrs prior to admission. The subject experienced recurrent pain. Summary - Cardiac structures - analysis of regional contractile function demonstrated moderate posterobasal hypokinesis . EF calculated by ventriculography was 45%. Coronary circulation; ostial left main, there was a discrete 30% stenosis , distal left main , there was a 30% stenosis RCA, the vessel was medium to large sized and mildly calcified. Angiography showed severe arthrosclerosis. Proximal RCA; There was a tubular 99% stenosis. The lesion was irregularly contoured, complex and was associated with a moderate filling defect consistent with thrombus. There was TIMI grade 1 flow through vessel (slow flow without perfusion) and poor collateral

* 新薬承認情報提供時に置き換え
blood supply to the distal myocardium. The lesion is a likely culprit for the subjects recent myocardial infarction, mid RCA - there is a 100% stenosis. There was TIMI grade 0 flow through the vessel (no flow). 1st lesion intervention; an unsuccessful attempt at thrombectomy with stent and balloon angioplasty was performed on the 100% lesion in the proximal RCA. Following intervention there was an excellent angiographic appearance with 0% residual stenosis. Transluminal extraction atherectomy was performed. The subject tolerated the procedure well. Impressions: There is significant single vessel coronary artery disease, Successful percutaneous coronary intervention of the right coronary artery, mid left main and 99-100% RCA with faint collaterals. Successful aspiration thrombectomy and DES to RCA with 0% residual TIMI flow. Inferior hypokinesis and mid -mod LV dysfunction.

Additional information received 25 July c* from clinical:

Concomitant medications also included aspirin, metoprolol tartrate, glucosamine chondroitin complex, Truvada, valerian, and trazadone.

The patient was recently hospitalized for acute myocardial infarction. He had intervention with angioplasty and stent placement. He has done quite well. He has been placed on lipid lowering therapy. He has also been suggested to discontinue tobacco use. At this point, I think it is safe for him to continue on his study medication. While it is difficult to exclude contribution of the medicine to his recent diagnosis, I think his underlying risk factors for coronary artery disease are the most likely culprit for his recent events. Risk modification of lipids and smoking cessation are most important at this time. The patient understands the risk of further heart disease without modification of these risk factors. He also understands there may be some inherent risk of HIV disease to the development of heart disease.

Protocol Id: ING112276
Investigator Number: 065769
Subject Number: 000076
Treatment Number: 3017
Case Id: Z0005514A
Suspect Drugs: Dolutegravir
Serious Events: Pyrexia

This 2-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 11 September 2020.

The subject was randomized to receive dolutegravir 50 mg once daily.

Concomitant medications included Truvada.
On 29 August b*, 352 days after the start of dolutegravir, the subject developed fever of unknown origin and chills. The subject was hospitalised. The investigator reported possible diagnosis of probable viral syndrome. Treatment with dolutegravir was continued. The event resolved on 31 August b*. No relevant assessments were reported. The investigator considered that there was no reasonable possibility that the fever of unknown origin and chills may have been caused by dolutegravir.

Investigator text:

Subject admitted to the hospital by ER physician for chills and fever. No other information available at this time discharged from hospital on 31 AUG b* with diagnosis of "probable viral syndrome."

This 45-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject was randomized to receive dolutegravir 25 mg once daily from 15 September to 20 July c*. The subject switched to the open-label phase and received oral dolutegravir 50 mg per day from 21 July c*.

The subject had a history of bipolar disorder and hypertension. Concomitant medications included Truvada.

On 15 August c*, 699 days after the start of investigational product and 25 days after the start of open-label dolutegravir, the subject developed grade 3 or severe meningitis. The subject presented to the ER on 17 August c* complaining of 2-day history of headache, neck pain, and fever up to 102.7F. Headache was reported as gradual onset, diffuse, with associated photophobia. Reported headache was constant and had no alleviating or exacerbating factors. The subject was hospitalised. CT of brain and chest x-ray were both negative; CSF Fluid 17Aug c*: WBC 375 (0-5/cmm) Poly 1% (3-7%), Lymph 53 (28-96%), RBC 49 (0/cmm), Protein 97 (15-45); CSF cultures were negative; cryptococcal culture was negative. Laboratory test results dated 18 August c* included haematocrit 39.8% (normal range 42-50). WBC, haemoglobin, platelets and creatinine were within normal range. The subject was treated with vancomycin and Bactrim. Treatment with dolutegravir was continued. The event resolved on 23 August c*. The investigator considered that the possible cause of the SAE was intercurrent illness and that there was no reasonable possibility that the meningitis may have been caused by investigational product and dolutegravir.
Investigator text:

Subject presented to the ED on 17Aug c*, after returning from Nicaragua the previous day with complaints of 2 days headache, neck pain, and fever up to 102.7F. Headache was reported as gradual onset, diffuse, with associated photophobia. Reported headache as constant and has no alleviating or exacerbating factors. CT of brain, chest x-ray both negative. CSF cultures were negative. Cryptococcal culture negative. -
This 42-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 22 October.

This subject was randomised to receive dolutegravir 25 mg once daily.

The subject's past medical history included lumbar puncture, nausea and vomiting. Medical conditions at the time of the event included hypertension and neurosyphilis. Concomitant medications included Epzicom.

On 11 January b*, 81 days after the start of investigational product, the subject developed grade 2 or moderate headache. The subject was hospitalised. The subject was treated with paracetamol, morphine and hydrocodone. On 11 and 12 February b*, laboratory test results showed random urine protein (29H) Reference (0-12) Units mg/dl; Serum Iron 38L Reference (65-175) Units mcg/dL; Hematocrit (27.9L) Reference (40.0-52.0) Units g/dL. Treatment with investigational product was continued. The event resolved on 14 January b*. The investigator considered that there was no reasonable possibility that the headache may have been caused by investigational product and that the event was occurred as a result from complications of the lumbar puncture.

Investigator text:

Pt returned to clinic four days after lumbar puncture for headache. Blood patch ordered, performed in Emergency Room. Pt admitted due to inability to obtain approval from his insurance company for home IV therapy. IV therapy was started in hospital and once approval was obtained pt was discharged on home therapy. Subject was admitted to hospital on 1/11/b* due to headaches. Pt. was discharged from hospital on 1/14/b*. SAE was a result from complications of lumbar puncture. Relevant medications for SAE are added to SAE report. Concomitant medications will be added to concomitant medication page. -

b*: Following year

* 新薬承認情報提供時に置き換え
This 26-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 13 October.

Medical conditions at the time of the event included hydrocephalus and ventricular-peritoneal shunt. Concomitant medications included pantoprazole, ondansetron hydrochloride, cephazolin sodium, Hydrocodone APAP, promethazine and Epzicom.

On 31 May, 595 days after the start of investigational product, the subject developed grade 3 or severe worsening hydrocephalus. The subject was hospitalised on 31 May after presenting to the ER with acute confusion, history of hydrocephalus and VP shunt blockage. Treatment with dolutegravir was continued. The subject was discharged on 02 June. The subject was re-hospitalised for planned treatment (ventriculoperitoneal shunt exploration and replacement of peritoneal catheter) on 27 June. The event was resolved on 01 July and the subject was discharged. The investigator considered that there was no reasonable possibility that the worsening hydrocephalus may have been caused by investigational product.

Investigator text:

Pt admitted to the hospital 5/31/c after presenting the ER with acute confusion and hx hydrocephalus and VP shunt blockage. He was admitted for evaluation and released on 6/2/c. Further information will be provided after records are received. 7/5/c- Subject called to make sure we were aware he was in the hospital from 6/27/c - 7/1/c for his scheduled/ planned Ventriculoperitoneal shunt exploration and replacement of peritoneal catheter. We had not received a discharge summary from the 5/31/c visit. Per pt he was scheduled with the neurologist for surgery, VP Shunt Revision on 6/27/c after his initial discharge. -

The subject's past medical history included hydrocephalus. Concomitant medications included cephazolin sodium, ceftriaxone, pantoprazole, prochlorperazine, vancomycin, Lomotil, ondansetron hydrochloride, promethazine, efavirenz and abacavir sulphate + lamivudine (Epzicom).

On 27 July, 652 days after the start of investigational product, the subject developed grade 3 or severe ventriculoperitoneal shunt malfunction. The subject was hospitalised and the event was life-threatening. The subject presented to the ER with an unbalanced
gait, difficulty with memory and vision. The subject underwent surgery for ventriculoperitoneal shunt revision and replacement of distal catheter. He was discharged in a stable condition on 29 July c*. The subject was readmitted on 06 August c* due to shunt malfunction and revision, and was discharged on 08 August c*. The subject was then hospitalized again on 14 August c* due to shunt malfunction and revision / replacement. The subject was treated with vancomycin, ceftriaxone sodium and ertapenem sodium. Treatment with investigational product was continued on 12 September c*. The event resolved on 07 September c*. The investigator considered that there was no reasonable possibility that the ventriculoperitoneal shunt malfunction may have been caused by investigational product.

Investigator text:

Pt presented to the ER on 7/27/c* with unbalanced gait, difficulty with memory and vision. Same symptoms as previous month when he had a VP Shunt malfunction. Pt was admitted and taken to surgery for a Ventriculoperitoneal shunt revision and replacement of distal catheter. He was discharged in stable condition on 7/29/c*.

Pt was admitted to the hospital again on 8/6/c* - 8/8/c*, shunt malfunction and revision. Hospitalized again 8/14/c*, shunt malfunction and revision/replacement. Pt was released from the hospital on 9/7/c* after treatment for Hydrocephalus shunt infection.

Protocol Id: ING112276
Investigator Number: 067140
Subject Number: 000551
Treatment Number: 3042
Case Id: Z0007273A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia

This 21-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 05 October b*. The subject was randomized to receive dolutegravir 50 mg once daily. The subject was a current smoker.

On 30 December b*, 451 days after the start of investigational product, the subject developed grade 4 pneumonia aggravated. The subject presented to the ER with cough. The subject was hospitalised on 30 December b*. Chest X-ray was normal; thoracic CT scan showed alveolar infection of left inferior pulmonary lobe. Laboratory test results dated 30 December b* included partial pressure of oxygen 64 mmHg (NR: 80.0-100.00) and C-reactive protein 346 mg/l (NR: 0.0-3.0). The subject was treated

b*: Following year
c*: 2 years later
with Augmentin, terbutaline sulphate, salbutamol sulphate and paracetamol. On 03 January c*, C-reactive protein was 62.9 mg/l. Treatment with investigational product was interrupted 30 December b* because the subject did not bring the investigational product with him during his hospitalisation. Treatment was restarted on 06 January c*. No diagnosis for the aetiology of the pneumonia was reached. The event resolved with sequelae on 10 January c*. The sequelae for pneumonia aggravated was radiological signs (left alveolar opacity). The investigator considered that there was no reasonable possibility that the pneumonia aggravated may have been caused by investigational product.

Investigator text:

cough since 27/12/b*, the patient went to the emergency unit, CT scan found alveolar infection 72h00 later the hospitalisation clinical status improvement with cough and inflammatory syndrome decrease. CRP 62.9 mg/l. No more lung crepitation.

Protocol Id: ING112276
Investigator Number: 066775
Subject Number: 000614
Treatment Number: 4005
Case Id: Z0002709A
Suspect Drugs: Dolutegravir
Serious Events: Joint dislocation

This 40-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 08 September a*.

This subject was randomised to receive dolutegravir 10 mg once daily.

Concomitant medications included Truvada and enoxaparin.

On 06 November a*, 59 days after the start of investigational product, the subject accidentally slipped on the floor. An X-ray on 26 November a*, showed he had developed moderate patella dislocation. The subject did not experience any associated events / conditions. He was hospitalized and underwent surgery on 21 December a*. Treatment with investigational product was continued. The event resolved on 24 December a*. The investigator considered that there was no reasonable possibility that the patella dislocation may have been caused by investigational product.

Investigator text:

On 6th of November a*. subject slipped accidentally at the floor. X-ray showed a Patellaluxation of left knee. Yesterday Patient went to hospital for surgery due to the
Patellaluxation. Personal communication: SAE recovered without sequelae. Hospital report not available.
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Module 2.7.4 Summary of Clinical Safety

Protocol Id: ING112276
Investigator Number: 066775
Subject Number: 000616
Treatment Number: 3018
Case Id: Z0010918A
Suspect Drugs: Efavirenz
Serious Events: Depression

This 26-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 14 September.

Medical conditions at the time of the event included depression. Concomitant medications included Truvada.

On 23 July, 677 days after the start of investigational product, the subject developed grade 2 or moderate worsened depression. The subject was hospitalised. The subject was treated with lorazepam, citalopram and quetiapine. Treatment with investigational product was continued. The event resolved on 15 September and the subject was discharged. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by investigational product.

Investigator text:

Admission to psychiatric hospital by subject (himself). During hospitalisation psychotherapeutic treatment. Discharge date from Hospital on 15 Sep. c*

Protocol Id: ING112276
Investigator Number: 066775
Subject Number: 000623
Treatment Number: 3061
Case Id: Z0009763A
Suspect Drugs: Dolutegravir
Serious Events: Cholelithiasis

This 23-year-old female subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 14 October.

This subject was randomised to receive dolutegravir 10 mg once daily.

Concomitant medications included pantoprazole and Truvada.

c*: 2 years later
On 16 May c*, 579 days after the start of dolutegravir, the subject developed grade 1 or mild gallstone. The subject had no past history of gallstones. The subject was hospitalised and a cholecystectomy performed on 16 May c*. Treatment with dolutegravir was continued. The event resolved on 02 June c*. The investigator considered that there was no reasonable possibility that the gallstone may have been caused by dolutegravir.

Investigator Text:

Surgery due to gall stones

the patient was admitted to the hospital on 27.05. c* for a planned laparoscopic cholecystectomy. Surgery took place on 30.05. c* without any problems. The patient was discharged on 2.6. c*

This 21-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 03 November a*.

This subject was randomised to receive dolutegravir 10 mg once daily.

The subject had no known medical conditions or risk factors. Concomitant medications included Truvada and ibuprofen.

On 07 November a*, four days after the start of investigational product, the subject developed moderate maxillary abscess. The subject was hospitalised. The subject also experienced a painful swollen right cheek. The abscess was lanced and the tooth was extracted. The subject was treated with phenoxyymethylpenicillin potassium. Treatment with investigational product was continued. The event resolved on 14 November a*. The investigator considered that there was no reasonable possibility that the maxillary abscess may have been caused by investigational product.

Investigator text:

An abscess at the right maxilla was diagnosed. Therefore, a hospitalization was initiated. The abscess was lanced and the tooth was extracted. The patients could be discharged as recovered on 14th Nov a*.
This 39-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 04 September.

The subject was randomized to receive dolutegravir 50 mg once daily.

Medical conditions at the time of the event included medical consultation. Concomitant medications included Truvada.

On 21 March, 563 days after the start of dolutegravir, the subject slipped on stairs, fell on the left arm and developed grade 2 or moderate subcapital humerus fracture. The subject was hospitalised and surgery performed. The subject was treated with dipyrone, nadroparine calcium, etoricoxib and tilidine hydrochloride. Treatment with dolutegravir was continued. The event resolved on 13 July. The investigator considered that there was no reasonable possibility that the subcapital humerus fracture may have been caused by dolutegravir.

Investigator text:

Patient slipped on the basement stairs and fell on the left arm.

This 33-year-old female subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 12 October to 14 August.

The subject was randomized to receive dolutegravir 10 mg once daily. The subject switched to the open-label phase and received oral dolutegravir 50 mg per day from 15 August.

Investigator text:

Patient slipped on the basement stairs and fell on the left arm.

* New confidentiality agreement applied.
Medical conditions at the time of the event included pancytopenia. Concomitant medications included nevirapine and Truvada.

On 30 August c*, 687 days after the start of investigational product, 15 days after the start of open-label dolutegravir and nine days after the last dose, the subject developed grade 2 or moderate exanthema. The subject experienced fever of unknown cause on 30 August c*. On 02 September c* the subject developed an additional exanthema on the body. The subject was hospitalised for observation. The investigator considered that there was no reasonable possibility that the exanthema may have been caused by dolutegravir and that the event was possibly due to the concomitant medication, nevirapine or due to possible other viral infection due to underlying pancytopenia.

The subject also experienced drug exposure during pregnancy. The pregnancy was confirmed by urine pregnancy test on 01 September c*. Date of last menstrual period was 28 July c*; estimated date of delivery was 03 May d*. The exanthema resolved on 05 September c*. The subject was hospitalized on 30 April d* and on 01 May d*, at 39 weeks gestation, the subject gave spontaneous birth to a normal female infant, weighing 2695 g, Apgar score first assessment 08, second assessment 09.

Follow up received on 21 September c* on paper pregnancy form:

The subject stopped contraception on date of visit due to pregnancy. Treatment with dose-blinded dolutegravir was completed on 14 August c*. Treatment with open-label dolutegravir was stopped on 21 August c*.

Investigator text:

Since 30 Aug c* subject showed fever unknown cause. On 02 Sep c* subject got additional exanthema on the body. Fever and exanthema was possible NVP related, possible other viral infection due to underlying pancytopenia. Subject is pregnant (only confirmed by urine pregnancy test on 01 Sep c*). Intake of Nevirapine and Truvada was stopped on 02 Sep c*. Admission to hospital for observation Last Menses 28.07.c*. Estimated delivery date 03.05.d*. On 01 May d* spontaneous birth of a female infant without any complications. Hospitalisation 30 Apr. to 02 May d*. No birth defects or other disorders. Infant length 48 cm, weight 2695 g. Apgar score first assessment 08, second assessment 09. Gestational weeks at birth: 39. No further drug exposures during pregnancy. -
This 27-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 29 October.

This subject was randomised to receive dolutegravir 50 mg once daily.

Medical conditions at the time of the event included human immunodeficiency virus infection. Concomitant medications included Ampicillin + sulbactam, ciprofloxacin, allopurinol, itraconazole, fluconazole, bisoprolol, ramipril, gemfibrozil, valaciclovir hydrochloride, Piperacillin/tazobactam, amikacin, vancomycin, ranitidine hydrochloride, omeprazole, ceftazidime sodium and methylprednisolone.

On 23 March b*, 145 days after the start of investigational product, the subject developed grade 4 Burkitt like Non Hodgkin Lymphoma. The subject also experienced fever, night sweats, weight loss, arthro-myalgiae, thoracic pain, bilateral leg edema and increasing anaemia. The subject was hospitalised. Laboratory tests showed haemoglobin on 9.2 g/dL (14 - 18), white blood cell count 15.900 cells/ul (normal range 4 - 10), C-reactive protein 340 mg/l (normal range 1-5) on 01 April b*, haemoglobin was 8.7 g/dL on 02 April b* and lactic dehydrogenase was 1053 u/l (125 - 220), white blood cell count 11.540 cells/ul (normal range 4-10), C-reactive protein 252.35 mg/l (normal range 1-5), erythrocyte sedimentation rate 54mm (normal range 2-28) on 02 April b*.

On the 02 April b*, the subject did an abdomen echography showing an iso-iper-ipo-echogenic mass involving the liver, the walls of the stomach and of the gallbladder. It showed also other intra-abdominal masses causing a compression of the left ureter. On the same day, he did a thorax-abdomen-pelvis TAC confirming these data and adding information about the involvement of different lymph nodes and multiple intestinal loops. It showed also a small nodule in the right lung, pericardic and left pleural effusions. On 07 April b*, he did a cytological exam of an abdominal lymph node, on 08 April b* an osteo-medullar biopsy and on 09 April b* a biopsy of a gastric mass: all of these exams confirmed a Non-Hodgkin lymphoma (subtype: Burkitt like). The gastroscopy showed also an erosive esophagitis and a double duodenal ulcer, unknown before. On the 09 April b*, the colonoscopy showed a constriction of the sigma by an abdominal mass, while a brain TAC on 08 April b* was negative for lesions. Treatment with investigational product was discontinued on 03 April b* and the subject was withdrawn from the study. The subject was treated with cyclophosphamide, rituximab, methotrexate and vincristine. Burkitt like Non Hodgkin Lymphoma was unresolved at the time of reporting. The investigator considered that there was no reasonable possibility that the Burkitt like Non Hodgkin Lymphoma may have been caused by investigational product.

Follow up information received on 24 May b*, 26 May b*, 01 June b* from medical monitor:

A malignancy or tumour was suspected so the subject was admitted and the following work ups were performed: colonoscopy, gastroscopy and CT scan. On CT scan, a large
mass was seen in the intestine especially in the stomach. On gastroscopy, erosive esophagitis was seen, the cause of which is unclear. Roughly 10 small masses or polypoid lesions were seen in the stomach curvature. In one of the gastric masses an ulceration was seen. Any ulceration visualised in the stomach appeared in the polypoid lesion and was not seen on normal gastric lining. The pylorus appeared normal. The duodenum also had a large mass which was hyperaemic and had a double ulcer contained within the mass. An upper endoscopy was never performed because he had not experienced any symptoms consistent with peptic ulcer disease or esophagitis. He was not using FANS. For erosive esophagitis, a possible infectious aetiology was not tested. The investigator reported that it was impossible to establish the cause for the erosive esophagitis and duodenal ulcers.

Biopsies were taken from the masses/ulcers in the stomach and the pathology revealed Burkitt's lymphoma. Overall, the intestinal findings were felt to be related to the Burkitt’s lymphoma which was felt to be related to the HIV so the events were reported as unrelated to treatment with investigational product. Medical report included CT scan report, pictures from the gastroscopy, a report from the gastroscopy and the pathology report from the gastric biopsies.

Follow up information received on 10 June b* from medical monitor:

Diagnostic assessment included endoscopy of the upper digestive on 09 April b* which showed multiple linear non-confluent erosions > 5 mm long of the mucous surface of distal oesophagus. Cardia in correct position. Gastric hypersecretion coloured with bile, present in the cavity with fasting patient. Between body and fundus, in the body and between body and pyloric antrum, presence of multiple vegetative and ulcerated lesions (approximately 10), with diameter of 15 to 45 mm, traces of hematin, easily bleeding when touched, suspected as loci of lymphoproliferative process; multiple biopsies are carried out. Patent pylorus. Hyperemic duodenal ampulla, congest and deformed by the presence of two "kissing" ulcerative lesions with 20 and 10 mm diameter, respectively. The ulcer on the anterior wall has haematin on ulcer base (Forrest IIc). No lesions in the second duodenal portion.

The conclusions were erosive esophagitis (grade B Los Angeles), Multiple gastric neoformations: biopsies. Double duodenal ulcer.

A gastric mucosa sample was examined under microscope. The sample consisted of multiple fragments of gastric mucosa taken from the antrum and the body; several fragments show proliferation of medium and large lymphoid elements with hyperchromic nucleus, aggressive and partially destructive to glandular structures, diffusely positive for CD20, BCL6, and CD10; weak BCL2 expression, negative for CD5.

The conclusions were Non-Hodgkin medium and large B-cell gastric lymphoma, morphologically and phenotypically consistent with Burkitt/Burkitt-like lymphoma.

In addition, chest and abdomen pelvis CT was performed. This showed the following;
In the anterior basal segment of the right inferior right lobe, a small 5 mm parenchymal nodule is seen. Small nonspecific subpleural nodules are also recognizable in the right superior lobe, few millimeters long. Left pleural effusion of limited entity. The impregnation of the hepatic parenchyma is uneven, the liver is enlarged, on the posterior side of the left lobe the parenchyma cannot be distinguished from hypodense tissue, probably connected to the gastric wall at the antrum. Such tissue, which seems to infiltrate the hepatic parenchyma in certain areas, is almost 5 cm thick.

The spleen is enlarged. Marked thickening of a loop, probably of the small bowel, located in the pelvis and in the right median and paramedian area, touching the anterior abdominal wall. The wall of the thickened loop is over 2 cm thick. It is hardly distinguishable from adjacent loops and from large adenopathies located in the mesentery, the largest one on the front of the carrefour on the right lateral side is over 8 cm.

Multiple lymph nodes are seen along the inferior mesenteric vessels in front of the sacrum and along the coccyx in the right pararectal area and along the right hypogastric vessels; the larger lymph nodes have a transverse diameter of 5,7 cm in the right pararectal area and of 5 cm in the left presacral area. Small-sized adenopathic tissue in the interaortocaval and left para-aortic area.

In conclusion, it was reported most likely abdominal lymphoproliferative disease with multiple loci at the intestinal loops, including the stomach, the latter one indistinguishable from the liver.

Investigator text:

On 1st of April b* the patient was hospitalized in our unit because of fever, night sweats, weight loss, arthro-myalgiae, thoracic pain, bilateral leg oedema, increasing anaemia since a week before. In the days after, the blood test (particularly, high LDH), the echography and the TAC of the abdomen suggested a lymphoproliferative pathology, confirmed by the cytological exam of an abdominal lymph node, by the gastric and the osteo medullar biopsy, and characterized as a Non-Hodgkin lymphoma Burkitt/Burkitt like, an AIDS-defining condition. On the 12th of April, the patient went to the department of haematology to start the specific chemotherapy.
This 27-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 08 October.

This subject was randomised to receive dolutegravir 25 mg once daily.

Medical conditions at the time of the event included hypertension and smoking. The subject also had a long standing issue with an increased creatinine level.

On 31 January c*, 480 days after the start of dolutegravir, the subject developed grade 2 or moderate pneumococcal pneumonia. The subject presented to a local centre due to fever, dyspnoea, diarrhoea and vomiting on 29 January c*. Laboratory tests performed on that day indicated alteration of renal function. The subject was discharged with oral hydration. On 31 January c*, the subject returned to the centre with worsening symptoms and was hospitalised. Laboratory test results dated 31 January c* included creatinine 2.18 mg/dl (NR: 0.3-1.3), d-dimmer 1010 mg/ml, and C-reactive protein 8 mg/dl (NR: 1.0). The subject was treated with levofloxacin. Treatment with dolutegravir was interrupted on 31 January c*. The event resolved on an unspecified date and the subject was discharged. Treatment with dolutegravir was re-started on 03 March c*.

The investigator considered that there was no reasonable possibility that the pneumococcal pneumonia may have been caused by dolutegravir.

Follow up received via email on 07 February c*:

The subject was hospitalised on 31 January c*: for acute renal renal insufficiency based on altered creatinine values (2.18 mg/dl) Rehydration was started and the current HAART temporarily stopped on admission. The day after the creatinine value improved (1.71 mg/dl), but the subject showed worsening oxygen saturation (pO2 :58 mmHg). On 02 February c*, an x-ray scan of the thorax revealed the appearance of a reduced transparency in the middle of the lower region (not showed in a previous exam on admission). On 03 February c*, the pneumococcal antigen test was positive. Antibiotic therapy with levofloxacin was started. At the time of this report, the subject's clinical status was improving and remained in hospital. The diagnosis was pneumococcal pneumonia with acute renal insufficiency secondary to dehydration. The events were not related to the investigational product.

Investigator text:

on the 29 Jan c* the patient went to a local centre for fever, dyspnoea, diarrhoea and vomiting. Lab test performed on that date indicated an alteration of renal function. The patient was discharged with oral hydration. on the 31 Jan c*, the patient returned to our centre for a worsening of symptomatology. Patient was admitted and a retest was performed, confirming the elevated parameters: creatinine 2.18 mg/dl, d-dimmer 1010 mg/ml, and CRP 8 mg/dl.
This 30-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 08 October 2014. Concomitant medications included Kivexa.

On 25 February b*, 140 days after the start of efavirenz, the subject developed grade 2 or moderate acute epididymitis. The subject was hospitalised. The subject was treated with ceftriaxone, gentamicin sulphate, metronidazole and aspirin. Treatment with efavirenz was continued. The event resolved on 12 March b*. The investigator considered that there was no reasonable possibility that the acute epididymitis may have been caused by efavirenz.

This 30-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 15 October 2016. This subject was randomised to receive dolutegravir 10 mg once daily.

Concomitant medications included Kivexa.

On 13 July c*, 636 days after the start of investigational product, the subject died due to automobile accident and multiple injuries. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the multiple injuries and automobile accident may have been caused by investigational product.
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Module 2.7.4 Summary of Clinical Safety

Investigator Text:

On the 08Aug c* wife of the patient called the Investigator and informed that the patient died on 13Jul c* due to the car accident. During the event patient was driving. According to the patient's wife before car accident the patient did not any problems with his health. The another car moved into the opposite carriageway and crashed in the car of the patient. Patient died in the car due to multiple trauma and ongoing internal bleeding.

Protocol Id: ING112276
Investigator Number: 067273
Subject Number: 000833
Treatment Number: 1046
Case Id: Z0002540A
Suspect Drugs: Dolutegravir, Levonorgestrel
Serious Events: Dysmenorrhoea

This 2-year-old female subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 29 October.

This subject was randomised to receive dolutegravir 10 mg once daily.

Medical conditions at the time of the event included torpid endometritis. Concomitant medications included levonorgestrel, Kivexa, pefloxacin and metronidazole.

On 13 November a*, 15 days after the start of investigational product, the subject developed severe dysmenorrhea after intake of postinor. The subject was reported to have carried out a urine pregnancy test by herself, last menses was reported to be 31 October a*, however a local urine pregnancy test and intrauterine ultrasound carried out on 26 October a* were negative. The diagnosis of pregnancy was unconfirmed by the investigator. The subject was hospitalised and the event was disabling. The subject was not pregnant according to urine pregnancy test and ultrasound scan showed dysmenorrhoea, signs of endometritis. Treatment with investigational product was continued. The subject was treated with perfloxacin and metronidazole. The event resolved on 08 December a*. The investigator considered that there was no reasonable possibility that the dysmenorrhoea after intake of postinor may have been caused by investigational product and that the event was possibly due to the concomitant medication, levonorgestrel.

Information received from Medical monitor on 30 December a*:

The subject was hospitalised from 07 to 14 December a*, and was diagnosed with a "menstrual disorder in association with COS, smoldering endometritis, ARVI, herpes, and anaemia". Relevant test results included haemoglobin 107 g/l, white blood cell count 4.6x10^9/l, erythrocyte sedimentation rate 28 mm/h, platelet count 318x10^9/l (normal

a*: The year

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* 新薬承認情報提供時に置き換え

c*: 2 years later
ranges not provided). An ultrasound of the pelvis showed smooth, homogenous uterus (54x41mm). Conclusion of menstrual disorder - first phase of cycle; signs of endometritis, and no pregnancy.

Investigator text:

Subject was not reported to be pregnant as a urine pregnancy test and ultrasound scan results were both negative.

Protocol Id: ING112276
Investigator Number: 065722
Subject Number: 000904
Treatment Number: 4019
Case Id: Z0010364A
Suspect Drugs: Dolutegravir
Serious Events: Mallory-Weiss syndrome

This 33-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 30 September.

This subject was randomised to receive dolutegravir 25 mg once daily. On 29 June, 637 days after the start of investigational product, the subject developed grade 1 or mild Mallory-Weiss Syndrome. Small hiatus hernia was not an additional SAE. The subject was hospitalised. The subject was treated with omeprazole and terlipressin. Treatment with blinded trial medication was interrupted and restarted on 01 July. The event resolved on an unspecified date. The investigator considered that there was no reasonable possibility that the Mallory-Weiss Syndrome may have been caused by investigational product.

Follow-up information received via Clinical Study Team on 04 July:

The subject did not have coughing or vomiting (without hematemesis) prior to developing hematemesis. No other findings other than the Mallory Weiss tear were reported. There was evidence of an ulcer found during the subject's gastroscopy. No studies were conducted to assess for H. pylori. The subject was diagnosed with chronic hepatitis C, but there was no evidence of cirrhosis in previous blood test, abdominal echography (January) or fibroscan (May). No evidence of gastric or duodenal varices on the upper endoscopy. The Mallory Weiss tear did not appear to be healing on the upper endoscopy exam. There was evidence to show a decline in hemoglobin as a result of this event (from 144 g/l to 119 g/l).

Follow up received from the Medical Monitor on 01 July: An endoscopy performed on 30 June showed: oesophagus, mucosa and diameter was normal. There were no
oesophageal varices, stenosis or neoplasia. Cardia: hiatus at 37cm from dental arch with oesophagus-gastric union (EGU) at 35cm, just below (EGU) at 2 hours position a 6mm tear was present with a vein in the centre but without bleeding. Diluted adrenaline (1:100000) was injected around the lesion (3 cc in total) and then etoxisclerol in the vein. Stomach: spared blood remained high in the fundus that are aspirated. Subjacent mucosa was evaluated. No lesions were seen in the mucosa layer, fundus and body. Retroflexion showed that was no fundus, subcardia and other alterations. Pylorus: cantered and permeable. Duodenum upper: no peptic lesions nor steroids.

Endoscopic diagnosis:

Mallory-Weiss with a visible vein, but with no active bleeding. Endoscopic treatment with sclerosis. Small hiatus hernia

Follow-up information from medical monitor on 06July c*:

The subject woke up asymptomatic on 29June c* at 15:00. After an hour, he vomited the blood. After that, there were 3 or 4 vomiting with blood between 17:00 and 21:00. There were no nausea nor cough. The subject did not use any NSAID. He consumes alcohol occasionally, and the last time he did was the previous night before the SAE (1/3 litre of beer and two whiskeys). Local blood results and discharge report was pending at time of this report.

29June c*:

Alanine aminotransferase 29u/l(N=5-45); Albumin 4.1g/dl(N=3.5-5); Alkaline phosphatase 56u/l(N= 40-130); Aspartate aminotransferase 23u/l (N=5-37); Bilirubin 1.0 mg/dl (N= 0.2-1); Gamma GT 41u/l (N= 8-61); Haemoglobin 14.4g/dl (N=13.1-17.3); Platelet count 292x10^3/ul (N=120-313); Protein6.7g/dl (N=6-8); White blood cells 18.33x1000/ul (N=3.4-10.1)

30Jun c*: Haemoglobin 11.9g/dL; Platelet count 253x10^3/ul; White blood cells 12.51x10^3/ul

04July c*: Haemoglobin 9.8g/dL; Platelet count 256x10^3/ul; White blood cells 8.16x10^3/ul

Diagnostics:

ENDOSCOPIC DIAGNOSES: 1.- Mallory-Weiss with a visible vein, but with no active bleeding. Endoscopic treatment with sclerosis. 2.- Small hiatus hernia

COMMENTS: There are no images of the exploration as it has been done in the surgical room.

Investigator text:

The patient was admitted in the ER, hematemesis reported. Gastroscopy was performed and diagnosed Mallory-Weiss Syndrome (no active bleeding). Patient was discharged
asymptomatic with good health status. IP was restarted on 01 JUL c*. ENDOSCOPIC DIAGNOSE:

1.- Mallory-Weiss with a visible vein, but with no active bleeding. Endoscopic treatment with sclerosis.

2.- Small hiatus hernia

After reviewing endoscopy report, the event should be defined as mucous tear related to Mallory Weiss syndrome instead of ulcer. -

Protocol Id: ING112276
Investigator Number: 065726
Subject Number: 000925
Treatment Number: 2001
Case Id: Z0003181A
Suspect Drugs: Dolutegravir
Serious Events: Foot fracture, Foot fracture, Wrist fracture

This 32-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 30 September.

This subject was randomised to receive dolutegravir 50 mg once daily.

On 25 January b*, 117 days after the start of dolutegravir, the subject was in a traffic accident and developed grade 3 or severe scaphoid fracture, grade 3 or severe fracture of the fifth metatarsal and grade 3 or severe fracture of the cuboid bone. The subject was hospitalised. The subject was treated with ketoprofen and enoxaparin. Treatment with dolutegravir was continued. The fractured fifth metatarsal and fractured cuboid bone resolved with sequelae on 29 March b*, and the fractured scaphoid bone resolved on 05 April b*. The investigator considered that there was no reasonable possibility that the scaphoid fracture, fracture fifth metatarsal and fracture of the cuboid bone may have been caused by dolutegravir.

Investigator Text:

Patient who has had a traffic accident on 25/jan/b*. He was admitted to the hospital 24 hours; Actually, he is immobilized in 1/3 distal right leg and 1/3 distal of both upper limbs, because of the fractures. -
This 44-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 14 October.

Concomitant medications included Truvada.

On 05 July, 629 days after the start of investigational product, the subject developed grade 1 or mild acute gastroenteritis. The subject was hospitalised on 10 July in the ER due to an acute episode of diarrhoea. The subject experienced 5-7 bowel movements per day, liquid consistence, no pathologic products, abdominal pain, loss of appetite but no vomiting or high temperature. Physical examination was normal, non tender abdomen. Treatment consisted of fasting for 48 hours, except for medication, and intravenous fluids. Treatment with blinded trial medication-viiv was continued. The event resolved on 13 July and the subject was discharged. The investigator considered that there was no reasonable possibility that the acute gastroenteritis may have been caused by investigational product. The cause of the event was unknown.

Diagnostics:

Stools Culture: saprophytic flora, no other bacteria; Clostridium difficile toxin: negative.

Analytics: Haemoglobin 14.4, Leukocytes / mcL 7040 (4890 neutroph/mcL, 1370 lympho/mcL, 690 monocytes, 80 eos/mcL); biochemistry: AST 30 U/L, ALT 26 U/L, GammaGT 198 U/L, ALkPh 219/L, LDH 445 U/L, CPR 4.4 mg/dL; Creatinine 0.90 mg/dL. NORMAL RANGES. 1) BIOCHEMISTRY: GLUCOSE 70 - 110 MG/DL, LDH 240 - 480 UI/L, GOT 5 - 45 UI/L, GPT 5 - 45 UI/L, GAMMA GT 8 - 61 UI/L, ALkPh 40 - 130 UI/L, BILIRRUBIN 0.20 - 1.10 MG/DL, TOTAL PROTEIN 6.40 - 8.30 G/DL, ALBUMIN 3.50 - 5.00 G/DL, CREATININE 0.70 - 1.20 MG/DL, CALCIUM 8.40 - 10.20 MG/DL,

PHOSPHORUS 2.30 - 4.60 MG/DL, URIC ACID 2.20 - 7.00 MG/DL, CHOLESTEROL 120 - 200 MG/DL, TRYGLICERIDES 50-200 MG/DL, SODIUM 135 - 149 MEQ/L, POTASMIUM 3.50 - 5.00 MEQ/L, AMILASE 30 - 100 UI/L,

More information will be provided when available. Patient was admitted 10th July c* in the ER for an acute episode of diarrhoea, that started on 5th July c*; 5-7 bowel movements / day, liquid consistence, no pathologic products; abdominal pain, loss of appetite but no vomiting or high temperature. Physical examination was normal, non tender abdomen. Treatment consisted of fasting for 48 hours, except for medication, and intravenous fluids. Finally he recovered, with adequate oral intake and normal stool. He has been contacted home, and he is fine, with no diarrhoea at present. -

Protocol Id: ING112276  
Investigator Number: 66539  
Subject Number: 789  
Treatment Number: 1044  
Case Id: B0606009A  
Suspect Drugs: Efavirenz  
Serious Events: Suicide attempt

This 37-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 23 October a*. Medical conditions at the time of the event included depression. Concomitant medications included Kivexa.

On 18 November a*, 26 days after the start of efavirenz, the subject attempted suicide (grade 4). The subject was hospitalised. The subject had caused a deep wound in his abdomen with a knife, and underwent abdominal surgery. Treatment with efavirenz was interrupted on an unspecified date. The event was resolved on 28 November a*. The investigator considered that there was a reasonable possibility that the attempted suicide may have been caused by efavirenz.

Follow-up information received on 27 November a*:

The subject discontinued treatment with efavirenz on 18 November a* and was withdrawn from the study. The investigator reported that the subject secretly managed his depression with occasional cocaine abuse. After his mother had denied him money, he had hurt himself with a knife causing intestinal wounds with bleeding and initial peritonitis. He informed his sister by phone and went to hospital.

Follow-up information received on 04 December a*:

The investigator confirmed the subject denied previous attempts at suicide before this episode and before study enrolment.
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Follow-up information received on 09 December a*:

The investigator confirmed the bleeding and initial peritonitis symptoms occurred after the surgical procedures that the subject underwent after the suicidal attempt. The events were not considered to be separate serious adverse events, but part of the initial serious adverse events of attempted suicide.

Protocol Id: ING112276
Investigator Number: 65771
Subject Number: 83
Treatment Number: 3027
Case Id: B0661760A
Suspect Drugs: Dolutegravir

This 28-year-old female subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 15 September b*.

This subject was randomised to receive dolutegravir 10 mg once daily.

The subject's past medical history included spontaneous abortion and one previous normal birth. Father’s relevant medical history - HIV (+). Concomitant medications included levonorgestrel and Truvada.

The subject reported "During her gynaecological examination the physician could not locate the Mirena (IUD) threads. An ultrasound confirmed absence of the device. The subject was unaware of previous or recent IUD expulsion."

At an unknown time after the start of dolutegravir and Truvada, the subject was found to be pregnant. Her last menstrual period was 12 May b*. The subject had serum Human Chorionic Gonadotropin (hCG) test showed positive (twice) and an ultrasound. Treatment with the dolutegravir was stopped on 11 June b*. The subject was exposed to dolutegravir and Truvada before conception and during the first trimester. At the time of reporting the outcome of the pregnancy was unknown. The estimated date of delivery was on 15 February c*.

Follow-up information received on 07 March c*:

Concomitant medications included Darunavir, Truvada (non study medication), Ritonavir, Folic acid, Prenatal vitamins and ferrous gluconate.

On 24 February c*, at full term (37 to 42 weeks gestation), the subject gave birth by normal vaginal delivery to a normal male infant. Birth weight was 3546 grams with length of 49.5 cm. Apgar score (range 0 - 10) at 1 minute was 8 and at 5 minutes was 9.

a*: The year
b*: Following year
c*: 2 years later
9.6.1.2. Cases Reported Between 01 October to 25 June

For this study, with a completed interim statistical analysis more than six months prior to the planned submission date, a new safety data cut was taken for reporting in this ISS. The narratives included in this section correspond to the SAEs and Pregnancy cases reported from: the safety data lock point for the ING112276 Week 96 CSR; up to the 25 June cut-off date for inclusion of data from this study in the Integrated Safety Outputs, and includes all follow up information received by the company through 26 October. The data included here are not represented in the clinical study report(s) included in m5.3.5.1; however SAEs cumulative to 25 June for this study are included in the ISO Tables and Figures produced for the ISS, which are located in m5.3.5.3 along with the ISS.

Protocol Id: ING112276
Investigator Number: 065773
Subject Number: 000133
Treatment Number: 2008
Case Id: Z0009855C
Suspect Drugs: Efavirenz
Serious Events: Cerebrovascular accident,

This -year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral efavirenz 600 mg once daily from 13 October.

The subject's past medical history included brain neoplasm. Medical conditions at the time of the event included ventriculo-peritoneal shunt. Concomitant medications included docusate sodium, efavirenz, Epzicom, clonazepam, lisinopril, ziprasidone hydrochloride, metoprolol, ciprofloxacin, Bactrim DS, paroxetine hydrochloride, bupropion hydrochloride, pantoprazole, bisacodyl, magnesium hydroxide and aspirin.

On 26 September, 713 days after the start of investigational product, the subject developed grade 3 or severe stroke. The subject was hospitalised and the event was life-threatening. CT of the head showed a right posterior cerebral artery occlusion and early ischemia. The subject was treated with enoxaparin. The event resolved on 28 October. The investigator considered that there was no reasonable possibility that the stroke may have been caused by investigational product.

Investigator text:

Pt was admitted to the hospital >6 hours after initial onset of stroke symptoms occurred. Mother notified our office today (9/30/c*). -
This 31-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 28 September.

The subject was randomized to receive dolutegravir 50 mg once daily.

Medical conditions at the time of the event included coronary artery disease and hyperlipidemia. The subject was also a smoker. Subject was adopted; no family information was available regarding relevant risk factors and family history of medical conditions.

Treatment with dose-blinded dolutegravir was completed on 12 August, and the subject received dolutegravir 50 mg once daily from 13 August.

On 05 January, 829 days after the start of dolutegravir, the subject developed grade 3 or severe anxiety. The subject also experienced shortness of breath and chest pain. The subject was hospitalised. Pulmonary CT and angiogram were both normal. Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the anxiety may have been caused by dolutegravir.

Investigator Text:

The patient went to the ER with chest pain and short of breath. ECG was done and cardiac enzymes were all normal. The patient is under a great deal of stress so a "possible anxiety attack" could not be ruled out. The patient was admitted for observation and discharged the next day. The patient also admitted to ethanol use again as this is a pattern of his. Final discharge diagnosis is 'Anxiety disorder' -

The subject received open-label oral dolutegravir 50 mg once daily from 13 August. He was also taking Truvada.

Medical conditions at the time of the event were unchanged from the event in January.

On 19 April, 934 days after the start of dolutegravir, the subject developed grade 4 myocardial infarction and died. The subject was found dead at the home, and a
presumptive diagnosis of myocardial infarction was made since no autopsy was performed. The subject’s partner stated that the subject was in his usual state of health and had no symptoms or complaints the week of the event. The investigator considered that there was no reasonable possibility that the myocardial infarction may have been caused by dolutegravir.

Information received from the medical monitor on 23 April *d*: The subject had been admitted on 14 July *c* due to chest pain. This episode was reported as an MI without ST elevation (onset on 14 July *c*; recovered on 16 July *c*; Grade 4; Relationship = Yes). The subject CK-MB, CK, and Troponin were elevated at that time when the subject ECG was unremarkable. Coronary angiography showed mid RCA stenosis (100%) and distal left main stenosis (30%).

This subject has also previously been noted to have issues with alcohol use/abuse. He had significant psychosocial stressors (job and health insurance loss) and symptoms consistent with anxiety but did not have prior suicide attempts, suicidal ideation or evidence for a suicide attempt prior to his death. The subject had been in touch with site coordinator earlier in the week he died and seemed to be doing fine. On 19-Apr-*d* the subject was found face down on kitchen floor. When medical assistance arrived, he was pronounced dead. The diagnosis of MI was assumed. The police was also called and their report stated that there was no foul play and no suspicion of suicide.

Investigator text:

It is believed that subject had a MI that resulted in death.

Protocol Id: ING112276
Investigator Number: 066775
Subject Number: 000642
Treatment Number: 4037
Case Id: Z0012478A
Suspect Drugs: Dolutegravir
Serious Events: Wrist fracture

This □-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 29 October □ to 25 August *c*. The subject switched to the open-label phase and received oral dolutegravir 50 mg per day from 26 August *c*.

This subject was randomised to receive dolutegravir 25 mg once daily.

Concomitant medications included Truvada.
On 20 October c*, 721 days after the start of investigational product and 55 days after the start of open label dolutegravir, the subject developed grade 3 or severe wrist joint fracture. The subject was hospitalised. Treatment with dolutegravir 50 mg was continued. The event resolved on 01 November c*. The investigator considered that there was no reasonable possibility that the wrist joint fracture may have been caused by investigational product and dolutegravir.

Investigator text:

on 20th october subject had an accident at work. fracture left wrist joint was diagnosed. hospitalisation for surgery procedures since 25th October c*

he made a wrong step on a ladder without any symptoms

Protocol Id: ING112276
Investigator Number: 065760
Subject Number: 000013
Treatment Number: 1001
Case Id: Z0013982A
Suspect Drugs: Dolutegravir
Serious Events: Upper gastrointestinal haemorrhage

This 44-year-old subject was enrolled in a Viiv-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir once daily from 08 September c*. The subject was randomized to receive dolutegravir 50 mg once daily. He was switched to open-label dolutegravir 50 mg on 25 July c*.

Medical conditions at the time of the event included gastroesophageal reflux disease. Concomitant medications included famotidine.

On 26 January d*, 185 days after the start of open-label dolutegravir 50 mg, the subject developed grade 3 or severe upper gastrointestinal haemorrhage. The subject had vomiting and epigastric tenderness. The subject was hospitalised for observation. Treatment with dolutegravir was continued. Upper gastroscopy was performed on 27 January d* which showed gastritis. The event resolved on 27 January d*. The investigator considered that there was no reasonable possibility that the upper gastrointestinal haemorrhage may have been caused by dolutegravir.

Investigator text:

Subject was seen in Emergency Dept on 26-Jan-c* for complaint of vomiting and epigastric tenderness. He was admitted at that time for observational purposes and an Upper GI was performed on 27-Jan-d*. Upper GI results showed gastritis per phone conversation with discharging physician.

* new therapeutic information provided at the time of replacement
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Hospital record pending at this time
This 2-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received dose-blinded oral dolutegravir from 29 October to 31 August. The subject was randomised to receive dolutegravir 25 mg once daily. He was switched to open-label oral dolutegravir at 50 mg per day from 02 September.

The subject has no relevant medical history or any predisposing risk factors. Concomitant medications included Kivexa.

On 10 March, 863 days after the start of the dose-blinded dolutegravir and 190 days after the start of the open-label dolutegravir, the subject developed grade 3 or severe appendicitis. The subject was hospitalized for acute abdomen on 10 March. A CT scan of the abdomen showed cecal appendix with thickened walls and oedema of the adjacent adipose tissue, ileum, colon and right pararenal band and possible buffered perforation. Blood test showed increased white cells count. An appendix biopsy revealed phlegmonous acute appendicitis. The subject underwent appendectomy surgery. The subject was treated with antibiotics. The postoperative hospitalization was complicated by (non-serious) wound infection (the wound was drained). Treatment with open-label dolutegravir was interrupted from 11 to 14 March due to fasting for the surgery. The subject was discharged on 22 March. The event improved on an unspecified date. On 10 May, the subject still complained of abdominal tenderness. The investigator considered that there was no reasonable possibility that the appendicitis may have been caused by dolutegravir.

Investigator text:

The patient was hospitalized for acute abdomen on March 10th and then underwent appendectomy surgery; postoperative hospitalization was complicated as often happened by wound infection (the wound was drained). The patient was discharged on March 22nd.
This 31-year-old female subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject received oral dose-blinded dolutegravir per day from 25 September until 1 August c*. The subject was randomized to receive dolutegravir 10 mg once daily. She was switched to open-label dolutegravir at a dose of 50 mg from 2 August c*.

Medical conditions at the time of the event included chronic lumbar pain, osteophytosis and right gonarthrosis with arthralgia. Concomitant medications included pantoprazole, lactulose, Gaviscon and Kivexa.

On 16 April d*, 934 days after the start of dolutegravir, the subject developed grade 3 or severe gonarthrosis and grade 3 or severe lumbar pain. The subject was hospitalised. Lumbar CT Scan and lumbar IRM showed discopathy at L4/L5 and L5/S1. The subject was treated with Lamaline, amitriptyline hydrochloride, ketoprofen, morphine, colecalkiferol, zolpidem, nefopam, paracetamol and diazepam. Treatment with dolutegravir was continued. The events resolved with sequelae on 10 May d*. The investigator considered that there was no reasonable possibility that the gonarthrosis and lumbar pain may have been caused by dolutegravir.

Investigator text:

patient had more and more pain on right knee. She went to medical specialist and hospitalisation had been organized for making more exams. Sequelae: For the moment, patient still have pain -

This 31-year-old male subject was enrolled in a ViiV-sponsored, dose-blinded study for the treatment of human immunodeficiency virus infection. The subject was randomized to receive dolutegravir 25 mg once daily and received oral dose-blinded dolutegravir per

\[c*: \text{2 years later}\]
\[d*: \text{3 years later}\]
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day from 14 October to 24 August. The subject started the open-label phase and received oral dolutegravir 50 mg once daily from 25 August.

Medical conditions at the time of the event included chronic alcohol abuse. Concomitant medications included lormetazepam and Truvada.

On 27 May, 956 days after the start of dolutegravir and 277 days after the start of open-label dolutegravir, the subject developed grade 2 or moderate seizure. The subject presented at the ER on 27 May sweating and vomiting, and reporting that he had abruptly withdrawn alcohol and lormetazepam. The subject was hospitalised. Cerebral CT scan showed diffuse atrophy (compatible with HIV infection and chronic alcohol abuse). EEG performed on 28 May showed sharp waves of mean voltage, isolated or in short sequences on left frontal and temporal regions spreading homolaterally and across the median line. MRI performed on 30 May showed diffuse atrophy mainly of the cortex with mild hyperintensity in T2 of the white periventricular matter. EEG performed on 31 May showed no more sharp waves at left, rare, isolated sharp waves of low voltage in the right frontal region. The subject was treated with alizapride hydrochloride, diazepam, thiamine and folic acid. Treatment with dolutegravir was continued. The event resolved on 31 May. The investigator considered that there was no reasonable possibility that the seizure may have been caused by dolutegravir.

Investigator text:

On May 27 the patient had only light breakfast. At noon he went to bed where his boyfriend found him with seizures at 6 pm. At 8 pm he arrived at the emergency Department of [deleted] Hospital, sweating and vomiting, reporting that he had abruptly withdrawn alcohol and lormetazepam since 3 days (but this morning he denied ever having done so). He was given iv sodium bicarbonate, omeprazole and alizapride, was sent to the CT scan, when he returned he had a new episode of seizures, the neurologist who visited him attributed the crisis to alcohol and drug withdrawal, however he was admitted in hospital for completion of exams. Today, May 28, he's expected to undergo electroencephalography.

9.6.1.3. Cases Reported Between 26 June to 26 October

There were no SAE or pregnancy cases reported for this study from the cut-off date for the Integrated Safety Outputs up to the final 26 October safety data lock point for the ISS.

9.6.2. ING113086 SAE and Pregnancy Case Narratives

It is important to note that, as this study is still ongoing; these cases are still subject to change. Additionally, discrepancies may also arise between subject age presented from

c*: 2 years later
d*: 3 years later

* 薬承認情報提供時に置き換え
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OCEANS data compared to age presented from the clinical trial database, since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

9.6.2.1. Cases Reported up to 02 March

The narratives included in this section correspond to the SAEs and Pregnancy cases included in the ING113086 Week 48 CSR (with a data lock point of 02 March for safety data), which is included in m5.3.5.1. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.

Protocol Id: ING113086
Investigator Number: 080914
Subject Number: 003015
Treatment Number: 1022
Case Id: Z0008412A
Suspect Drugs: Dolutegravir
Serious Events: Anaemia

This year old African-American female was randomized on 01 DEC to DTG 50 mg once daily and investigator selected NRTI of ABC/3TC. Baseline HIV-1 RNA viral load was 1503 c/mL and CD4+ cell count was 338 cells/µL. The subject had had isolated abnormal Hgb values from study start:

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Medical conditions at the time of the event included anaemia, dysfunctional uterine bleeding, fatigue and polycystic ovarian syndrome. Concomitant medications included iron supplements (taken inconsistently), ABC/3TC and ferrous sulphate.

On 09 MAR b*, 98 days after the start of IP, the subject developed grade 3 or severe anaemia aggravated. Subject reported she had been told she has anaemia, but she has never had transfusions, and that she takes iron supplements sporadically when she remembers. Per her primary care provider, Hgb is usually 8.5 to 9.5 g/dL (NR 12-15.6) chronically. The subject was hospitalized on 12 MAR b* with Hgb 7.8 g/dL. The subject presented with fatigue and low activity tolerance for 2 to 3 weeks which worsened over the last week. The subject reported 7 days of heavy bleeding when on menses. Laboratory test results dated 12 MAR b* included BilT 0.7 mg/dl (NR 0-1.3), Iron 26, Total Iron binding capacity (TIBC) 46, Iron saturation 6%, Hgb 7.8 g/dL, Mean

b*: Following year
corpuscular volume (MCV) 72.1 (NR 80-100) and International normalized ratio (INR) 26. INR of 26 with MCV of 72.1 indicated microcytic anaemia, likely secondary to iron deficiency. The investigator reported he did not think the subject was taking her iron supplements consistently and did not believe there was another cause for the low Hgb. Following a blood transfusion (2 units) on 12 MAR b*, the subject felt better and was less tired. Treatment with blinded trial medication was continued. On 13 MAR b*, Hgb was 9.7 g/dL and MCV 74.3. The event resolved on 13 MAR b* and the subject was discharged. The investigator considered that there was no reasonable possibility the anaemia aggravated may have been caused by IP, and that the event was possibly caused by menorrhagia.

Protocol Id: ING113086
Investigator Number: 080933
Subject Number: 003128
Treatment Number: 4008
Case Id: Z0007255A
Suspect Drugs: Raltegravir
Serious Events: Pneumonia cytomegaloviral

This 65 year old male subject was randomized to receive RAL 400 mg twice daily from 17 NOV a*

Medical conditions at the time of the event included chronic pneumonia. Concomitant medications included citalopram hydrobromide, seasonal trivalent influenza vaccine dresden, pneumonia vaccine (non-GSK), sodium chloride, Codeine + guaifenesin, lorazepam, zolpidem and esomeprazole.

On 04 JAN b*, 48 days after the start of IP, the subject developed Grade 3 or severe CMV pneumonitis. The subject was hospitalized with hypoxemia. The subject had experienced a cough, upper respiratory infection, hypoxemia and shortness of breath since NOV a*. A high-resolution chest CT scan showed extensive reticulonodular infiltrates bilaterally with tree-in-bud appearance mainly in the left lower lobes more than the right, consistent with possible Mycobacterium Avium-intracellulare (MAI). Subject was admitted to hospital with hypoxemia and underwent bronchoscopy and viral cultures, which indicated a diagnosis of CMV pneumonitis. The subject was treated with atovaquone, Symbicort, clarithromycin, ethambutol hydrochloride, heparin, levofloxacin, salbutamol sulphate, cefepime, ganciclovir and ipratropium bromide. Treatment with blinded trial medication was continued. The event resolved on 30 JAN b*. The investigator considered that there was no reasonable possibility that the CMV pneumonitis may have been caused by IP.
This 32 year old female was randomized to receive RAL 400 mg twice daily from 11 FEB.

Concomitant medications included Truvada, Bactrim DS, alprazolam, Vicodin, hydrochlorothiazide, diltiazem hydrochloride, montelukast sodium, Combivent, acyclovir, sertraline hydrochloride and lisinopril.

On 06 AUG a*, 176 days after the start of IP, the subject developed Grade 1 or mild ethanol intoxication. Inebriated, the subject fell down a flight of stairs and was admitted for observation. He was awake, alert, oriented and doing well. No treatment was administered. Treatment with blinded trial medication was continued. The event resolved on 08 AUG a*. The investigator considered that there was no reasonable possibility that the ethanol intoxication may have been caused by IP.

Diagnostics:

CT scan of the brain on 06 AUG a* revealed small parenchymal hemorrhage and small subdural hematoma with very small amount of blood, no midline shift and no drainable fluid. CT scan of the brain on 08 AUG a* showed resolution of these events.

This 47 year old male subject received IP from 02 FEB. This subject was randomized to RAL 400 mg twice daily. This subject was hospitalized and treated with aspirin, salbutamol sulphate, methylprednisolone, enoxaparin.

Medical conditions at the time of the event included chronic obstructive pulmonary disease. Concomitant medications included TDF/FTC.

On 12 MAR a*, 38 days after the start of IP, the subject developed Grade 1 or mild exacerbation of chronic obstructive pulmonary disease. The subject was hospitalized and treated with aspirin, salbutamol sulphate, methylprednisolone, enoxaparin.
azithromycin, ceftriaxone and Advair. Chest X-rays on 12 MAR a* revealed no acute cardiopulmonary process; as on a prior study, there were small nodular opacities in both lung bases which were symmetric and likely represented nipple shadows. Treatment with blinded trial medication was continued. The event resolved on 14 MAR a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the exacerbation of chronic obstructive pulmonary disease may have been caused by IP. Follow up received on 16 MAR a*: The subject did not require intubation.

On 08 AUG a*, 187 days after the start of investigational product, the subject presented to a hospital with grade 1 chest pain. He was admitted to the hospital for diagnostic workup. There was no evidence of acute cardiac ischemia. Cardiac enzymes remained negative. The subject was in no acute distress. The Investigator did not believe this event was related to study medication and the subject was continued on study medications.

Protocol Id: ING113086
Investigator Number: 081015
Subject Number: 003250
Treatment Number: 1029
Case Id: Z0007330A
Suspect Drugs: Abacavir sulphate, Dolutegravir
Serious Events: Drug hypersensitivity

This year old White male (Baseline HIV-1 RNA viral load of 7252 c/mL and CD4+ cell count of 416 cells/μL) was randomized to DTG 50 mg once daily on 06 DEC with investigator selected backbone of ABC/3TC. Medical history at Baseline included ongoing anxiety and respiratory, thoracic and mediastinal disorders NOS. The subject developed the single symptom of fatigue 15 days after starting study medication. Treatment with DTG and ABC/3TC was continued uninterrupted and he went on to develop a worsening of fatigue (Grade 2) three days later along with headache, lymphadenopathy and periorbital tenderness. DTG dosing was held in the clinic five days later (eight days after initial onset of symptoms), and the subject’s next dose of ABC/3TC was given resulting in a worsening of symptoms. He went on to receive his DTG dose that evening and switched from ABC/3TC to TDF/FTC the following day, continuing DTG; his symptoms were noted to be resolved at this time. Events were considered indicative of clinically suspected ABC HSR considered reasonably attributable to concurrent ABC/3TC, and not DTG, by the reporting investigator.

The subject's HLA-B*5701 status was negative at screening.
This 33 year old male subject received IP from 02 JAN. This subject was randomized to receive RAL 400 mg twice daily.

On 05 MAY, 123 days after the start of IP, the subject developed Grade 2 or moderate bacterial pneumonia. The subject also experienced shortness of breath, fatigue and malaise during a flight on this date. Difficulty breathing worsened on 06 MAY, and he was admitted to the hospital. Chest X-ray confirmed diagnosis of lower lobe pneumonia. Treatment with blinded trial medication was continued. The event resolved on 15 MAY. The investigator considered that there was no reasonable possibility that the bacterial pneumonia may have been caused by IP.

This 33 year old male subject received IP from 15 DEC. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included Truvada.

The subject's past medical history included cryptococcal meningitis. Medical conditions at the time of the event included dermatitis and hepatitis B. Concomitant medications included Bactrim and azithromycin.

On 27 DEC, 12 days after the start of IP, the subject was a victim of homicide and was found deceased at home on 28 DEC. Treatment with blinded trial medication was discontinued on 27 DEC, the date the subject died. Cause of death is unknown. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the homicide may have been caused by IP.
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Protocol Id: ING113086
Investigator Number: 081017
Subject Number: 003267
Treatment Number: 1093
Case Id: Z0008789A
Suspect Drugs: Raltegravir
Serious Events: Bacteraemia, Staphylococcal infection, Subcutaneous abscess

This 35 year old male subject received IP per day from 22 DEC. This subject was randomized to receive RAL 400 mg twice daily.

Medical conditions at the time of the event included anaemia, hepatitis C and type 1 diabetes mellitus. Concomitant medications included intermediate/long-acting insulin and insulin lispro.

On 31 MAR, 99 days after the start of IP, the subject developed Grade 3 or severe bacteremia, Grade 3 or severe methicillin-resistant staphylococcus aureus and Grade 3 or severe subcutaneous thigh abscess. The subject presented to the Emergency Room (ER) with left hip pain and was hospitalized. Blood cultures and abscess drainage material were positive for methicillin-resistant Staphylococcus aureus on 04 APR, and were negative at time of discharge on 06 APR. CT scan of the left hip revealed soft tissue infection. The subject was treated with mupirocin, daptomycin, vancomycin, piperacillin sodium, doxycycline and heparin. Treatment with blinded trial medication was continued. The events resolved on 27 APR. The investigator considered that there was no reasonable possibility that the bacteraemia, methicillin-resistant Staphylococcus aureus and subcutaneous thigh abscess may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 081007
Subject Number: 003337
Treatment Number: 1264
Case Id: Z0010718A
Suspect Drugs: Dolutegravir
Serious Events: Portal vein thrombosis

This 35 year old female subject received IP from 28 FEB. This subject was randomized to receive DTG 50 mg once daily.

The subject's past medical history included abdominal surgery. Concomitant medications included Epzicom, ceftriaxone, fentanyl, hydrocodone, paracetamol, magnesium hydroxide, morphine, pantoprazole, ondansetron hydrochloride, sodium chloride, Gastrografin, and oral contraceptive pills.

On 21 JUL, 143 days after the start of IP, the subject developed Grade 3 or severe portal vein thrombosis. The subject was seen in the ER with abdominal pains and was hospitalized.

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
Diagnostics:
Diagnostic Laparoscopy to rule out internal hernia: internal hernia was ruled out.
CT of abdomen and chest: revealed small right effusion and trace atelectasis, occlusive thrombosis present in the superior mesenteric vein and clot extends into the main portal vein.

INR levels were as follows, 1.2 (NR 2.0-3.0) on 21 JUL through 25 JUL, 1.3 on 26 JUL, 1.4 on 27 JUL, 1.5 on 28 JUL a*, 1.7 on 29 JUL, and 2.0 on 30 JUL. The subject was treated with heparin and warfarin sodium. Treatment with IP was continued. The event resolved on 30 JUL a*. The investigator reported that her treating physicians believed that her oral contraceptive pills likely contributed to the formation of her portal vein thrombosis. The investigator considered that there was no reasonable possibility that the portal vein thrombosis may have been caused by IP.

The subject is a 1 year old male randomized to RAL 400 mg twice daily on 10 FEB with a baseline HIV-1 RNA 1953 copies/ml and CD4+ 437 cells/mm³. Background medication was TDF/FTC. Screening HBsAg and HCV Ab tests were negative. Baseline LFTs and Prothrombin time were within normal limits (WNL).

On 12 APR a*, 60 days after the start of IP, the subject developed Grade 2 or moderate seizure and Grade 3 or severe elevated CPK. The events were clinically significant (or requiring intervention).

Investigator text:
Subject was on a bus with his son on 12 APR a*, and reported seeing bright white lights and then remembers nothing else. Had a seizure, witnessed by son, seizure was tonic/clonic generalized seizure. Subject was taken to the ER, where he was evaluated and monitored; no treatment was provided. Subject bit his tongue during seizure and also had a small hematoma on his upper forehead seen. He remained in the ER for 6 hours and was discharged with follow up by the Principal Investigator (PI) on 14 APR a*.
Lab work at a peripheral hospital confirmed increase in transaminases (similar to Week 8). A drug screen and alcohol screen were negative; no cause for seizure was identified.

Subject was seen in follow-up 14 APR, the history was confirmed and the subject complained of throbbing pain in the legs and difficulty lifting the right leg. Physical examination showed swollen tongue with necrotic area and subglossal hematoma.

a*: The year
explained by biting his tongue during seizure. There was mild weakness of right hip extension, generally brisk reflexes R>L, Babinski withdrawal; no other abnormality on examination. The liver was not enlarged or tender. Blood work showed increased bilirubin (total and conjugated), increase in transaminases (as before) and very marked increase in CK, likely explained by seizure. An unenhanced CT scan was normal. Study medication was held, and the subject was prescribed thiamine 50 mg daily TID.

The subject was seen for follow-up on 15 APR, was clinically stable with improvement in bilirubin, and further increase in CK. No new neurological findings were observed. The subject was reviewed again on 18 APR. Further clinical improvement was observed with very mild muscle tenderness only. Blood work continued to improve (CK 4525); liver enzymes were better; no weakness, and reflexes brisk but symmetrical. Subject has a long history of alcohol binge drinking and had drunk heavily for several days prior to seizure. No prior history of seizures or alcohol withdrawal symptoms.

Social worker provided diagnosis of alcohol dependency on visit JAN a*. Subject reported drinking up to 24 beers in 24 hours as frequently as every few days. Subject denies herbal or over the counter (OTC) medication use.

Investigator Opinion (26 APR a*): Reasonable probability that seizure and LFT elevations are associated with alcohol. Can’t definitively rule out at this time that this is a drug-related event, though this appears to be less likely.

Additional Medical Monitor History:

His viral load became suppressed by Week 4 and remained suppressed at Week 8 (08 APR).

Between 06 APR and 09 APR, he reports having an alcohol ‘binge’, preliminarily thought to consist of approximately 6-12 beers/day. He presented for his Week 8 visit on 08 APR, at which time he had mildly elevated transaminases, AST=294, ALT 136. The elevation was thought to be consistent with his previous alcohol consumption. He reported mild nausea at this visit.

On 12 APR, the subject suffered a seizure described as upper body shaking that lasted for minutes, plus tongue biting. He presented to the ER for evaluation where routine laboratories were drawn and a non-contrast head CT was negative. Significant laboratory values at that time revealed AST=378, ALT=158, BilT=48, DBili=19, GGT=739, Na=125. Urine toxicology was negative. He discontinued study drugs on 12 APR (last dose 11 APR) and the medication was held pending further workup. He reportedly was stable in the ER and he was not admitted for further evaluation. Alcohol withdrawal seizure was considered as a possible cause for the seizure.

On 14 APR, he followed up with the Investigator and was noted to be feeling relatively well but complained of R leg muscle tenderness; his Babinski was withdrawal. Repeat non-contrast head CT was negative. AST=332, ALT=116, CK=15,266
Lab draw on 15 APR revealed AST=352, ALT=116, ALP=164, BilT=22, CK=23,949.

On 18 APR, he was seen in clinic and was reported as being clinically stable. His muscle soreness was resolving. Neurology exam was reportedly normal at that time. An MRI and EEG was ordered. Labs were trending back down. ALT=121, AST=89, BilT=9, CK=4525. He was noted to be clinically well on 22 APR and will be seen in clinic again on 28 APR.

EEG and MRI brain were normal.

Subject evaluated again on 21 APR and was clinically well: nausea had resolved and tongue was healing well. Leg strength and reflexes were normal. He was seen again 28 APR by the physician and had no ongoing symptoms.

Protocol Id: ING113086
Investigator Number: 083031
Subject Number: 003442
Treatment Number: 3327
Case Id: Z0009856A
Suspect Drugs: Raltegravir
Serious Events: Convulsion

This 30 year old male subject received IP per day from 11 FEB. The subject was randomized to RAL 400 mg twice daily. His CD4+ cell count and viral load at the time of randomization were 508 and 14,985 c/mL, respectively.

The subject’s past medical history included seizure. Concomitant medications included sertraline, TDF/FTC and clonazepam.

On 31 MAY, 109 days after the start of IP, the subject developed Grade 1 or mild seizure. He was sitting in front of his computer, he recalls the screen “flickering” but did not have any other prodromal symptoms. He then stated that he “blackened out” (duration unknown) and when he “came to” he reported not recognizing his partner. The partner reports that the subject’s eyes rolled, he fell to the floor “body stretched and was shaking all over” x 2-5 minutes, and he was drooling. The event was clinically significant (or requiring intervention). Treatment with blinded trial medication was continued. The seizure event resolved on 31 MAY. The investigator considered that there was a reasonable possibility that the seizure may have been caused by IP.

The subject had a history of heavy alcohol abuse for 6 years and admits to drinking 3 x750 ml bottles of champagne or 15 beers approximately 4 times a week for the last 6 years. Medications included: Clonazepam, Trazadone and Sertraline. Laboratory data on 02 JUN included: AST 81, ALT 84, CPK 947. The subject had mild persistent Grade 1 AST and ALT elevations of approximately 2xULN since screening and mildly reduced creatinine (63-67 µmol/L) since screening. At his clinic visit on 02 JUN, he...
was noted to be well appearing and with a normal neurologic exam. He had evidence of having bit the right side of his tongue.

On 09 JUN a* a neurology consultation was performed. Neurologist described a seizure event as occurring after "a very strong use of alcohol with no nutrition and poor sleep." A seizure was described when he was around 14 years old while on an unknown treatment for obsessive compulsive disorder (OCD). The subject reported he cannot fix his alcohol problem. The subject also reported being very angry about his HIV diagnosis and that he has been "rebelling" because of it. There was no suicidality described. The subject also described a history of anxiety and frequent panic attacks. The neurologist reported a normal mental status exam and a normal neurologic exam. The neurologist’s impression was: "Obviously the seizures do not sound like epileptic seizures given the precursory of binge drinking of alcohol. This is likely to be alcohol mediated seizure with sleep deprivation."

Additional Medical Monitor History: Subject reports heavy alcohol intake for 6 years, averaging approximately 15 beers, 4 times per week. He denied illicit drug use. He has had a longstanding anxiety diagnosis dating back to childhood. He has mother with a history of grand mal seizures.

No further seizures have been reported in this subject at the time of this report.

Protocol Id: ING113086
Investigator Number: 083084
Subject Number: 003452
Treatment Number: 1011
Case Id: Z0011046A
Suspect Drugs: Raltegravir
Serious Events: Appendicitis

This 14 year old male subject was randomized to receive oral RAL 400 mg twice daily from 23 NOV.

Concomitant medications included zopiclone.

On 18 JUL b*, 237 days after the start of IP, the subject developed Grade 3 or severe acute appendicitis. The subject went to the ER with severe abdominal pain, and was diagnosed with appendicitis was diagnosed following an abdominal scan. The subject was hospitalized and underwent an appendectomy.

Treatment with blinded trial medication was continued. The event resolved on 05 AUG b*. The investigator considered that there was no reasonable possibility that the acute appendicitis may have been caused by IP.

a*: The year
b*: Following year
This 31 year old female subject was randomized to DTG 50 mg once daily from 03 DEC.

The subject's past medical history included three suicide attempts. Medical conditions at the time of the event included alcohol abuse and depression. Concomitant medications included KIVEXA.

On 04 OCT, 305 days after the start of IP, the subject developed Grade 4 attempted suicide. The subject was hospitalized and the event was life-threatening. It was noted that subject was feeling sad and started drinking which precipitated the event. The Investigator reported the subject had a number of recent personal stressors which had led to increased alcohol consumption. The subject was treated with paliperidone, paroxetine hydrochloride and quetiapine. The event resolved on 05 OCT. Treatment with IP was interrupted on 08 OCT until further information of predisposing factors could be identified. The subject was discharged on 18 OCT and restarted IP on 19 OCT. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by IP.

This 31 year old male subject was randomized to receive oral RAL 400 mg twice daily 07 DEC.

Concomitant medications included TDF/FTC.

On 01 APR, 115 days after the start of IP, the subject committed suicide by throwing himself under a train. Treatment with blinded trial medication was discontinued and the subject was withdrawn from the study. The investigator confirmed the date of death as 01 APR, and that an autopsy was performed but that no further information would be available. The investigator considered that there was no reasonable possibility that the suicide may have been caused by IP.
This 44 year old female subject was randomized to receive oral DTG 50 mg once daily from 05 JAN.

The subject's past medical history included family history of cancer (breast cancer mother, aunt and grandmother). Concomitant medications included TDF/FTC.

On 07 JUN, 153 days after the start of IP, the subject developed Grade 3 or severe breast cancer. The subject was hospitalized. Biopsy of the right breast showed weak and incomplete membrane marking of 60% of the infiltrating carcinomatous component; doubtful HER 2 state, moderate over expression of the protein HER 2 (score2+) which was to be confirmed by open biopsy. Ganglionic biopsy showed an absence of significant over-expression of the protein HER2 (score1+). The subject was treated with Ethinyl estradiol + levonorgestrel, epirubicin, cyclophosphamide, fluouracil, methylprednisolone, ondansetron hydrochloride and docetaxel. The subject had a good response to the chemotherapy (last treatment on 18 FEB). The subject underwent surgical removal of the tumour on 24 FEB. The subject was ultimately withdrawn from the study because of the need for concomitant use of cytotoxic chemotherapy. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the breast cancer may have been caused by IP.

After tumorectomy, surveillance and other exams are ongoing.

This 38 year old male received IP from 21 JAN. The subject was randomized to RAL 400 mg twice daily. Investigator selected Background medication was TDF/FTC.

Medical conditions at the time of the event included anxiety attack (non-serious), hypertension and diabetes. Concomitant medications included paroxetine hydrochloride, raccadotril, Aspegic, hydroxyzine hydrochloride and enoxaparin. The subject was an ex-smoker.

a*: The year
b*: Following year
On 12 MAR a*, 50 days after the start of IP, the subject developed Grade 3 or severe aphasia. The subject was hospitalized on 14 MAR a* for suspicion of cerebral vascular accident. The subject was very anxious with insomnia. All neurological exams were normal including cerebral scanography, MRI and EEG. The subject was treated with bromazepam, clonazepam, nefopam hydrochloride and paracetamol. Treatment with IP was continued. The event resolved on 15 MAR a*. The investigator considered that there was a reasonable possibility that the aphasia may have been caused by IP.
This 33 year old male subject received IP from 09 FEB 2018. This subject was randomized to receive RAL 400 mg twice daily.

The subject's past medical history included depression. Concomitant medications included bromazepam and KIVEXA.

On 26 OCT 2018, 259 days after the start of IP, the subject developed Grade 4 attempted suicide by overdosing on bromazepam (30 x 6 mg tablets swallowed). The subject was hospitalized for observation; no event treatment was given. Treatment with IP was continued. The event resolved on 27 OCT 2018. The investigator considered that there was no reasonable possibility the attempted suicide may have been caused by IP and that the event was possibly due to the concomitant medication, bromazepam and professional stress.

Follow up received via query response 10 MAY 2019:

The subject was admitted for survey and was not treated after admission.

This 32 year old male subject received IP from 04 JAN 2019. This subject was randomized to receive RAL 400 mg twice daily.

On 24 JUN 2019, 171 days after the start of IP, the subject developed Grade 3 or severe abscess of anal margin. The subject was hospitalized and underwent surgical removal of abscess from his scrotum. The subject was treated with amoxicillin trihydrate and paracetamol. Treatment with blinded trial medication was continued. The event resolved on 25 JUN 2019 and the subject was discharged. The investigator considered that there was no reasonable possibility the abscess of anal margin may have been caused by IP.
This 32 year old male subject received IP per day from 11 JAN. This subject was randomized to receive DTG 50 mg once daily.

Medical conditions at the time of the event included depression. Concomitant medications included TDF/FTC.

On 07 FEB a*, 27 days after the start of IP, the subject developed Grade 4 HIV encephalitis. The subject was hospitalized due to neuro-psychological problems (lack of memory, cognitive troubles, aggressiveness, manic-depressive state). The subject was noted by the investigator to have poor medication compliance with half full bottles noted 4 weeks into the study. MRI was compatible with HIV leukoencephalitis. The subject received citalopram, alprazolam, semisodium valproate and chlorpromazine hydrochloride. Treatment with IP was interrupted on 07 FEB a* with the intent to interrupt IP due to the SAE and poor compliance. The SAE resolved on 07 MAR a*.

The investigator considered there was no reasonable possibility the HIV encephalitis may have been caused by IP.

This 50 year old male subject received IP per day from 19 JAN. This subject was randomized to receive RAL 400 mg twice daily.

Medical conditions at the time of the event included chronic pancreatitis.

Screening tests for HBsAg, HCV Ab, HLA-B5701 were all negative. Microscopic hematuria was documented at Baseline, with normal renal function.

On 07 MAR a*, 47 days after the start of IP, the subject developed Grade 3 or severe pancreatic pseudocyst. The subject was hospitalized due to abdominal pain. Laboratory test results dated 07 MAR included C-reactive protein (CRP) 76 mg/l (NR 0-5) and lipase 15 U/L (NR 7-60). The subject was treated with morphine, paracetamol, macrogol 4000, mineral oil, tramadol hydrochloride and nefopam. Treatment with blinded trial...
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Module 2.7.4 Summary of Clinical Safety

medication was continued. The event resolved on 07 APR a*. The investigator considered that there was no reasonable possibility the pancreatic pseudocyst may have been caused by IP.

*a: The year
This 33 year old male subject received IP from 14 JAN. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included TDF/FTC.

On 23 MAR, 68 days after the start of IP, the subject developed Grade 4 iliac fossa pain. The subject was hospitalized due to abdominal pain with vomiting (suspected appendicitis) and augmented WBC count. The subject was treated with ceftriaxone sodium and ranitidine hydrochloride. Treatment with blinded trial medication was continued. The appendicitis was not confirmed, and the diagnosis at discharge was "right iliac fossa pain and augmented WBC in HIV+". Neutrophil count was 18,000/mm$^3$ at admission and 4000/mm$^3$ at discharge (NR 1800-7200/mm$^3$). The event resolved on 26 MAR and the subject was discharged. The investigator considered that there was no reasonable possibility the iliac fossa pain may have been caused by IP.

This 36 year old female subject received IP from 08 FEB. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included Truvada.

On 07 JUL, 149 days after the start of IP, the subject developed Grade 2 or moderate bacterial pneumonia. The subject developed fever and cough on 07 JUL, and was hospitalized on 14 JUL. Complete blood count was not performed. The subject was treated with azithromycin and ceftriaxone. Treatment with blinded trial medication was continued. The event resolved on 29 JUL and the subject was discharged. The investigator considered that there was no reasonable possibility that the bacterial pneumonia may have been caused by IP.
This 31 year old male subject received IP from 08 FEB. This subject was randomized to receive RAL 400 mg twice daily.

Concomitant medications included Truvada.

On 09 AUG a*, 182 days after the start of IP, the subject developed Grade 3 or severe skin melanoma. The event was life-threatening. Histology diagnosed a non-metastatic pT3a melanoma. The oncologist decided not to treat the subject with chemotherapy. The subject underwent surgical removal of the skin melanoma. Treatment with blinded trial medication was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility the skin melanoma may have been caused by IP.

This 31 year old male subject received IP from 17 DEC. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included metronidazole and ibuprofen.

On 17 AUG b*, the subject developed Grade 2 or moderate condyloma acuminatum. The subject was hospitalized, was treated with imiquimod and underwent surgery. Treatment with blinded trial medication was continued. The event resolved on 19 AUG. The investigator considered that there was no reasonable possibility the condyloma acuminatum may have been caused by IP.

a*: The year
b*: Following year
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Module 2.7.4 Summary of Clinical Safety

Protocol Id: ING113086
Investigator Number: 082953
Subject Number: 003832
Treatment Number: 3119
Case Id: Z0008630A
Suspect Drugs: Raltegravir
Serious Events: Ulcerative proctitis

This 33 year old male subject received IP per day from 22 DEC 2019. This subject was randomized to receive RAL 400 mg twice daily.

The subject's past medical history included alcohol abuse and unprotected sexual intercourse. Concomitant medications included ibuprofen, dipyrone and TDF/FTC.

On 15 FEB 2020, 55 days after the start of IP, the subject developed Grade 3 or severe ulcerative proctitis. The subject experienced diarrhoea since 15 FEB 2020 and obstipation since 14 MAR 2020. Chlamydia trachomatis was detected in a serological sample. The subject was hospitalized and treated with mesalazine and Movicol. Treatment with blinded trial medication was continued. The event resolved on 22 MAR 2020 and the subject was discharged. The investigator considered that there was no reasonable possibility the ulcerative proctitis may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 082955
Subject Number: 003846
Treatment Number: 3026
Case Id: Z0009870A
Suspect Drugs: Dolutegravir
Serious Events: Cellulitis

This 33 year old male subject received IP per day from 26 NOV 2019. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included TDF/FTC.

On 05 JUN 2020, 191 days after the start of IP, the subject developed Grade 3 or severe phlegmon of the foot. The subject was hospitalized with redness of left foot and massive swelling of the left groin. During physical examination, phlegmon with massive lymphangitis was diagnosed. The subject had a 1.5 cm ulcer on the sole of the left foot with necrosis, and was treated with ampicillin trihydrate. Laboratory test results dated 06 JUN included c-reactive protein 87 mg/L (NR: 0.0-10.0) and CPK 272 U/L (NR: 0.0-190.0). Cardiac workup revealed a Grade 2 pericarditis which was confirmed to be a non-serious event by the investigator. Treatment with blinded trial medication was continued. The event resolved on 10 JUN 2020 and the subject was discharged with oral antibiotics. The investigator considered that there was no reasonable possibility the phlegmon of foot may have been caused by IP.

b*: Following year

* 新薬承認情報提供時に置き換え
This 31 year old female subject was received IP from 17 NOV. This subject was randomized to receive RAL 400 mg twice daily.

Medical conditions at the time of the event included human papilloma virus (HPV) positive in high risk group; no family history known. Concomitant medications included ibuprofen.

On 07 FEB, 82 days after the start of IP, the subject developed Grade 1 or mild precancerosis of the cervix. The subject was hospitalized, and underwent planned surgical treatment with excision of the lesion. On 07 FEB, a pap smear was performed. Treatment with blinded trial medication was continued. The event resolved on 08 FEB. The investigator considered there was no reasonable possibility that the precancerosis of cervix may have been caused by IP.

At an unknown time after the start of IP, the subject was found to be pregnant. Her last menstrual period occurred on 25 MAY. No prenatal diagnostic tests were reported. Treatment with blinded trial medication was continued. The subject was exposed to the IP before conception and during first trimester. At the time of reporting, the outcome of the pregnancy was unknown. The estimated date of delivery was 15 FEB.

Follow-up information received 11 APR:
The subject underwent elective termination on 01 AUG; at 14 weeks gestation. Infant's sex was unknown. Foetal status was normal. Additional concomitant medication included ferrous glycine sulphate.

This 31 year old male subject received IP from 17 NOV. This subject was randomized to receive RAL 400 mg twice daily.
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Module 2.7.4 Summary of Clinical Safety

The subject's past medical history included depression. Concomitant medications included KIVEXA. The subject was not on any antidepressants.

On 04 AUG b*, 260 days after the start of IP, the subject developed Grade 4 worsened depression. The subject was hospitalized. The subject was discharged at his own request on 08 AUG b* and attempted to commit suicide on the same day. The subject was readmitted. The subject was treated with citalopram and lorazepam. Treatment with IP was continued. The attempted suicide was resolved on 09 AUG b*, and the worsened depression was resolved with sequelae on 07 OCT b*. The investigator considered that there was no reasonable possibility the worsened depression and attempted suicide may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 083015
Subject Number: 003876
Treatment Number: 1019
Case Id: Z0010433A
Suspect Drugs: Raltegravir
Serious Events: Anal fissure

This 36 year old male subject received IP from 29 NOV. This subject was randomized to receive RAL 400 mg twice daily.

The subject had no relevant medical history. Concomitant medications included ABC/3TC.

On 27 JUN b*, 210 days after the start of IP, the subject developed Grade 2 or moderate anal fissure. The subject was hospitalized, underwent surgery, and was treated with ciprofloxacin. The subject was discharged after two days without further treatment. Treatment with IP was continued. The event resolved on 06 JUL b*. The investigator considered that there was no reasonable possibility the anal fissure may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 083015
Subject Number: 003877
Treatment Number: 4012, 4012
Case Id: Z0013648A, Z0013648B
Suspect Drugs: Dolutegravir
Serious Events: Pneumothorax, Rib fracture

This 36 year old female subject received IP from 23 NOV. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included TDF/FTC.

b*: Following year
On 31 DEC b*, 403 days after the start of IP, the subject fell after consuming alcohol and developed Grade 2 or moderate serial costal rib fracture. The subject was hospitalized on 31 DEC b*. Chest X-ray showed serial rib fracture; abdominal sonography was without findings. The subject was treated with dipyrone, tilidine hydrochloride, enoxaparin and pantoprazole. Treatment with blinded trial medication was continued. The subject was discharged on 04 JAN c*. The event resolved with sequelae (painful movement restriction) on 31 January c*. The investigator considered that there was no reasonable possibility the serial costal rib fracture may have been caused by IP.

On 11 JAN c*, 414 days after the start of IP, the subject developed Grade 4 pneumothorax. The subject was hospitalized, and chest X-ray confirmed pneumothorax of the right lung. The subject was treated with drainage from 11 JAN to 17 JAN c*. Treatment with blinded trial medication was continued. The event resolved on 31 JAN c*. The investigator considered that there was no reasonable possibility the pneumothorax may have been caused by IP, and that the event was an effect of serial rib fracture.

This 32 year old male subject received IP from 07 DEC b-. This subject was randomized to receive DTG 50 mg once daily.

The subject's past medical history included nephrolithiasis. Concomitant medications included ABC/3TC.

On 28 OCT b*, 325 days after the start of IP, the subject developed Grade 4 exacerbation of nephrolithiasis. The subject developed dysuria in OCT 2011, suspected to be stricture of the urethra. The subject was treated with tamsulosin without an effect. The subject was hospitalized on 23 NOV b* and diagnosed with nephrolithiasis. The subject underwent ureterotomy and implantation of a ureteral catheter. The subject was treated with diclofenac and pantoprazole. Treatment with blinded trial medication was continued. The event resolved on 26 NOV b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the exacerbation of nephrolithiasis may have been caused by IP.
This 35 year old male subject received IP per day from 10 DEC. Background medications were TDF/FTC.

Medical conditions at the time of the event included 24 smoking pack year history and chronic obstructive pulmonary disease. The subject had no cardiac history and was hepatitis B and C negative at screen. The subject suffered mild or moderate AEs of depression, tinea, a tooth infection requiring root canal, and diarrhoea (clindamycin related), all of which resolved by 20 MAY.

On 24 JUN, 196 days after the start of IP, the subject developed Grade 3 or severe cardiac arrhythmia. The subject was hospitalized. ECG revealed Sinus rhythm, 123 bpm, multiple Ventricular Ectopic Beats, self limiting runs with up to 5 beats, and no signs of infarction, ischemia or cardiovascular disease. The subject was treated with magnesium salt and amiodarone. Treatment with IP was discontinued on 30 JUN and the subject was withdrawn from the study. The event resolved on 01 JUL. The investigator considered that there was a reasonable possibility that the cardiac arrhythmia may have been caused by IP.

Additional Medical Monitor History:

On 27 MAY, the subject completed his Week 24 visit without incident. There were no clinically significant lab events through Week 24. From Screening (17 NOV) through Week 24 (27 MAY), the liver enzymes (ALT, AST) were normal, with ALT ranging from ~10-25, AST ~24-41. The BilT was normal (~8-17 µmol/L) up until Week 24 visit (24 µmol/L, NR - 0-22).

On 24 JUN, the subject contacted the site over the phone to report 2 days of episodic dizziness and weakness. There was no LOC, no pre-syncpe, no chest pain and no other associated symptoms.

On 29 JUN, the subject was seen in the clinic for evaluation and was asymptomatic. An ECG was performed which demonstrated short runs of non-sustained ventricular tachycardia. His BP was 110/70. No labs were drawn in the clinic. He was referred to the ER for evaluation of the arrhythmia. Investigational product was held on 29 JUN.

From 29 JUN to 01 JUL, the subject was admitted to the hospital. In the ED, he was noted to have NSVT, premature ventricular contractures (PVCs) and bigeminy on telemetry. Admission ECG demonstrated NSVT without evidence of ischemia or QT...
prolongation. He complained of some dizziness and was given 1 ampule of amiodarone and magnesium. His physical exam was unremarkable with a BP of 105/70 and HR 87, 98% sat on room air. Admission labs revealed ALT=122. Calcium, LDH, CK, NA, CRP, CBC and TSH was normal. On 30 JUN, his ALT=111. No troponin or Utox is reported. His rhythm returned to normal fairly quickly and he remained on cardiac monitoring and remained asymptomatic. A trans-esophageal echo was normal. He was discharged on 01 JUL.

On 13 JUL, the subject followed up in the clinic. He was clinically well. Multiple ECGs revealed PACs and occasional PVC’s without NSVT. Labs revealed AST=455, ALT=471, Bilirubin=1.64 (<1.1), ALP=319. Troponin T <.01, CKMB=17, BNP=44 (<150). WBC=2.8. Hepatitis C PCR was positive at 25,500 IU/ml. EBV PCR was negative. Potassium and Magnesium levels were normal. The site considers acute hepatitis C as the cause for the LFT elevations and plans to monitor LFTs weekly and will consider starting treatment for Hepatitis C.

On 22 JUL, the subject presented for his WD visit and had no symptoms.

On 25 JUL, a cardiology consultation was performed. A 12-lead EKG showed sinus arrhythmia. Cardiac stress test showed no evidence of ischemia and no inducible arrhythmia.

On 28 JUL, a follow up visit was conducted. The subject had no symptoms. AST and ALT were nearly normalized.

Lab trend:

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<th>W24 (May 27)</th>
<th>June 29 (IP Held)</th>
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<th>July 13</th>
<th>WD - July 20</th>
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year old with no significant cardiac history presented on 29 JUN complaining of 5 days of intermittent dizziness and was noted to have new onset NSVT. He remained hemodynamically stable. Hospital workup revealed NSVT, PVCs, and bigeminy without evidence of ischemia (no troponin drawn). Trans-esophageal cardiac echo did not show any cardiac dysfunction, endocarditis or overt structural anomalies. He was discharged two days later, asymptomatic and with occasional ectopy. He was also noted on 29 JUN to have a newly elevated ALT with transaminases that continued to rise through follow up on 13 JUL, ALT=471, AST=455, Bilirubin=1.64. Cardiology follow up on 25 JUL revealed a tendency toward ventricular ectopy during a Holter and a normal stress test. He is currently asymptomatic and without complaints.

NSVT – Initial EKGs were evaluated by three independent cardiologists, all of whom suggested that the rhythm was consistent with Right Ventricular Outflow Tract Ventricular Tachycardia (RVOT VT). This diagnosis frequently presents in this age group and can take a benign course, though it can also be associated with RV structural abnormalities and sudden death. There is no evidence that RVOT VT is associated with raltegravir nor is there a clear association with drug toxicity. There is no evidence for QT prolongation or electrolyte abnormalities. There is no evidence for cardiac ischemia by admission labs or stress testing. His RVOT VT rhythm has resolved post a single dose of amiodorone and he only demonstrated occasional PVCs on follow up EKGs from July 13th. 24-hr Holter demonstrated a sinus rhythm with a slight tendency to tachycardia. There was one ventricular ectopy, some polytope ventricular ectopies and short events of bigeminy and trigeminy. One VT with 6 beats and a maximal frequency of 180 bpm was recorded in early morning. Notably, the Holter was performed nearly a month after IP was discontinued. RVOT VT is unlikely to be a drug induced event.

Hepatitis – This subject was Hep C Ab and HBsAg negative at screening. He had normal LFTs through Week 24 on therapy and has now been diagnosed with acute Hepatitis C by PCR screening. EBV viral capture antigen IgM and CMV IgM were also noted to be positive on liver event testing. He has remained clinically asymptomatic from the acute hepatitis. Follow up LFTs from 29 JUL demonstrate resolution of the hepatitis. It is felt that the hepatitis is related to acute Hepatitis C infection, and is not likely to be related to study drug.

The subject has withdrawn from the study.

This  year old male subject received IP per day from 03 DEC . This subject was randomized to receive DTG 50 mg once daily.
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Module 2.7.4 Summary of Clinical Safety

The subject does not have any relevant medical history or risk factors to lead this SAE. Concomitant medications included TDF/FTC.

On 01 FEB b*, 60 days after the start of IP, the subject developed Grade 4 appendicitis. The subject was hospitalized. Abdominal echography revealed large appendix compatible with acute appendicitis. The subject underwent surgical treatment. The subject was treated with ketoprofen, paracetamol and metamizole magnesium. Treatment with blinded trial medication was continued. The event resolved on 04 FEB b*. The investigator considered that there was no reasonable possibility the appendicitis may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 083401
Subject Number: 003970
Treatment Number: 3047
Case Id: Z0009167A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia aspiration, Suicide attempt

This 18 year old male subject received IP from 03 DEC b*. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included pyrazinamide, rifampicin and isoniazid. The subject had a history of chronic depression and bipolar disorder, which was controlled with medication for many years. The subject's emotional state prior to event was stable and well controlled.

On 20 APR b*, 138 days after the start of IP, the subject developed Grade 4 attempted suicide and Grade 2 or moderate bronchial aspiration pneumonia diagnosed by X-ray of thorax. The subject was hospitalized on 20 APR b* and discharged on 09 MAY b*.

The subject was treated with omeprazole, levofloxacin, ertapenem, paracetamol, Distraneurine, thiamine hydrochloride, meropenem, flumazenil, Augmentin intravenous (IV) and heparin sodium. Treatment with blinded trial medication was interrupted on 21 APR b* and re-started on 25 MAY b*. The events resolved on 25 MAY b*. The investigator considered that there was no reasonable possibility the attempted suicide and bronchial aspiration pneumonia diagnosed by X-ray of thorax may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 083402
Subject Number: 003994
Treatment Number: 3223
Case Id: Z0013916A
Suspect Drugs: Lorazepam, Raltegravir
Serious Events: Intentional overdose, Suicide attempt

b*: Following year
This year old male subject received IP from 14 JAN. This subject was randomized to receive RAL 400 mg twice daily.

The subject has no relevant medical history. Concomitant medications included lorazepam, TDF/FTC and duloxetine.

On 23 JAN, 374 days after the start of IP, the subject developed Grade 2 or moderate attempted suicide and Grade 4 intentional drug overdose. The subject took 50 lorazepam tablets. The subject underwent gastric lavage on the same day with clinical improvement, and was started on duloxetine for depression management. The subject was hospitalized on 24 JAN and the events were life-threatening. Treatment with blinded trial medication was continued. The intentional drug overdose resolved on 23 JAN. The subject was discharged on 27 JAN in good condition. The attempted suicide resolved on 31 JAN. The investigator considered that there was no reasonable possibility that the attempted suicide and intentional drug overdose may have been caused by IP and that the events were possibly due to the concomitant medication, lorazepam.

Protocol Id: ING113086
Investigator Number: 083403
Subject Number: 004001
Treatment Number: 3063
Case Id: Z0010695A
Suspect Drugs: Raltegravir
Serious Events: Laceration

This year old male subject received IP from 10 DEC. This subject was randomized to receive RAL 400 mg twice daily.

Concomitant medications included TDF/FTC and ketoprofen.

On 08 JUN, 180 days after the start of IP, the subject developed Grade 3 or severe cut into the 4th and 5th fingers of the hand (injury that required nerve and tendon surgery). The subject was hospitalized. The subject was treated with Augmentin. Treatment with IP was continued. The event resolved with sequelae on 21 JUN. The investigator considered that there was no reasonable possibility the cut into the 4th and 5th fingers of the hand may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 083408
Subject Number: 004075
Treatment Number: 1064
Case Id: Z0008179A
Suspect Drugs: Dolutegravir
Serious Events: Immune reconstitution syndrome, Meningitis tuberculous

b*: Following year
This 32 year old male subject received IP per day from 16 DEC. This subject was randomized to receive DTG 50 mg once daily. At baseline he had a HIV-1 viral load of 98,329 copies/ml, Screening CD4+ was 231 (5%) with negative HLA-B*5701 and HBsAg, but positive HCV Ab test. ALT was 47 and AST was 45 at Screening with normal synthetic function (prothrombin time 10 sec).

Concomitant medications included fluconazole, tramadol hydrochloride, paracetamol, ketoprofen, omeprazole, enoxaparin and ABC/3TC.

On 01 MAR, 75 days after the start of IP, the subject developed Grade 3 or severe tubercular meningitis and Grade 3 or severe immune reconstitution syndrome. The subject was hospitalized. His general condition was reported as good, and the only relevant symptom was the presence of pains of great intensity in the axial skeleton. Treatment with blinded trial medication was continued. Investigations included a head scan, back MRI and cerebrospinal fluid (CSF) examination. The whole body PET-CT only showed an area of high intensity at the third costochrondral joint and in the spinal medulla at level C3-C4 and T2-T3. The subject received anti-tuberculcous therapy of isoniazid, ethanbutol, pyrazinamide and moxifoxacin, as well as steroids. Rifampicin was a component of the anti-TB therapy but use with IP is contraindicated; thus, the subject was withdrawn from the study. The events resolved with sequelae on 21 OCT.

Protocol Id: ING113086
Investigator Number: 083408
Subject Number: 004076
Treatment Number: 1065
Case Id: Z0007204A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Drug hypersensitivity

This 32 year old male subject received IP from 16 DEC. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included ABC/3TC. HLA-B*5701 at screening was negative.

On 22 DEC, six days after the start of IP, the subject developed Grade 2 or moderate hypersensitivity reaction to ABC/3TC. The event was clinically significant (or requiring intervention). The subject also experienced generalize rash, fever (38.5°C), progressive malaise, weakness, nausea and without appetite. On 27 DEC, he came to the ER, was diagnosed with an allergic reaction, and was given 40 mgs Methyl-Prednisolone. On 28 DEC, the subject did not take ABC/3TC and felt better. He was without fever, his rash looked to have improved, and he showed a general clinical improvement. Although the investigator could not confirm that the event was an ABC HSR, it was decided to stop ABC/3TC on 28 DEC. The subject switched

* 新薬承認情報提供時に置き換え
background therapy to TDF/FTC. Treatment with blinded trial medication was continued. The event resolved with sequelae on 29 DEC a*. The investigator considered that there was no reasonable possibility the HSR to ABC/3TC may have been caused by IP and that the event was possibly due to the concomitant medication, ABC/3TC.

+a*: The year
This 22 year old male subject received IP from 22 DEC. This subject was randomized to receive DTG 50 mg once daily.

The subject's past medical history included anal fistula. Concomitant medications included TDF/FTC.

On 08 NOV, 321 days after the start of IP, the subject developed Grade 2 or moderate worsening of anal fistula. The subject was hospitalized and underwent surgical treatment on the same day. The subject was treated with Augmentin, dipyrone, paracetamol and ketoprofen. Treatment with blinded trial medication was continued. The event resolved on 13 NOV. The investigator considered that there was no reasonable possibility the worsening of anal fistula may have been caused by IP.

This 22 year old male subject received IP from 27 DEC. This subject was randomized to receive RAL 400 mg twice daily.

Past medical conditions included smoker until 1 year ago. Concomitant medications included ABC/3TC.

On 20 MAR, 83 days after the start of IP, the subject developed Grade 2 or moderate pneumonia. Three days before admission, the subject experienced a productive cough and fever for 1 day. The subject was hospitalized on 20 MAR. Laboratory test results dated 20 MAR included CRP 235 mg/L (NR 0-5). Chest X-ray performed on 20 MAR showed alveolar infiltrates in the left superior lobe. Repeat chest X-ray performed on 22 MAR showed a similar result. The subject was treated with levofloxacin, paracetamol, dalteparin sodium and omeprazole. Treatment with blinded trial medication was continued. At discharge on 22 MAR, the subject was instructed to take levofloxacin for 7 additional days at home. The event resolved on 12 APR. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by IP.
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Module 2.7.4 Summary of Clinical Safety

On 12 APR b*, 106 days after the start of IP, the subject developed Grade 3 or severe lung carcinoma. The subject was hospitalized on 12 MAY b*, and the event was life-threatening. A chest X-ray and bronchoscopy diagnosed small cell lung cancer with metastasis to the lymph nodes and liver. The subject also developed vocal cord paralysis as a complication of lung tumour. The subject was treated with carboplatin, etoposide, Urbason, enoxaparin and prednisone. Treatment with blinded trial medication was continued until 30 MAY b*. The event was unresolved at the time of reporting. The investigator considered that there was no reasonable possibility the lung carcinoma may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 084346
Subject Number: 004158
Treatment Number: 1082
Case Id: Z0012954A
Suspect Drugs: Raltegravir
Serious Events: Pyrexia

This 68 year old female subject received IP from 22 DEC b*. This subject was randomized to receive oral RAL 400 mg twice daily.

Concomitant medications included ABC/3TC, metoclopramide and dipyrone.

On 12 NOV b*, 325 days after the start of IP, the subject developed Grade 2 or moderate acute febrile syndrome. The subject experienced fever, vomiting and disorientation. The subject was hospitalized. Brain MRI and lumbar puncture were normal. The subject was treated with omeprazole, paracetamol, acyclovir, metoclopramide and dipyrone. Treatment with blinded trial medication was continued. After 72 hours of admission, the subject was asymptomatic. There was no definitive aetiology. The event resolved on 16 NOV b*. The investigator considered that there was no reasonable possibility that the acute febrile syndrome may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 084347
Subject Number: 004168
Treatment Number: 1113
Case Id: Z0010072A
Suspect Drugs: Raltegravir
Serious Events: Polyserositis

This 68 year old male subject received IP from 28 DEC b*. This subject was randomized to receive oral RAL 400 mg twice daily.

The subject had no relevant medical history. Concomitant medications included ABC/3TC.

b*: Following year

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On 138 days after the start of IP, the subject developed Grade 3 or severe polyserositis. The subject was hospitalized to investigate pleural effusion and pericardic effusion. Transthoracic echocardiogram, bronchoscopy and biopsy results were negative. The subject was treated with paracetamol, tramadol hydrochloride and levofloxacin. Treatment with blinded trial medication was continued. The event resolved on 03 JUN b*. The investigator considered that there was no reasonable possibility that the polyserositis may have been caused by IP and that the event was possibly due to viral infection.

This 44 year old male subject received IP per day from 16 DEC b*. This subject was randomized to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included nephrolithiasis. Concomitant medications included TDF/FTC.

On 133 days after the start of IP, the subject developed Grade 2 or moderate renal colic. The subject presented at the ER twice due to renal pain. The subject was treated with analgesics and discharged. On 30 APR b*, the subject returned to the ER due to maintained pain. The subject received more analgesics and was discharged again. On 02 MAY b*, he returned to the ER and was hospitalized for 25 hours. The subject was treated with metamizole magnesium, diclofenac, ketoprofen, omeprazole, paracetamol and tramadol hydrochloride. Treatment with blinded trial medication was continued. The subject was discharged on 02 MAY b* with analgesics. The event resolved on 13 MAY b*. The investigator considered that there was no reasonable possibility the renal colic may have been caused by IP.

This 44 year old male subject received IP from 27 DEC b*. This subject was randomized to receive DTG 50 mg once daily.
The subject had no relevant medical history or predisposing risk factors. Concomitant medications included dexamethasone, TDF/FTC and metoclopramide hydrochloride.

On 23 DEC b*, 361 days after the start of IP, the subject developed Grade 1 or mild vertiginous syndrome. The subject developed lower back pain and was treated with dexamethasone (Inzitan) at a private clinic. In the afternoon, he started vomiting and feeling sick. The subject was hospitalized. CT scan was normal. The subject was treated with betahistine. Treatment with blinded trial medication was continued. The event resolved on 27 DEC b*. The investigator considered that there was no reasonable possibility that the vertiginous syndrome may have been caused by IP.

This year old male subject received IP from 08 FEB a*. This subject was randomized to receive DTG 50 mg once daily.

Medical conditions at the time of the event included HIV infection. Concomitant medications included TDF/FTC, diazepam, bromazepam, Glucose saline, Ringer lactate solution and lorazepam.

On 08 FEB a*, the same day as the start of IP, the subject developed Grade 2 or moderate metastatic melanoma. An epidermic lesion at the left abdominal region was discovered at the Day 1 visit on 08 FEB. The subject was hospitalized on 16 MAR a* and underwent a biopsy, resulting in diagnosis of melanoma (Breslow 1.76mm, Clark level III). The subject was then hospitalized from 01 JUN to 03 JUN, to widen the margins and carry out sentinel node test and biopsy. Since the diagnostic of this biopsy was two nodes affected, a left axillary lymphadenectomy was performed during hospitalization from 15 JUL to 29 JUL a*. The result of the pathological anatomy showed two additional nodes affected by metastasis of melanoma among the 18 nodes extirpated in total. The subject also was treated with ketoprofen, paracetamol, omeprazole, allopurinol, enoxaparin, metamizole magnesium, ranitidine hydrochloride and Augmentin (oral). Treatment with blinded trial medication was continued. The event was unresolved at the time of reporting. The investigator considered that there was no reasonable possibility the metastatic melanoma may have been caused by IP.

* a*: The year
* b*: Following year

Protocol Id: ING113086
Investigator Number: 084352
Subject Number: 004208
Treatment Number: 3310
Case Id: Z0009857A
Suspect Drugs: Dolutegravir
Serious Events: Metastatic malignant melanoma
This 32 year old female subject received IP per day from 09 FEB. The subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included ABC/3TC. The investigator reported no other relevant concomitant medications.

The subject was doing well on study until 01 JUN, at which time she was noted to have an asymptomatic elevation of ALT 272, AST 302 U/L and a normal bilirubin. Follow up testing on 14 JUN revealed a normal AST and ALT. Shortly before a visit on 22 JUL, which was prompted by follow up of liver enzyme elevations noted at the Week 16 visit, the subject continued to feel well but noted scleral icterus (in morning of 21 JUL) and dark urine. On 22 JUL, lab testing revealed a Grade 4 AST and ALT elevation as detailed below. The investigator considered there was a reasonable possibility that the hepatitis may have been caused by IP.

Additional information received 25, 26, 28, & 30 JUL from Medical Monitor:

Local laboratory results from 22 JUL included alanine transaminase (ALT) 496 U/l (normal range up to 40), aspartate transaminase (AST) 690 U/l (normal range up to 40), lactate dehydrogenase (LDH) 118 U/l (NR 225 - 451), gamma-glutamyl transferase (GGT) 16 U/l (female NR up to 39), ALP 120 U/l (NR 64 - 306), amylase 190 U/l (NR up to 220), glucose 4.4 mmol/l (NR 4.2 - 6.4), BilT 26 µmol/l (NR up to 19), direct bilirubin 19 µmol/l (NR up to 4.3), total protein 82 g/l (NR 66 - 87), albumin 46 g/l (NR 38 - 51), creatinine 76 µmol/l (female NR 44 - 80), blood urea nitrogen (BUN) 4.2 mmol/l (female NR 1.7 - 8.3), total cholesterol 3.2 mmol/l (NR up to 5.7), high density lipoprotein (HDL) 0.1 mmol/l (NR more than 0.9), low density lipoprotein (LDL) 3.6 mmol/l (NR up to 4.38), and triglycerides 1.62 mmol/l (NR up to 1.71).

Central laboratory results from 22 JUL included ALT 552 U/l (NR 0 - 48), AST 777 U/l (NR 0 - 42), ALP 139 U/l (NR 20 - 125), BilT 169 µmol/l (NR 0 - 22), direct bilirubin 80 µmol/l (NR 0 - 6), CPK 50 U/l (NR 0 - 190), and LDH 262 U/l (NR 0 - 250).

History: Subject 4319 is a 32 year old female who was diagnosed with HIV in APR. She likely was infected by her husband, who is reported to use illicit drugs and was diagnosed with HIV in g but currently is not receiving therapy. The husband has chronic hepatitis C infection. This subject was doing well on study (randomized on 09 FEB) until shortly before a visit on 22 JUL, which was prompted by follow up of liver enzyme elevations noted at the Week 16 visit. The subject continued to feel well but noted scleral icterus (in morning of 21 JUL) and dark urine. She continued with those symptoms on the visit today. She denied fever, nausea, vomiting, diarrhoea, stool

* 新薬承認情報提供時に置き換え
colour changes, stool consistency changes, weight loss, shortness of breath, rash, light-headedness, or other systemic symptoms. She denied any recent insect or tick bites, new medications (herbal, OTC, or prescription), changes in diet.

Central laboratory results included:

17 JAN a* (screening): ALT 8, AST 18, ALP 63, BilT 6, CPK 54, lipase 60 (NR 7 - 60), HBsAg and HCV Ab were both non-reactive.

09 FEB a*: ALT 9, AST 20, ALP 58, BilT 11, CPK 62, and lipase 57.

24 FEB a*: ALT 8, AST 14, ALP 60, BilT 9, CPK 67, and lipase 76.

09 MAR a*: ALT 13, AST 22, ALP 54, BilT 9, CPK 70, and lipase 60.

06 APR a*: ALT 11, AST 21, ALP 59, BilT 9, CPK 81, and lipase 43.

05 MAY a*: ALT 50, AST 52, ALP 52, BilT 8, CPK 78, and lipase 64.

01 JUN a*: ALT 272, AST 302, ALP 70, BilT 7, CPK 68, and lipase 51.

14 JUN a*: ALT 8, AST 16, ALP 88, BilT 8, CPK 74, and lipase 29.

22 JUL a*: Hep C RNA negative, Hep A IgM negative, Hep B s Ag negative, ANA negative, EBV IgM negative, CMV IgM negative, and Hep B C IgM negative.

27 JUL a*: ALT 326, AST 620, ALP 100, BilT 239, direct bilirubin 83, lipase 85, acetaminophen negative, LKM IgG negative, and actin Ab IgG 22 units (weak positive).

Additional local laboratory results included, on 27 JUL a*, ALT 326 U/l (NR 0 - 48), AST 620 U/l (NR 0 - 42), and BilT 329 µmol/l (NR 0 - 22). Syphilis (RPR) test was negative.

On 27 JUL a* the subject was reported as doing well clinically, with the only complaints being scleral icterus and dark urine.

The subject remains stable without any clinical signs of liver insufficiency and has no complaints. The subject denied any new clinical symptoms on 01 AUG a* and 03 AUG a*. Hep E IgM was negative.

Additional laboratory results from 03 AUG a* included ALT 241 U/l, AST 527 U/l, ALP 96 U/l, BilT 186 µmol/l, direct bilirubin 79 µmol/l, and ferritin 37 µg/l (NR 10 - 154).

The results of an ultrasound scan performed 04 AUG a* were as follows:
Liver: acoustic access - satisfactory. dimensions of liver are not changed: oblique vertical size of right hepatic lobe - 120 mm, cranio-caudal size of left hepatic lobe -
65 mm. Parenchymal structure - homogenous. Echogenicity is comparable to the renal cortex. Vascular pattern is not changed. Portal vein is not dilated (d=7 mm). No space-occupying lesion. Intrahepatic bile vessels are not dilated. Choledochus: d=5 mm Gallbladder: Location - common. Increased in size: longitudinal axis - 100 mm, diameter - 40 mm. Structure is heterogenous. Identified multiple concrements ranging in size from 4 to 30 mm. One of them is fixed in the gallbladder neck. Bladder wall -irregularly thickened (5-7 mm). Pancreas: Location - common. Shape - variant of normal feature. Dimensions are increased: head of pancreas - 33 mm; body - 17 mm; tail - 19 mm. Parenchymal structure - homogenous. Boundaries are smooth and clear. Echogenicity is slightly increased (compared to liver). No space-occupying lesion.

Spleen: Location - common. Shape - variant of normal feature. Boundaries are smooth and clear. Capsule is not changed. Size is not changed. Parenchymal structure - heterogenous: 3 calcified foci are revealed. Echogenicity is medium. Splenic vein is not dilated. No space-occupying lesion.

Conclusion - resolved acute calculous cholecystopancreatitis.

Additional information received 10 & 16 AUG a* from Medical Monitor:
On 10 AUG a*, following telephone contact with the subject by the investigator, it was reported that the subject was well and that there were no yellow sclera.

Additional laboratory results included:
03 AUG a*: ALT 241, AST 527, BilT 186, repeat Hep C PCR negative, anti-neutrophil cytoplasmic Ab (ANCA) negative, ferritin normal, ceruloplasmin normal, alpha-1 antitrypsin normal, repeat actin IgG normal.
12 AUG a*: ALT 90, AST 142, ALP 81, BilT 83, Parvovirus pending.

Follow-up information 17 AUG a* from site:
Subject denies any complaints of previous gallbladder disorders that she remembers, no previous clinical manifestations. F/U US exams are planned in the beginning of September. The subject denies any clinical symptoms at her 12 AUG visit.

12 AUG a* AST 142, ALT 90, BilT 83
19 AUG a* AST 49, ALT 33, BilT 52
23 AUG a* – SAE considered resolved
29 SEP a* – Subject reported to be asymptomatic, with normal chemistries.
14 NOV a* – Repeat abdominal ultrasound demonstrated cholelithiasis

Final assessment: The Investigator and Sponsor could not rule out DILI as a contributing factor in this case. The observed gallstone disease was considered a co-suspect contributing factor.
This 32 year old male subject received IP from 02 FEB. This subject was randomized to receive RAL 400 mg twice daily.

The subject has no history of respiratory illness. Concomitant medications included ABC/3TC.

On 15 MAY, 102 days after the start of IP, the subject developed Grade 2 or moderate pneumonia. The subject developed a body temperature of 37.6°C. Chest X-ray performed on 16 MAY at an outpatient department showed right-sided pneumonia. The subject was hospitalized on 16 MAY, and treated with cephalosporins and bromhexine. Treatment with blinded trial medication was continued. The event resolved on 02 JUN and the subject was discharged. The investigator considered that there was no reasonable possibility the pneumonia may have been caused by IP.
This 53 year old male subject received IP from 17 FEB to 27 FEB. The subject was randomized to RAL 400 mg twice daily.

The subject's past medical history included acute respiratory viral infection, lymphadenitis and pharyngotraheitis. Medical conditions at the time of the event included hepatitis. Concomitant medications included ABC/3TC, paracetamol, amoxicillin trihydrate, Antigrippin, cefotaxime, clarithromycin, nitrofurazone, fluconazole, Ascorutin, pancreatin, inosine pranobex, papaverine, diclofenac, Essliver Forte, Phosphoglif, ascorbic acid and drotaverine.

On 24 FEB, seven days after the start of IP, the subject developed Grade 2 or moderate toxico-allergic reaction, Grade 2 or moderate influenza, Grade 2 or moderate cytolytic hepatitis and Grade 2 or moderate viral cervical lymphadenitis. The subject was hospitalized and the events were clinically significant (or requiring intervention). The subject experienced a fever up to 39.9-40 degrees Celsius, enlargement and swelling of the lymph nodes (submaxillary, both front and back of the neck lymph nodes). Those symptoms did not convince investigator that the event was hypersensitivity reaction. The subject took paracetamol to lower the temperature. On 25 FEB and 26 FEB, the subject received Amoxycillin. He noticed further enlargement of the lymph nodes and associated pain, and swelling of the neck. On 27 FEB, the subject developed rash on the skin of the chest, neck and face as well as itching, fever and watery stool three times a day. Treatment with blinded trial medication was discontinued on 27 FEB and the subject was withdrawn from the study. During a physical examination on 28 FEB, swelling of the lymph nodes (including axillary) and hyperemia of pharynx with petechial rash were noted. The subject had a rash on his trunk and extremities, which was more prominent on the torso (confluent rash). On 28 FEB, he did not experience itching. Spleen was unable to palpate, hepar - +2 cm beneath the costal arch. The subject was hospitalized on 28 FEB. Laboratory test results dated 28 FEB included ALT 310 U/L (NR 0-45), ALP 137 U/L (NR 53-128), AST 273 U/L (NR 0-35), bilirubin 21.9 µmol/l (NR 0-20), blood pressure 130/80 mmHg, erythrocyte sedimentation rate (ESR) 6 mm/h, gamma-glutamyltransferase (GGT) 514 U/L (NR 0-55), haematocrit 43.5%, HgB 152 g/l, lymphocytes 18%, monocytes 7%, MCHC 28.5 CU, respiratory rate 18 per minute, platelets 108x10^9/L, red blood cells (RBC) 5.34x10^{12}/L, WBC count 5.1x10^9/L. Laboratory test results dated 01 MAR included ALT 230 U/L, albumin 63 g/dl, AST 228 U/L, bilirubin 19.8 µmol/l, creatinine 74 µmol/l, eosinophils 1%, ESR 2 mm/h, fasting blood glucose 3.3 mmol/l, hemoglobin 132 g/l, lymphocytes 37%, monocytes 13%, platelets 200x10^9/L, RBC count 4.2x10^{12}/L.
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WBC count 5.2x10^9/L. Laboratory test results dated 09 MAR a* included ALT 116 U/L, AST 156 U/L, bilirubin 10.5 µmol/l, eosinophils 4%, ESR 10 mm/h, Hgb 146 g/l, lymphocytes 53%, monocytes 6%, WBC count 6.3x10^9/L. On 13 MAR a*, blood pressure was recorded 110/70 mmHg. Laboratory test results dated 17 MAR a* included ALT 91 U/L and AST 84 U/L. On 18 MAR a*, heart rate was 72 bpm. The subject was treated with loratadine. According to the subject, on 01 MAR a* the rash diminished to "practically non-existent". The events resolved on 18 MAR a* and the subject was discharged. Influenza serology result was received; Influenza A Ab more than 1:64, Influenza B Ab 1:8 (more than 1:8 - the threshold for Ab detection, more than 1:64 - indicative of infection).

According to the discharge report, the final diagnosis was recorded as acute respiratory viral infection, pharyngotracheitis, moderate intensity; lymphadenitis; chronic hepatitis C - possible reactivation (a-HCV IgG positive – 01 MAR a*); hepatic cytolysis syndrome; psoriasis - stationary stage. The investigator considered that there was a reasonable possibility that the toxico-allergic reaction may have been caused by the IP and that one of the possible causes was the concomitant medication, ABC/3TC. The investigator reported influenza, cytolytic hepatitis and viral cervical lymphadenitis as unrelated to treatment with IP.

Protocol Id: ING113086  
Investigator Number: 083153  
Subject Number: 004520  
Treatment Number: 2002, 2002  
Case Id: Z0011755A, Z0011755B  
Suspect Drugs: Raltegravir  
Serious Events: Status epilepticus, Urinary tract infection

This 25 year old male subject received IP from 17 NOV. This subject was randomized to receive RAL 400 mg twice daily.

Concomitant medications included paracetamol.

The subject's past medical history included seizure l*-j* following a head injury.

On 13 SEP b*, 300 days after the start of IP, the subject developed Grade 3 or severe possible urinary tract infection. The subject also experienced bilateral flank, loin pain, urinary frequency, dysuria and penile discharge. The subject was hospitalized. The subject was treated with azithromycin and ceftriaxone. Treatment with blinded trial medication was continued. All cultures were negative. The event resolved on 15 SEP b* and the subject was discharged. The investigator considered that there was no reasonable possibility the possible urinary tract infection may have been caused by IP.

On 15 DEC b*, 393 days after the start of IP, the subject developed Grade 4 status epilepticus. The subject reported three weeks of flu-like symptoms, including headache and photophobia. He was hospitalized on 15 DEC b* with seizures, followed by
persistent partial seizures with secondary generalization. MRI and lumbar puncture tests were normal. His urine drug screen was negative. The subject was treated with midazolam, clonazepam and phenytoin. The seizures were thought to be secondary to a viral infection. The subject had a history of seizures from l*–j* secondary to head trauma. Treatment with blinded trial medication was continued. The event resolved on 20 DEC b*. The subject was discharged on 21 DEC b*. The subject was to commence Keppra and Epilim (sodium valproate). The investigator considered that there was no reasonable possibility that the status epilepticus may have been caused by IP and that the event was possibly caused by viral infection.

Protocol Id: ING113086
Investigator Number: 083153
Subject Number: 004529
Treatment Number: 2016
Case Id: Z0007139A
Suspect Drugs: Abacavir sulfate + lamivudine, Dolutegravir
Serious Events: Drug hypersensitivity

This 6 year old male subject received IP from 10 DEC. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included ABC/3TC.

Relevant test results from screening (11 NOV a*) included ALT 44 U/l (NR 0 - 48), AST48 U/l (NR 0 - 42), and BilT 6 µmol/l (NR 0 - 22).

On 19 DEC a*, nine days after the start of IP, the subject developed Grade 4 drug HSR. Flu like symptoms (fever and body aches) were noted approximately ten days after commencing IP, which progressed over the course of four days to include symptoms of rash (profuse, purpuric and coalescing), joint swelling and pain, palpable liver, jaundice and atrial fibrillation. On 22 DEC a*, the subject presented to the investigator with fever, jaundice, and rash, and was noted to have elevated ALT 1081 U/l (NR 0 - 45), AST 906 U/l (NR 0 - 34), BilT 52 µmol/l (NR 0 - 21), and gamma-glutamyltransferase (GGT) 253 µmol/l (NR 0 - 64). Repeat HLA-B*5701 testing and HCV serologies were obtained. On 24 DEC a*, additional evaluation was made and labs were obtained through Quest, which verified a Hy's law event with elevated ALT 349 U/l (NR 0 - 48), AST 119 U/l (NR 0 - 42), BilT 104 µmol/l (NR 0 - 22), and direct bilirubin 44 µmol/l (NR 0 - 6). The subject was hospitalized and the event was clinically significant or requiring intervention (suspected hypersensitivity to abacavir and possible drug-induced liver injury with hyperbilirubinemia; 'Hy's' law event). The subject was treated with oseltamivir phosphate for suspected influenza, prednisolone, sotalol and aspirin for atrial fibrillation which developed on 24 DEC a*, and omeprazole. Treatment with IP was discontinued on 22 DEC a* and the subject was withdrawn from the study. The event was resolved with sequelae on 27 DEC a* and the subject was discharged from hospital as the liver chemistries were improving.

a*: The year
b*: Following year
j*: 6 years ago
l*: 8 years ago
Relevant test results from 31 DEC a* included ALT 142 U/l (NR 0 - 45), AST 43 U/l (NR 0 - 34), ALP 126 U/l (NR 35 - 110), and GGT 144 U/l (NR 0 - 64). The investigator confirmed that the subject still had rash on the arms (very faint) and mild joint pain on the 14 JAN b*. LFT's were reported as improved on the 29 APR b*. On 8 JUN b*, the subject was reported as well with no further reactions. The event resolved on 08 JUN b*. The investigator considered that there was a reasonable possibility that the drug HSR may have been caused by IP and that the event was possibly due to the concomitant medication, ABC/3TC.
Additional tests:

24 DEC a*: Hepatitis A Ab IGM, B sAg, B CORE IGM Ab, E Ab IGM - non-reactive.  
24 December a*: CMV IGM Ab, Epstein-Barr VCA IGM, ANA screen - negative.  
HCV RNA - less than 43IU/l.  Actin Ab IgG - less than 20 units.  Liver-Kidney  
Microsome (LKM) Ab IgG - less than 20 units

Investigator text:

Presented 22 DEC a* with lethargy, fever, heavy chest and skin rash.  Bloods performed.  
Presented 23 DEC with jaundice, maculopapular rash over body arms and legs,  
hypersensitive / paraesthia on finger and toes.  All meds have been ceased.  Awaiting  
further blood results.

Presentation on 24 DEC: Subject rash worse. Subject referred onto hospital for further  
tests and monitoring over the Christmas holidays.

There was further progression of subject condition on review on 24 DEC a*. Study  
medication had been ceased on 22 DEC a* when the subject presented for review with 3  
day history of lethargy and fever and was found to be febrile 37.7 with skin rash.  No  
relevant medical history or risk factors to add.

24 DEC a* - increasing constitutional symptoms of fever, lethargy and aches.  On  
examination, vasculitic rash on upper and lower limb & ears, jaundice, hepatomegaly and  
eck neck stiffness.  Admitted to hospital - elevated liver enzymes, electrolyte imbalance and  
atrial fibrillation with suspected HSR.  25 DEC a*- responding to therapy- fever  
resolution- rash & liver enzymes improving.  27 DEC a*- continues to improve-  
discharged home.

Additional Information received via Medical Monitor:

The subject was previously well.  There were no ill family or friends, no raw seafood  
consumption, no illicit drugs taken, and no travel.  HLA-B*5701 negative at screening,  
repeat HLA-B*5701 performed on 23 DEC a*, and HBV DNA, HCV RNA, and drug  
screen performed during hospitalization.  Subject was Hep C Ab (IgG) negative; Hep B  
sAg at screening and ALT/AST were normal at screening and day 1.  Hepatitis serology  
Hep B sAg negative, Hep B Ab positive (reflecting past HBV), Hep A IgG positive, IgM  
negative, and Hep C Ab negative.  Syphilis serology obtained via local labs were  
reportedly negative.  Transaminases were elevated prior to oseltamivir dosing.  
Acetaminophen overdose was ruled out by report from the treating physician.  Skin  
biopsy performed during hospitalization reveals leukocytoclastic vasculitis.  No  
peripheral eosinophilia (total eosinophil count per Quest 24 DEC a* - 0.03 GI/l (NR  
0.05 - 0.55). The following OTC supplements had been taken by the subject on a regular  
daily basis and had not been changed in quantity or brand; Blackmores mega vitamin,  
Tribulus - herbal extract to boost testosterone, Blackmores Bio C 1000 mg, Blackmores  
glucosamine 1500 mg, Vitamin E 500IU, Blackmores fish oil 1000 mg BID, pre-workout  

a*: The year

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gym powder of amino acids and caffeine. The subject denied use of anabolic steroids. Subject was discharged from hospital on 27 DEC a*, with liver chemistries normalizing.

Relevant laboratory data on 27 DEC a*, INR 1.0 and on 29 DEC a*, INR 0.9. On 06 JAN b*, ALT 79 and BilT 18. On 14 JAN b*, ALT 52 and BilT 8. On 08 JUN b* - AST 47 U/L (NR 0-42), ALT 35 U/L (NR 0-48), BilT 8 µMOL/L (NR 0-22).

Follow-up information received on 28 DEC a*:

There was further progression of the subject’s condition on review on 24 DEC. Study medication had been ceased on 22 DEC when the subject presented for review with 3 day history of lethargy and fever and was found to be febrile 37.7°C with skin rash.

Company Comment 31 DEC a*:

Following review of the case by the Company, ABC/3TC was recorded as a co-suspect medication as the event was considered to be a possible ABC HSR.

Follow-up information received 17 & 20 JAN b*:

Repeat HLA-B*5701 on 23 DEC a* was negative and the investigator reported ABC/3TC to be a non-suspect concomitant medication. However the Company still considers ABC/3TC as a co-suspect medication as the event was considered to be a possible ABC HSR.

Additional Information received via Medical Monitor (14, 16, 18 JAN b*):

Review of hospitalization notes on 14 JAN confirmed the following information: Upon admission (per hospital records), the subject was noted to be afebrile (36.9°C) with BP of 131/61, sinus rhythm with a regular heart rate of 78 bpm, and O2 saturation of 94% on room air. He then developed atrial fibrillation with rapid ventricular rate (120-132 bpm) and was also placed on supplemental O2 (8L, subsequent O2 sat of 100%). The hospital notes indicate complaint of headache and neck pain in addition to other noted symptoms above, but the subject denied shortness of breath or chest pain. Arterial blood gas results (presumably obtained on O2 but unconfirmed) on 24 DEC were as follows: pH 7.556, pCO2 23 kPa, PaO2 111 kPa, HCO3 20.4. Sotalol 40 mg twice daily was started for the atrial fibrillation, which resolved later in the day on 24 DEC. Bedside transthoracic echocardiogram performed on 25 DEC showed normal left ventricular function and no atrial dilatation.

Skin biopsy report confirms leukocytoclastic vasculitis. Received: 16 JAN b*

On 06 JAN b*, AST 48, ALT 79, Bili 18, ALP 140, plus most recent ALT 52, AST 40, Bili 8, ALP 145 taken on 14 JAN, received on 16 JAN.

a*: The year
b*: Following year
Subject reintroduced all herbal supplements as previously listed with no adverse effects: received on 16 JAN.

Clinical status update of the subject - continues to improve, mild desquamation of the skin over resolving rash. Received 18 JAN b*.

Additional information received from the Clinical team on 08 JUN b*:

The 24 hour abacavir patch test result was negative.

The 48 hour abacavir patch test was negative.

Assessment: The Investigator and Sponsor believe that a drug induced HSR related to DTG cannot be ruled out in this case. The Sponsor believes that an abacavir reaction is co-suspect in this case.

Protocol Id: ING113086
Investigator Number: 083149
Subject Number: 004549
Treatment Number: 4096, 4096
Case Id: Z0010733A, Z0010733B
Suspect Drugs: Dolutegravir, Vancomycin
Serious Events: Arthritis bacterial, Osteoarthritis, Renal impairment

This 70 year old male subject received IP from 05 JAN. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included vancomycin, Coloxyl + senna, Bactrim and TDF/FTC.

The subject's past medical history included septic hip.

On 21 JUL a*, 197 days after the start of IP, the subject developed Grade 4 septic arthritis of hip. The subject was hospitalized with groin pain and rash. The subject was treated with Bactrim, enoxaparin, loratadine, clotrimazole, oxycodone hydrochloride and paracetamol. The subject underwent hip aspirate (positive for Staphylococcus aureus) and hip wash-out and was begun on vancomycin. Treatment with IP was continued. On 04 AUG a*, the subject developed Grade 3 or severe renal function aggravated. Blood results showed elevated creatinine. Treatment with IP was continued. The septic arthritis of hip resolved on 09 AUG a* and the subject was discharged. The renal function aggravated resolved on 14 OCT a*. The investigator considered that there was no reasonable possibility that the septic arthritis of hip and renal function aggravated may have been caused by IP and that the renal function aggravated was possibly due to vancomycin given as treatment of septic arthritis of hip.

a*: The year
b*: Following year
On 25 OCT a*, 293 days after the start of IP, the subject developed grade 2 or moderate osteoarthritis of hip. The subject was hospitalized with pain in the left hip on 25 OCT a*. The subject was treated with Panadeine Forte and ibuprofen. Treatment with blinded trial medication was continued. The event resolved on 26 OCT a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the osteoarthritis of hip may have been caused by IP.

a*: The year
This 32 year old male subject received IP from 24 NOV. He was randomized to RAL 400 mg twice daily.

Concomitant medications included TDF/FTC.

On 26 NOV, two days after the start of IP, the subject developed Grade 2 or moderate diarrhoea. The subject was hospitalized. The subject was treated with ondansetron hydrochloride. Treatment with IP was interrupted. The event resolved on 09 DEC. IP was restarted on 19 DEC. The event did not recur on restarting IP. The investigator considered that there was a reasonable possibility that the diarrhoea may have been caused by IP and that the event was possibly due to the concomitant medication, TDF/FTC.

Additional Investigator Text:

Subject commenced study medications on the 24 NOV. At this time, he had ongoing dermatitis treated with topical steroids and left otitis externa for which he was prescribed ear drops. He reported by telephone the onset of diarrhoea and nausea from the 26 NOV and was assessed at an unscheduled outpatient visit on the 30 NOV. He complained of ongoing diarrhoea, nausea, with some possible mild fever and sweats and an increase in long-standing vertigo, and post-shingles left anterior chest pain. He had ceased ART (Truvada and study medication) on 29 NOV (3 missed doses). On examination, he had evidence of left otitis externa with no mastoid tenderness. Otherwise he appeared well, hydrated with mild oral thrush and mild central abdominal tenderness. The remainder of exam was normal. Full blood exam demonstrated stable eosinophilia; electrolytes confirmed stable renal impairment, liver function tests and a CRP were normal. A CT scan of his abdomen and pelvis was normal. A chest X-ray showed minor right middle lobe atelectasis. He was advised to take regular Maxalon with his medications, use previously prescribed ear drops and oral Nilstat, and to restart his ART, including study medication. His symptoms improved, but ongoing nausea, diarrhoea, lower abdominal cramps, poor oral intake and weight loss led him to cease ART on 03 DEC. He was not in contact with research staff until the Week 2 Visit, 07 DEC, when he described left flank pain. On exam, his weight had decreased 0.9 kg since 24 NOV. He was hydrated and had generalized mild abdominal tenderness, maximal in the left lower quadrant, without any guarding or rebound tenderness. He was tender in the right renal angle. He was admitted to hospital for investigation of his symptoms and for recommencement of ART. On admission, the
working differential diagnosis was an intercurrent bacterial enteritis, pyelonephritis or a form of IRIS.
This 60 year old male subject received IP from 02 FEB. This subject was randomized to receive DTG 50 mg once daily.

The subject's past medical history included acute myocardial infarction and coronary artery bypass graft surgery. Medical conditions at the time of the event included ischemic heart disease. Concomitant medications included TDF/FTC, aspirin, Methohexal and Simvastatin/Ezetimibe.

On 02 FEB, same day as the start of IP, the subject developed Grade 2 or moderate exacerbation of chest pain. The subject experienced mild symptoms intermittently since 31 JAN. The subject was hospitalized for monitoring and exclusion of cardiac cause of chest pain. The subject was treated with nitroglycerine and aspirin. His ECG was unchanged from baseline and serial CK and troponins were normal. Treatment with blinded trial medication was continued. The event resolved on 04 FEB. The subject was discharged the same day with resolution of chest tightness and no abnormalities were detected on examination. The investigator considered that there was no reasonable possibility that the exacerbation of chest pain may have been caused by IP.

Additional Investigator text:

On 03 FEB, subject reported worsening of central chest pain. Subject stated he had had mild symptoms intermittently since the 31 JAN but had not informed staff previously. These symptoms subsequently worsened on 03 FEB. Given the subject's previous history of ischemic heart disease and coronary artery bypass graft surgery, he was admitted to ER for monitoring and exclusion of cardiac cause of chest pain. Subject was discharged on 04 FEB with resolution of chest tightness and no abnormalities detected on examination. The subject underwent a thalium scan on the 08 FEB which reported a negative study for inducible myocardial ischemia on clinical, ECG and scintigraphic criteria at a good exercise workload.

*a*: The year
This 30 year old male subject received IP from 03 FEB. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included oxycodone hydrochloride, temazepam and ABC/3TC.

On 14 SEP, 223 days after the start of IP, the subject developed Grade 3 or severe secondary syphilis. The subject developed headaches from 14 SEP, followed by diffuse macular rash on 25 SEP. The subject presented with diffuse macular rash on 28 SEP and was hospitalized on 30 SEP. The subject tested positive for syphilis and was referred to neurologist to exclude neurosyphilis. The subject was treated with benzylpenicillin. Treatment with blinded trial medication was continued. The event resolved on 09 OCT. The investigator considered that there was no reasonable possibility that the secondary syphilis may have been caused by IP.

This 30 year old male subject received IP from 26 JAN. This subject was randomized to receive RAL 400 mg twice daily.

On 12 AUG, 198 days after the start of IP, the subject developed Grade 2 or moderate viral infection. The subject was hospitalized with a 2-day history of fever, chills, pain muscle and shivering. Blood test revealed neutropenia of 1600 neutrophils/ml (NR 1800-7500 neutrophils/ml) and thrombocytopenia of 106,000 platelet/ml (NR 140,000-450,000/ml). Neutropenia and thrombocytopenia were considered non-serious AEs. Serology test (Brucella, Toxoplasmosis, CMV, EBV, Mycoplasma Legionella, Chlamyphila pneumoniae, Coxiella burneti, Ricketsia) was negative. Blood tests on 16 AUG showed ALT at 40 U/L (NR 0 to 38). The subject was treated with paracetamol. Treatment with IP was not interrupted. The event resolved on 17 AUG. The investigator considered that there was no reasonable possibility that the viral infection may have been caused by IP.

*a*: The year
This 56 year old male subject received IP per day from 28 DEC 2008. This subject was randomized to receive DTG 50 mg once daily.

The subject had no medical history or medical disorder or allergy or surgery relevant to this event. Concomitant medications included ABC/3TC.

On 05 MAY 2009, 128 days after the start of IP, the subject developed Grade 2 or moderate acute GI infection. The subject presented to the ER after 24 hours of general symptoms of fever, arthralgia and muscle pain, in addition to abdominal cramping pain, with diarrhoea. The subject was hospitalized. The subject was treated with ciprofloxacin, hyoscine butylbromide and amoxicillin trihydrate. Treatment with IP was continued. The subject was discharged on 08 MAY 2009. The event resolved on 16 MAY 2009.

The investigator considered that there was no reasonable possibility that the acute GI infection may have been caused by IP.

This 56 year old male subject received IP from 14 DEC 2008. This subject was randomized to receive RAL 400 mg twice daily.

The subject's past medical history included herpes zoster, HIV encephalopathy, pneumonia and post herpetic neuralgia. Concomitant medications included Cotrim, fluconazole, paracetamol, tilidine hydrochloride, acyclovir, pregabalin, metoclopramide, TDF/FTC, RAL and gabapentin.

On 17 APR 2009, 124 days after the start of IP, the subject developed Grade 3 or severe abscess supraclavicular area, Grade 2 or moderate abnormal axillary lymph node and Grade 3 or severe atypical mycobacterial infection. The subject was hospitalized. Punction of the livid tumour performed on 28 APR 2009 found pus. The subject was treated with clarithromycin, ethambutol and rifabutin. Treatment with blinded trial medication was discontinued on 05 MAY 2009 and the subject was withdrawn from the study. The investigator confirmed that bacteria causing tuberculosis were not found. The
events resolved on 01 JUN b*. The investigator considered there was no reasonable possibility that the abscess supraclavicular area, abnormal axillary lymph node and atypical mycobacterial infection may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 083400
Subject Number: 004749
Treatment Number: 3197
Case Id: Z0012388A
Suspect Drugs: Dolutegravir
Serious Events: Upper limb fracture

This 37 year old male subject received IP from 10 JAN b*. This subject was randomized to receive DTG 50 mg once daily.

The subject has no relevant medical history or risk factors predisposing the event. Concomitant medications included TDF/FTC.

On 26 AUG a*, 228 days after the start of IP, the subject developed Grade 1 or mild fracture of elbow. The subject fell from his own height and broke his left elbow. The subject presented to the ER where the joint was immobilized and the subject was discharged. The subject was then hospitalized and underwent surgical treatment on 02 SEP a*. The subject was treated with paracetamol and ibuprofen. Treatment with blinded trial medication was continued. The subject was discharged on 05 SEP a* and started physiotherapy on an unspecified date. The event resolved on 12 DEC a*. The investigator considered that there was no reasonable possibility that the fracture of elbow may have been caused by IP.

Protocol Id: ING113086
Investigator Number: 084346
Subject Number: 004776
Treatment Number: 4069
Case Id: Z0009708A
Suspect Drugs: Raltegravir
Serious Events: Abortion spontaneous

This 29 year old female subject received IP per day from 21 DEC b* to 28 JAN b*. This subject was randomized to receive RAL 400 mg twice daily.

The subject had a previous history of four pre-term pregnancies, two which resulted in spontaneous abortions, and two elective abortions.

The subject was screened on 06 DEC a* with a HIV-1 RNA viral load of 140,527 c/mL and CD4+ count of 548 cells/mm³. Serum pregnancy test was negative at screening visit. The subject's method of contraception was reported as condom use.
At the Week 4 study visit on 19 JAN b*, the subject tested positive for both serum and urine HCG test. The subject's last menstrual period was on 25 DEC a* and her estimated date of delivery was SEP b*.

On 03 FEB b*, 44 days after the start of IP and six days after the last dose, the subject developed Grade 1 or mild spontaneous abortion. The event was clinically significant (or requiring intervention). Treatment with blinded trial medication was stopped on 28 JAN b* due to the pregnancy. Until 03 FEB b*, the subject was seen on several occasions by the gynaecologist for suspected ectopic pregnancy, but this was not confirmed. The subject was referred to the pregnancy follow-up visit, but she did not attend. On 15 FEB b*, there was a follow-up visit without any analytical tests performed. On 23 MAR b*, the subject had a negative pregnancy test, no voluntary abortion was performed, so the investigator suspected that the subject had a spontaneous abortion, although she remained asymptomatic and thought her periods were normal. The event resolved on 23 MAR b*. The investigator considered that there was no reasonable possibility that the spontaneous abortion may have been caused by IP.

This 30 year old male subject received IP from 21 JAN b*. This subject was randomized to receive RAL 400 mg twice daily.

The subject's past medical history included abdominal pain (onset date 12 AUG a*).

On 12 AUG a*, 203 days after the start of IP, the subject developed Grade 2 or moderate appendicitis confirmed by ultrasound. The subject was hospitalized with abdominal pain. The subject underwent surgery and was treated with paracetamol. Treatment with blinded trial medication was continued. The event resolved on 15 AUG a*. The investigator considered that there was no reasonable possibility that the appendicitis may have been caused by IP.
This female subject received IP from 27 DEC to 17 APR b*. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included TDF/FTC and mirtazapine. The subject had two previous pre-term pregnancies (one spontaneous abortion and one elective abortion); and one full term pregnancy (normal birth).

At an unknown time after the start of IP, the subject became pregnant. The method of contraception used was condoms. The subject's last menstrual period was on 11 MAR b*, 15 days after starting IP. Treatment with blinded trial medication was discontinued on 17 APR b* and the subject was withdrawn from the study.

Follow up information indicated the subject had an elective abortion on 10 MAY b*; gestational age at termination was 9 weeks.

Protocol Id: ING113086
Investigator Number: 83505
Subject Number: 4311
Treatment Number: 1201
Case Id: B0725417A
Suspect Drugs: Dolutegravir
Pregnancy

This 34-year old female subject received IP from 04 FEB b*. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included ABC/3TC.

At an unknown time after the start of IP, the subject became pregnant. Date of last menstrual period was 29 APR a*. Method of contraception was double method (condom male and spermicidal cream). The subject had three previous elective abortions and 1 normal birth. On 24 MAY a*, the subject had a pregnancy termination; there was no hospitalization and no complications. The investigator reported the subject had a positive pregnancy test at Week 16 analysis and the pregnancy was terminated (elective) before Week 16 on 24 May a*. Investigational product and ABC/3TC were discontinued on 03 JUN a*.

Protocol Id: ING113086
Investigator Number: 83517
Subject Number: 4355
Treatment Number: 2057
Case Id: B0771245A
Suspect Drugs: Dolutegravir
Pregnancy

a*: The year
b*: Following year
This 3 year old female subject received IP from 09 FEB to 29 NOV a*. This subject was randomized to receive DTG 50 mg once daily.

Concomitant medications included ABC/3TC.

At an unknown time after the start of IP, the subject became pregnant. The subject's last menstrual period was on 26 OCT a*. A 28 NOV a* pregnancy test (human chorionic gonadotropin) was 4773 mme/ml; an ultrasound confirmed the pregnancy. The estimated date of delivery is 02 AUG b*. Factors that may have an impact on the outcome of the pregnancy were HIV infection and a right ovarian cyst. Treatment with blinded trial medication was discontinued on 29 NOV a* and the subject was withdrawn from the study.

Follow up information received on 05 OCT b*: Concomitant medications included Kaletra, drotaverine, ethamsylate and dydrogesterone. The subject delivered a normal neonate on 25 JUL b* at 39 gestational weeks. The delivery method was not specified. The neonate was female, weighed 3050 g and her length was 51.0 cm. Her APGAR score on the first and second assessment was 8.

Protocol Id: ING113086
Investigator Number: 083517
Subject Number: 4358
Treatment Number: 1219
Case Id: Z0012654A
Suspect Drugs: Dolutegravir
Pregnancy

This 4 year old female subject received IP from 09 FEB. This subject was randomized to receive DTG 50 mg once daily.

The subject's past medical history included missed abortion and premature birth. Concomitant medications included ABC/3TC and Kaletra.

On 21 SEP a*, approximately seven months after the start of IP, the subject had a positive pregnancy test (serum), and on 22 SEP a* had a positive urine pregnancy test. The subject was reported as having experienced drug exposure during pregnancy. The last menstrual period was on 20 AUG a* and the estimated date of delivery was 25 MAY b*. Treatment with IP was discontinued on 23 SEP a* and the subject was withdrawn from the study.

On 25 OCT a*, 258 days after the start of IP and 32 days after the last dose, the subject developed Grade 2 or moderate threatened miscarriage. The subject was hospitalized. The subject was treated with drotaverine, ethamsylate and dydrogesterone. The event resolved on 31 OCT a*. The investigator considered that there was no reasonable possibility that the threatened miscarriage may have been caused by IP. The investigator reported that the threatened miscarriage was not considered to be a SAE.

a*: The year
b*: Following year
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Follow-up information received 04 JUN b*: The pregnancy outcome was a still birth; the neonatal status was normal. The birth occurred on 22 MAY b*, female infant, length 50cm; weight 3.3kg. The APGAR score was not available at time of reporting. Additional concomitant medications included raltegravir, ferrum lek, zidovudine.

Follow-up information received 21 JUN b*: The pregnancy outcome was a live birth of a normal female neonate. APGAR scores were not available at the time of reporting.
This **year** old female subject received DTG per day from 11 FEB *a* to 11 OCT *a*.

Concomitant medications included ABC/3TC, RAL and otological preparation.

The subject had three previous pregnancies of which one was a normal birth; two were aborted electively.

The subject's partner was HIV negative.

On 21 OCT *a*, seven months after the start of IP, the subject was found to be pregnant. Contraception used was a male condom. Her last menstrual period occurred on 20 SEP *a*. Pregnancy confirmed via serum test on 23 SEP *a* and again on 05 OCT *a*. Treatment with IP was discontinued on 11 OCT *a* and the subject was withdrawn from the study. The subject was exposed to IP at 0-3 weeks gestation, before conception and during the first trimester. At the time of reporting, the outcome of the pregnancy was unknown. The estimated date of delivery was 26 JUN *b*.

Follow-up information received 05 OCT *b*:

The subject continued receiving Kivexa and Kaletra from 12 OCT *a*. The subject gave birth to a normal male neonate on 20 JUL *b* at 40 weeks gestation. The neonate weighed 2813g and was 48.0cm long. APGAR scores were not available. The investigator noted that "taking into account that gestational age at the time of delivery was 40 weeks and that the last pregnancy test result was borderline 26.10. *a* can be assumed that the Subject 4411 became pregnant after study drug discontinuation. 11.10.2 *a* = last dose. Conception date approx 03.11. *a*.

Follow up information received on 17 OCT *b*:

The delivery method was vaginal.

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*a*: The year

*b*: Following year
This 23 year old female subject received IP per day from 15 FEB to 15 MAR. This subject was randomized to receive RAL 400 mg twice daily.

At an unknown time after the start of IP, the subject was reported to be pregnant. Investigational product was discontinued on an unknown date. Details regarding the subject's last menstrual date and expected date of delivery were unknown at the time of reporting. The investigator reported that the subject did not want to continue with the pregnancy and wished to undergo an elective termination. Further details were unspecified at the time of reporting.

Follow up information received on 22 MAR:

The investigator reported that IP was discontinued on 13 MAR and the subject was withdrawn from the study. Number of previous preterm pregnancies (elective terminations) was five, with one full term normal birth. Date of last menstrual period was 28 FEB and estimated date of delivery 20 NOV. Method of contraception was condoms and medoxyprogesterone. The subject's pregnancy was terminated on 15 MAR.

9.6.2.2. Cases Reported Between 03 March to 18 June

For this study, with a completed interim statistical analysis more than six months prior to the planned submission date, a new safety data cut was taken for reporting in this ISS. The narratives included in this section correspond to the SAEs and Pregnancy cases reported from: the safety data lock point for the ING113086 Week 48 CSR; up to the 18 June cut-off date for inclusion of data from this study in the Integrated Safety Outputs, and includes all follow up information received by the company through 26 October. The data included here are not represented in the clinical study report included in m5.3.5.1; however SAEs cumulative to 18 June for this study are included in the ISO Tables and Figures produced for the ISS, which are located in m5.3.5.3 along with the ISS.
This 50-year-old male subject received oral investigational product from 30 NOV 2020.

The subject's past medical history included syphilis. Concomitant medications included phenoxymethylpenicillin potassium and Truvada.

On 08 May c*, 525 days after the start of investigational product, the subject developed grade 3 or severe neurosyphilis. The subject complained of left ear hearing loss over the past 3 months. Rapid plasma regain (RPR) test performed on 08 May c* showed result of 1:256. The subject presented to the ER, where WBC count showed result of 25 (units and normal ranges unknown). The subject was hospitalised and treated with phenoxymethylpenicillin potassium. Treatment with investigational product was continued. The subject was discharged on 09 May c* to complete the course of treatment at home. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the neurosyphilis may have been caused by investigational product.

Investigator text:

Subject has a history of syphilis in a*, treated with Bicillin shot x 1. Lumbar puncture performed in local ER showed WBC of 25. Patient subsequently admitted to hospital for treatment. Started course of Penicillin 4 million units IV every 4 hours x 2 weeks.

This 50-year-old male subject received oral investigational product from 11 JAN 2021.

The subject was randomized to receive raltegravir 400 mg, twice daily.

Concomitant medications included metoclopramide, ranitidine hydrochloride and sodium chloride. No relevant medical conditions were noted.

*a*: The year
*c*: 2 years later
On 10 MAY a*, 120 days after the start of investigational product, the subject developed grade 2 or moderate appendicitis. The subject presented to the primary care physician with upper abdominal pain. The physician suspected gastroesophageal reflux disease or possible food poisoning and the subject was prescribed metoclopramide. The subject took metoclopramide and ranitidine, but his pain worsened. The subject presented to the emergency room, where a CAT scan revealed a highly inflamed appendix. The subject was hospitalised and received intravenous saline solution for hydration. Appendectomy was performed on 11 MAY a*. The subject was treated with Hydrocodone acetaminophen, ciprofloxacin, metronidazole, saline and docusate sodium. Treatment with blinded trial medication was continued. The subject was discharged on 12 MAY a* with antibiotics and stool softener. The event resolved on 08 JUN a*.

The investigator considered that there was no reasonable possibility that the appendicitis may have been caused by investigational product.

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**Protocol Id:** ING113086  
**Investigator Number:** 082926  
**Subject Number:** 003472  
**Treatment Number:** 3029  
**Case Id:** Z0014978A  
**Suspect Drugs:** Raltegravir  
**Serious Events:** Arthritis bacterial, Cellulitis

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This 27-year-old male subject received oral investigational product from 29 NOV a*. The subject was randomized to receive Raltegravir 400 mg twice daily.

Medical conditions at the time of the event included alcoholism, recurrent cellulitis and recurrent phlebitis. Concomitant medications included thiamine, phosphate, diazepam, nicotine, zopiclone, naloxone, nalbuphine, dimenhydrinate, ondansetron hydrochloride, prochlorperazine, sennosides, docusate sodium, bisacodyl and ranitidine hydrochloride.

Subject has a history of recurrent cellulitis and phlebitis in his legs as well as long standing alcoholism.

On 30 MAR c*, 487 days after the start of investigational product, the subject developed grade 3 or severe recurrent cellulitis of the leg. On 08 APR c*, 496 days after the start of the investigational product, the subject developed grade 3 or severe septic knee. The subject was seen at the ER on 30 March c* due to chest pain, non-trauma, nausea and vomiting, as well as pain in his left knee. He was discharged home the same day with a diagnosis of alcohol withdrawal. The subject returned to the ER on 02 APR c* due to worsening left knee pain and inflammation in the left lower limb. The subject was hospitalised with cellulitis of the left leg requiring intravenous antibiotics. Cultures were positive for E. coli. The subject was treated with enoxaparin, cephazolin sodium, Piperacillin/tazobactam, vancomycin, clindamycin, celecoxib, paracetamol, hydromorphone hydrochloride, morphine and ceftriaxone. On 08 APR
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c*, the subject was taken to the OR for irrigation, debridement and fasciotomy of the left lower leg as well as irrigation, debridement, arthrotomy and complete synovectomy of the left knee joint. Treatment with investigational product was continued. The subject had two further surgeries on 10 APR and 18 APR for debridement and irrigation. On 30 APR c*, he returned to the ER with septic left knee. The subject returned to the ER on 17 MAY c* for further irrigation and debridement as well as skin graft from left thigh to left lower extremity. The events resolved on 26 MAY c* and the subject was discharged. He continues on IP and IV Ceftriaxone.

The investigator considered that there was no reasonable possibility that the recurrent cellulitis of leg and septic knee may have been caused by investigational product.

Follow-up information received on 23 APR c* via answered query report:

The left knee pain was also considered to be a symptom of cellulitis

Follow up information received on 02 MAY c* via answered query report:

The subject was reported to be still in hospital.

Relevant diagnostic tests:

X-ray of left ankle indicates small ankle effusion. No fracture. Anatomic alignment. Chest X-ray done 02 APR 2 was normal. Biopsy/ Tissue culture, Left knee synovium tissue: Escherichia coli isolated from fluid medium only. Biopsy/Tissue, deep posterior tissue, LT: microscopy: many pus cells seen. Culture: Scant growth of Escherichia coli

Protocol Id: ING113086
Investigator Number: 083675
Subject Number: 003515
Treatment Number: 1074
Case Id: Z0014712A
Suspect Drugs: Dolutegravir
Serious Events: Lung infection

This -year-old female subject received oral investigational product from 18 DEC .

This subject was randomised to receive oral dolutegravir 50 mg once daily.

The subject's past medical history included aspergillus fumigatus bronchopulmonary infection, bronchitis pneumococcal and pulmonary tuberculosis. Medical conditions at the time of the event included smoking related chronic obstructive airways disease and tobacco use. Concomitant medications included Kivexa, Symbicort and salbutamol sulphate.
On 08 MAR c*, 446 days after the start of dolutegravir, the subject developed grade 3 or severe common infectious pneumopathy. The subject was hospitalised with a one week history of fever, cough and dyspnoea. The subject was treated with azithromycin and ceftriaxone sodium. Treatment with investigational product was continued. The event resolved on 30 MAR c*.

The investigator considered that there was no reasonable possibility that the common infectious pneumopathy may have been caused by investigational product.

Diagnostics:

Hypoxémie :9.5kPa .Hyperleucocytosis with neutrophil leukocyt at 12.4 Giga/L. CRP/112

Investigator text:

No focus at XRay Apyrexy on 24 hour with Rocéphine. Hospitalisation for 16 MAR to 21 MAR.

*: 2 years later
This 30-year-old male subject received oral investigational product from 03 January 2021.

The subject was randomized to receive dolutegravir 50 mg once daily.

The subject had no relevant medical history. Concomitant medications included emtricitabine, tenofovir and pantoprazole.

On 09 APR b*, 462 days after the start of investigational product, the subject developed grade 3 or severe corneal abscess. The subject developed red eyes and pain on 09 APR b* and was hospitalised on 11 APR b*. The subject was treated with azithromycin, bacitracin, ceftazidime sodium, paracetamol, Imipenem + cilastatine, sodium hyaluronate, retinol and TobraDex. Treatment with blinded trial medication was continued. The subject was discharged on 30 APR b*. The event resolved with sequelae on 03 SEP b*. The investigator considered that there was no reasonable possibility that the corneal abscess may have been caused by investigational product.

Diagnostics:

An ophthalmologist diagnosed an abscess of cornea. The bacteria is neisseria elongate

Follow up information received on 01 OCT b* via answered query report:

The investigator considered that the sequelae was "visual deficiency".

Investigator text:

Hospitalization was from 11 APR to 30 APR b*. He maintains a visual deficiency on 21th MAY.

b*: Following year
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Protocol Id: ING113086
Investigator Number: 082943
Subject Number: 003790
Treatment Number: 4036
Case Id: Z0015258A
Suspect Drugs: Raltegravir
Serious Events: Gastroenteritis

This 25-year-old male subject received oral investigational product from 07 DEC.

The subject was randomized to receive Raltegravir 400 mg twice daily.

The subject had no relevant medical history and received no concomitant therapy. Concomitant medications included Truvada.

On 18 APR, 498 days after the start of investigational product, the subject developed grade 3 or severe gastroenteritis. Associated symptoms included abdominal pain and diarrhoea. The subject was hospitalised and treated with symptomatic infusions and diet. Treatment with blinded trial medication was continued. The event resolved on 21 APR. The investigator considered that there was no reasonable possibility that the gastroenteritis may have been caused by investigational product.

Diagnostics:
Stool cultures negative.

Protocol Id: ING113086
Investigator Number: 083402
Subject Number: 003994
Treatment Number: 3223
Case Id: Z0013916B
Suspect Drugs: Duloxetine, Ibuprofen, Metamizole magnesium, Paracetamol, Raltegravir
Serious Events: Intentional overdose, Suicide attempt

This 24-year-old male subject received oral investigational product from 14 JAN.

This subject was randomised to receive oral raltegravir 400 mg twice daily.

The subject's past medical history included suicidal attempt. Concomitant medications included Truvada, paracetamol, ibuprofen, duloxetine, metamizole magnesium and acetylcysteine.

On 07 MAY, 479 days after the start of raltegravir, the subject developed grade 2 or moderate attempted suicide and grade 4 intentional drug overdose. The subject had a

b*: Following year
c*: 2 years later

* 新薬承認情報提供時に置き換え
discussion with his partner and attempted suicide. The subject was hospitalised and the events were life-threatening. Laboratory test results dated 07 MAY b* included creatinine 1.7 mg/dl (normal range 0.5-1.3). Treatment with raltegravir was discontinued on 08 May b* and the subject was withdrawn from the study. The events resolved on 09 May b*. The investigator considered that there was no reasonable possibility that the attempted suicide and intentional drug overdose may have been caused by raltegravir and that the events were possibly due to the concomitant medication, paracetamol, ibuprofen, duloxetine and metamizole magnesium.

Follow-up information received on 11 MAY b* via query response:

Subject is checked in to psychiatric unit.

Investigator text:

He presented vomiting and he was asymptomatic during the event.

There wasn’t any abnormal laboratory results. He presents an initial renal condition and was treated with aceticcisteine and fluides. He was discharged on 9 MAY b*. He’s doing well.

Protocol Id:  ING113086
Investigator Number:  083153
Subject Number:  004534
Treatment Number:  1062
Case Id:  Z0014805A
Suspect Drugs:  Raltegravir
Serious Events:  Tibia fracture

This 22-year-old male subject received oral investigational product from 17 DEC c*.

This subject was randomised to receive raltegravir 400 mg twice daily.

On 05 MAR c*, 444 days after the start of investigational product, the subject jumped a 6 foot fence and developed grade 3 or severe fracture of medial distal tibia. The subject was hospitalised. CT scan showed fracture of the medial distal tibia. The subject underwent a reduction and internal fixation of left distal tibia. The subject was treated with Panadeine Forte, enoxaparin, ibuprofen and oxycodone. Treatment with blinded trial medication was continued. The subject was discharged on 07 MAR c* with crutches and a camboot. X-ray performed on 07 MAY c* showed the fracture was filling. Camboot was removed and physiotherapy commenced. The event resolved with sequelae on 09 MAY c*. The investigator considered that there was no reasonable possibility that the fracture of medial distal tibia may have been caused by investigational product.
Follow-up information received on 23 MAY c* via answered query report:

The investigator confirmed the nature of sequelae was the subject still required physiotherapy and has a limp.

Protocol Id: ING113086
Investigator Number: 083153
Subject Number: 004538
Treatment Number: 4103
Case Id: Z0015161A
Suspect Drugs: Raltegravir
Serious Events: Laceration

This 3-year-old male subject received oral investigational product from 10 JAN b*.

The subject was randomized to receive Raltegravir 400 mg twice daily.

The subject has no relevant medical history. Concomitant medications included Truvada.

On 06 APR b*, 452 days after the start of investigational product, the subject slipped on stairs and developed grade 3 or severe laceration to elbow. The subject was hospitalised on 08 APR b*. The subject underwent surgical debridement and suturing. The subject was treated with cephalaxin and Panadeine Forte. Treatment with blinded trial medication was continued. The event resolved with sequelae on 13 APR b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the laceration to elbow may have been caused by investigational product.

Diagnostics:

X-ray found gas in region of olecranon - no fracture

Follow-up information received on 23 MAY b* via answered query report:

The investigator reported the event had resolved with sequelae of pain and discomfort.

Protocol Id: ING113086
Investigator Number: 083149
Subject Number: 004549
Treatment Number: 4096
Case Id: Z0010733D
Suspect Drugs: Dolutegravir
Serious Events: Osteomyelitis chronic

This 3-year-old male subject received oral investigational product from 05 JAN b*.

b*: Following year
C*: 2 years later
This subject was randomised to receive oral dolutegravir 50 mg once daily.

Concomitant medications included Kivexa.

On 16 FEB b*, 407 days after the start of investigational product, the subject developed grade 3 or severe chronic osteomyelitis of hip. The subject was hospitalised and underwent uncomplicated excision arthroplasty of left hip on 16 FEB b*. The subject was treated with vancomycin, enoxaparin and tramadol hydrochloride. Treatment with blinded trial medication was continued. The event resolved on 27 FEB b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the chronic osteomyelitis of hip may have been caused by investigational product.

Diagnostics:

All blood tests within normal range. X-ray showed no abnormalities.

Protocol Id: ING113086
Investigator Number: 083150
Subject Number: 004582
Treatment Number: 3273
Case Id: Z0015832A
Suspect Drugs: Dolutegravir
Serious Events: Cholecystitis, Hepatitis C

This 35-year-old male subject received oral investigational product from 31 January b*. The subject was randomized to receive dolutegravir 50 mg once daily.

The subject's past medical history included drug addiction (recent methadone detox followed by heroin use) and past hepatitis C coinfection (HCV RNA negative). Concomitant medications included Truvada.

On 01 June b*, 487 days after the start of investigational product, the subject developed grade 3 or severe acute hepatitis C infection and grade 2 or moderate acalculous cholecystitis. The subject was hospitalised on 06 JUN b* with abdominal pain and jaundice. Laboratory test results dated 06 JUN b* included ALT 1083 U/L (normal range 0-48), alkaline phosphatase 213 U/L (normal range 20-125), AST 536 U/L (normal range 0-42), bilirubin total 78 umol (normal range 0-22), GGT 238 U/L (normal 0 - 51 U/L) and WBC count 10.1x10*9/L (normal 3.5 - 11.0 x 10*9/L). The subject was treated with Timentin, oxycodone and buprenorphine. Treatment with blinded trial medication was continued. The subject was discharged on 15 JUN b*. The events resolved on 23 JUL b*. The investigator considered that there was no reasonable
possibility that the acute hepatitis C infection and acalculous cholecystitis may have been caused by investigational product.

Follow-up received via answered query 30 JUL b*: 

The subject did not receive any treatment for hepatitis C.

Diagnostics:

Abdominal ultrasound 07-Jun-b* showed evidence of acalculous cholecystitis.

06-Jun-b* hepatitis C Quantitation RNA 1690000IU/ml.

Hepatitis C antibodies positive.

Hepatitis C log10 Value 6.23 log10

Protocol Id: ING113086
Investigator Number: 84343
Subject Number: 4125
Treatment Number: 3332
Case Id: B0806287A
Suspect Drugs: Raltegravir
Pregnancy

This 21-year-old female subject received oral investigational product from 11 FEB b*.

Concomitant medications included Truvada.

On an unspecified date the subject was found to be pregnant. Her last menstrual period occurred on 14 APR b*. Treatment with the investigational product was stopped on 29 MAY b*. The subject was exposed to the investigational product before conception and during the first trimester. At the time of reporting, the outcome of the pregnancy was unknown. The estimated date of delivery is 20 JAN c*.

Follow-up information received 08 JUN b*:

The site did a local pregnancy test on 01 JUN b*, and the subject was referred to a gynaecological service.

**9.6.2.3. Cases Reported Between 19 June b* to 26 October c***

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the cut-off date for the Integrated Safety Outputs up to the final
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26 October [redacted] safety data lock point for the ISS, and includes all initial reports and follow up information received by the company through 26 October [redacted]. The data included here are not represented in the clinical study report included in m5.3.5.1, nor in the ISO Tables and Figures produced for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials’ database in preparation of these narratives.

Protocol Id: ING113086
Investigator Number: 081018
Subject Number: 003284
Treatment Number: 2014
Case Id: Z0016702A
Suspect Drugs: Raltegravir
Serious Events: Self-injurious ideation

This [redacted] year-old male subject received oral investigational product from 08 DEC [redacted].

The subject was randomized to receive Raltegravir 400 mg twice daily.

Medical conditions at the time of the event included bipolar disorder, depression and substance abuse. Concomitant medications included trazodone, mirtazapine and Epzicom.

On 16 AUG [redacted], 617 days after the start of investigational product, the subject developed grade 4 intent to harm himself. The subject voluntarily admitted himself to hospital on 16 AUG after expressing a clear and credible intent to harm himself. Treatment with investigational product was continued. The subject was hospitalised. The event resolved on 20 AUG [redacted]. The investigator considered that there was no reasonable possibility that the intent to harm himself may have been caused by investigational product.
This 361-year-old male subject received oral investigational product from 21 DEC 361.

The subject was randomized to receive Raltegravir 400 mg twice daily.

Medical conditions at the time of the event included depression. Concomitant medications included Kivexa.

On 22 JUL c*, 579 days after the start of investigational product, the subject developed grade 3 or severe suicidal ideation. The subject was hospitalised on 22 JUL c*. No investigations were performed. The subject was treated with venlafaxine hydrochloride and quetiapine. Treatment with blinded trial medication was continued. The subject was discharged on 24 JUL c*. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the suicidal ideation may have been caused by investigational product.

Follow-up information received on 29 AUG c* via query response:

Subject is being followed by a psychiatrist.

This 361-year-old male subject received oral investigational product from 17 DEC 361.

The subject was randomized to receive dolutegravir 50 mg once daily.

Concomitant medications included Kivexa.

On 12 OCT c*, 665 days after the start of investigational product, the subject developed grade 3 or severe brittle diabetes. The subject was hospitalised. The subject was treated with insulin. Treatment with blinded trial medication was continued. The event was unresolved at time of reporting. The investigator considered that there was no
reasonable possibility that the brittle diabetes may have been caused by investigational product.

This 38-year-old female subject received oral investigational product at 50 mg per day from 10 MAR 2020.  

The subject's past medical history included two abortions.  Concomitant medications included Truvada, raltegravir, mifepristone and oral contraceptive.

On 29 JUN 2020, 477 days after receiving investigational product and Truvada, the subject had her last menstrual period.  On 27 JUL 2020, she underwent a medical abortion using mifepristone and misoprostol.

This 38-year-old male subject received oral investigational product from 04 DEC 2019.  

The subject was randomized to receive dolutegravir 50 mg once daily.

Concomitant medications included Truvada and levofloxacin.

On 24 APR 2021, 507 days after the start of investigational product, the subject developed grade 2 or moderate coronal hypospadias.  The subject was hospitalised.  Treatment with investigational product was continued.  The event resolved on 30 April 2021.  The investigator considered that there was no reasonable possibility that the coronal hypospadias may have been caused by investigational product.

Follow up information received on 12 OCT 2021 via query response:
The surgical operation was done due to a piercing in the penis. This is not in the medical history and no signs or symptoms occurred. Subject received Tavanic as a concomitant medication.

Follow up information received on 18 OCT c* via answered query response:

The subject did not receive any relevant concomitant medications at the time of the SAE.

Investigator text:

Meatoglanduloplastic per surgery set-in.

Protocol Id: ING113086
Investigator Number: 082953
Subject Number: 003835
Treatment Number: 3299
Case Id: Z0016560A
Suspect Drugs: Dolutegravir
Serious Events: Cerebrovascular accident

This 36-year-old male subject received oral investigational product from 04 FEB .

The subject was randomized to receive dolutegravir 50 mg per day.

No relevant medical history and / or risk factors. Concomitant medications included Truvada.

On 03 AUG b*, 546 days after the start of investigational product, the subject developed grade 3 or severe suspected apoplexy. The subject presented at the hospital due to diploptic images starting on 03 AUG b*. The subject was hospitalised. and treated with aspirin. Treatment with blinded trial medication was continued. The event resolved with sequelae (hyaesthesia and hypalgesia right hand palmar and ulnar) on 10 AUG b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the suspected apoplexy may have been caused by investigational product.

Follow-up information received on 03 SEP b* via query response:

The only sign were diploptic images; there were no other signs of an apoplex; named medication (Ceftriaxon, Ramilich and Heparin) was not given as part of SAE

Diagnostics:

Cerebral CTs (03 AUG b* and 07 AUG b*) and cerebral MRI (03 AUG b*) without pathological findings. Diploptic images were not confirmed during hospitalization. A complete neurological exam was done on 03 AUG b*. The only
pathological finding was a hyaesthesia and hypalgesia right hand palmar and ulnar and a reduced pallaesthesia bimalleolar (5/8). Both findings were caused probably by known degeneration of spinal column. We have documented these findings as sequelae because these are the only neurological symptoms around the event and it is unknown when symptoms started. Evaluation of cognition, perception and language were normal. Ultrasound assessment showed normal flow levels inside and outside of the cranium. There were only minimal macroangiopathic changes.

Investigator text:

The only symptom were diploptic images; there were no other signs of an apoplext; diagnosis apoplex was not confirmed but was documented as suspected in discharge letter; patient discharged in better condition at 10 AUG b*, rehabilitation is planned for end of AUG b*.

Protocol Id: ING113086
Investigator Number: 083264
Subject Number: 003910
Treatment Number: 4027
Case Id: Z0016801A
Suspect Drugs: Raltegravir
Serious Events: Appendicitis

This 20-year-old male subject received oral investigational product from 03 DEC . The subject was randomized to receive Raltegravir 400 mg twice daily.

Concomitant medications included Truvada.

On 25 AUG c*, 631 days after the start of investigational product, the subject developed grade 2 or moderate acute appendicitis. The subject presented to the ER on 26 AUG with a one day history of abdominal pain. The subject did not experience nausea, vomiting, diarrhoea, fever or any other symptomatology. The subject was given analgesia and was discharged the same day. The subject returned to the ER on 27 AUG c* due to non-improvement of abdominal pain. The subject was diagnosed with acute appendicitis and was hospitalised for surgical treatment. The subject was treated with hyoscine butylbromide, paracetamol and IV Augmentin . Treatment with blinded trial medication was continued. The event resolved on 31 AUG c*. The investigator considered that there was no reasonable possibility that the acute appendicitis may have been caused by investigational product.
This 3-year-old male subject received oral investigational product from 10 JAN.

The subject was randomized to receive Raltegravir 400 mg twice daily

Concomitant medications included Kivexa.

On 31 MAR a*, 80 days after the start of investigational product, the subject
developed grade 1 or mild squamous papilloma nasal cavity. The subject was
hospitalised. The subject underwent surgical exeresis on 19 SEP a* without
complications. The subject was treated with Amoxicillin sodium + clavulanic acid,
paracetamol, dipyrone and pantoprazole. Treatment with blinded trial medication was
continued. The event resolved on 19 SEP a*. The investigator considered that there
was no reasonable possibility that the squamous papilloma nasal cavity may have been
caused by investigational product.

This 3-year-old male subject received oral investigational product from 07 FEB b* to
29 JUN b*.

The subject was randomized to receive Raltegravir 400 mg twice daily.

The subject's past medical history included alcohol abuse. Medical conditions at the time
of the event included hepatitis C. Concomitant medications included Kivexa.

On 26 JUN b*, 505 days after the start of investigational product, the subject
developed grade 2 or moderate hepatotoxicity. The event was clinically
significant/requiring intervention. Laboratory test results dated 25 JUN b* showed
ALT of 177 U/L (normal range 0-48) and AST of 203 U/L (normal 0-42). The subject
also experienced increased temperature (max 39.3°C), sickness, weakness since 26 JUN
b* to 27 JUN b*, pain in epigastria on 26 JUN b*, sweating more at nights,
bubble rash on the skin of his forearms, legs, thighs, and the front surface of the abdomen
since 26 JUN b*. The subject improved from 28 JUN b*; his temperature was
normal with no new elements skin rashes after 26 JUN b*. Treatment with blinded

a*: The year
b*: Following year
trial medication was discontinued on 29 JUN b* and the subject was withdrawn from the study. Repeat blood test performed on 02 JUL b* showed ALT 121 U/L and AST 128 U/L; on 10 JUL b* ALT was 197 U/L and AST 285 U/L. The rash on the skin disappeared on 10 JUL b*. Repeat laboratory test performed on 18 JUL b* showed ALT 66 U/L and AST 65 U/L; on 26 JUL b* ALT was 72 U/L and AST was 57 U/L; on 27 AUG b* ALT was 28 U/L and AST 27 U/L. The event resolved on 27 AUG b*. The investigator considered that there was no reasonable possibility that the hepatotoxicity may have been caused by investigational product.

Follow up information received on 06 JUL b* via query response:

The investigator commented "the symptoms (increased temperature, sickness, weakness, pain in epigastria, sweating at nights, bubble rash) did not relate to CONART Kivexa. The subject did not receive any drug therapy".

Follow up information received from medical monitor on 08 July b*:

004337 NARRATIVE

Medical history was significant for past gastrointestinal bleeding, current blood and lymphatic system disorder, current hepatobiliary disorder (subject is HCV positive), current infection or infestation other than HIV-1, and current hypertriglyceridemia.

Concomitant ART includes Kivexa.

Concomitant medication used within 90 days of the SAE include paracetamol (15-Jun-b* to 17-Jun-b*).

Other AEs reported to the subject included anorexia (G1, unrelated, 8-Feb-a* to 13-Feb-a*), thin stools (G1, unrelated, 8-Feb-a* to 15-Feb-a*), dry mouth (G1, unrelated, 8-Feb-a* to 13-Feb-a*), sleepiness (G1, unrelated, 8-Feb-a* to 20-May-a*), acute respiratory disease (G2, unrelated, 8-Feb-a* to 11-Mar-a*), Cardialgia (G1, unrelated, 12-Jul-a* to 14-Jul-a*), Elevated level of ALT (G2, unrelated, 19-Sep-a* to 02-Nov-a*), Elevated level of AST (G2, unrelated, 19-Sep-a* to 02-Nov-a*), Elevated level of ALT (G1, unrelated, 02-Nov-a* to 11-Jan-b*), and Elevated level of AST (G1, unrelated, 02-Nov-a* to ongoing).

On 25-Jun-b* the subject attended the study week 72 visit. For a long period (25-May-b* to 21-Jun-b*) before week 72 visit the subject had alcohol abuse issues. It was documented at the CRF that at that date the liver chemistry results reached protocol defined IP stopping criteria. ALT from this date was G2 (177 U/L; 3.7 x ULN) and total bilirubin was normal. During these 72 weeks on the study no HCV RNA test was performed.

On 26-Jun-b* the subject started presenting with weakness, abdominal pain, night sweating, pruriginous skin rash in forearms, legs, thighs, buttocks and abdomen, and
fever (39.3 C; 102.7F). Fever subsided on 27-Jun-b*, when the subject started presenting with anorexia and nausea. ct started improving on 28-Jun-b*.

On 29-Jun-b* the subject presented to the site. The subject's general well-being compromise was considered moderate in severity and stable. Vital signs showed BP of 130/78 mmHg, HR of 80 per min, normal temperature. A vesicular rash, on the back, upper and lower extremities, abdomen and buttocks was seen. The liver was enlarged (1.5 cm below the lower ribs level). No additional diagnostic tests were performed.

The ART was withheld on 29-Jun-b* and an SAE of hepatotoxicity was reported as related to IP by the investigator.

The event is ongoing.

Diagnostics:

Elastography 10-Jul-b*: fibrosis of the 2nd grade.

Ultrasound 10-Jul-b*: hepatosplenomegaly, dilatation of v.porte and v.lienalis. HCV RNA, PCR 02-Jul-b* - 431000 IU/ML.

Follow-up subsequently retrieved from the liver CRFs included:

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the previous week. The subject consumed alcohol. The average number of units consumed per week was 77.

The subject had no liver disease medical conditions, no drug related liver disease conditions and no other relevant medical conditions.

There were diagnostic imaging tests performed on 10 July b*. The liver imaging method was elastography. The images were optimal for technical adequacy. The liver was not applicable, texture was suggestive of fibrosis, and diffuse and/or geographic fatty infiltrate grade was not applicable - no fatty infiltration. Ascites was not present, no hepatic lesions, no gallstones or gallbladder lesions, no biliary ductal lesion, Portal vein enlargement was seen.

The liver imaging method was ultrasound. The images were optimal for technical adequacy. The liver was enlarged (hypertrophic), texture was heterogenous, and diffuse and/or geographic fatty infiltrate grade was not applicable - no fatty infiltration. Ascites was not present, no hepatic lesions, no gallstones or gallbladder lesions, no biliary ductal lesion, Portal vein enlargement was seen.

There were no liver biopsies performed.

Follow-up information received via query response dated 07AUG b*: 
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The hepatotoxicity and the reported symptoms is due to poor alcohol abuse. The outcome was still unresolved. The normalization of ALT is waited. Next FU visit is planned.

Investigator text:

Seriousness of AE is due to importance of medical event that may result hospitalization.

Protocol Id: ING113086
Investigator Number: 083153
Subject Number: 004520
Case Id: Z0011755C, Z0011755D, Z0011755E, Z0011755F
Suspect Drugs: Raltegravir
Serious Events: Costochondritis, Meningitis, Pneumocystis jiroveci pneumonia, Thrombosis

This -year-old male subject received oral investigational product from 17 NOV. This subject was randomised to receive oral raltegravir 400 mg twice daily.

The subject's past medical history included seizure and status epilepticus. Concomitant medications included valproate sodium, levetiracetam and Kivexa.

On 14 AUG c*, 636 days after the start of investigational product, the subject developed grade 3 or severe pneumocystis carinii pneumonia (PCP). The subject experienced rib pain due to PCP pneumonia. The subject originally had some chest pain and dyspnoea 2 days prior that subsequently developed into fevers and rigors leading up to admission. During hospital transfer, the subject appeared to have suffered a seizure (non-serious). The subject was hospitalised. X-rays showed an increased opacity in bilateral mid and lower zones; no fractures viewed. Brain CT was also taken with no result available. No chest CT was performed. The subject was treated with Bactrim DS, oxycodone hydrochloride, oxycodone, morphine, fentanyl, midazolam, ketamine, paracetamol and diclofenac. Treatment with blinded trial medication was continued. The event resolved with sequelae (chest pain and returned to hospital with Costochondritis=Z11755D) on 24 AUG c*, and the subject was discharged. The investigator considered that there was no reasonable possibility that the pneumocystis carinii pneumonia may have been caused by investigational product.

Follow-up information received on 10 SEP c* via query response:

Sequelae: Subject had chest pain and returned to hospital with Costochondritis (Z11755D)

Epilim and Keppra were continued at dose levels already taken.

It is unknown if the subject had an anaphylactic reaction and seized due to morphine.

c*: 2 years later
It is not believed that seizure is also an SAE.

Investigator text:

Patient experienced rib pain due to PCP pneumonia. Concomitant medications included valproate sodium, levetiracetam, Kivexa and Bactrim.

On 27 AUG c*, 649 days after the start of investigational product, the subject developed grade 2 or moderate costochondritis. The subject presented with left-sided pleuritic chest pain and dyspnea, was not mobilizing much and had sore left calf. The subject was hospitalised. Chest sounded normal and X-ray ruled out pneumonia. Blood test results did not show any significant findings. The subject was treated with ketamine, oxycodone hydrochloride, oxycodone and Coloxyl + senna. Pain spontaneously resolved following ketamine infusion. Treatment with investigational product was continued. The event resolved on 29 AUG c* and the subject was discharged. The investigator considered that there was no reasonable possibility that the costochondritis may have been caused by investigational product.

Follow-up information received on 10 September c* via query response:

It is believed that pains and dyspnoea started day of admission.

Investigator text:

The subject's past medical history included costochondritis and PCP pneumonia. Concomitant medications included valproate sodium, levetiracetam, Kivexa and Bactrim.

On 01 SEP c*, 654 days after the start of investigational product, the subject developed grade 2 or moderate thrombosis of the left arm. The subject experienced some numbness in fingers. The subject was hospitalised. Ultrasound performed on left arm showed an extensive thrombus in left basilic vein, approx 50 cm long extending 3 cm above wrist to 5cm below axillary vein commencement. The subject was treated with oxycodone, enoxaparin and flucloxacillin sodium. Treatment with investigational product was continued. The event resolved with sequelae (ongoing pain in arm) on 05 SEP c* and the subject was discharged. The investigator considered that there was no reasonable possibility that the thrombosis of arm may have been caused by investigational product.

Investigator text:

Concomitant medications included Kivexa.

On 17 OCT c*, 700 days after the start of investigational product and 29 days after the last dose, the subject developed grade 3 or severe meningitis. The subject was hospitalised. Outcome was unknown at time of reporting. The investigator considered that there was no reasonable possibility that the meningitis may have been caused by investigational product.
This 59-year-old male subject received oral investigational product from 05 JAN 2022.

This subject was randomised to receive oral dolutegravir 50 mg once daily.

On 12 JUL 2022, 554 days after the start of investigational product, the subject developed grade 3 or severe chronic osteomyelitis of hip and was hospitalised. The subject was treated with flucloxacillin sodium, cephazolin sodium, enoxaparin and tramadol hydrochloride. Treatment with investigational product was continued. The event resolved on 16 JUL 2022. The investigator considered that there was no reasonable possibility that the chronic osteomyelitis of hip may have been caused by dolutegravir.

Diagnostics:

Intraoperative cultures yielded no growth.

Investigator text:

Elective left total hip replacement following septic joint. Experienced an uncomplicated post-op recovery. Mobilizing with walking stick independently at discharge. Cultures grew no growth, no antibiotics needed at discharge.

On 07 OCT 2022, 641 days after the start of investigational product, the subject developed grade 3 or severe abscess on buttock. The subject was hospitalised. Treatment with investigational product was continued. The event improved on an unspecified date.

The investigator considered that there was no reasonable possibility that the abscess on buttock may have been caused by investigational product.
This 371-year-old male subject received oral investigational product from 18 JAN 371.

The subject was randomized to receive dolutegravir 50 mg once daily.

The subject has a long history of intravenous amphetamine use. Concomitant medications included Truvada.

On 03 SEP b*, 594 days after the start of investigational product, the subject developed grade 2 or moderate cognitive impairment. The subject was hospitalised on 04 SEP b* for neuropsychological assessment to work-up newly recognised moderate cognitive impairment. These investigations revealed moderate deficits in new learning and higher cognitive function, and mild changes on MRI of the brain. These findings are consistent with long history of intravenous amphetamine use. Treatment with investigational product was continued. The subject was discharged on 06 SEP b*. Lumbar puncture was performed on 13 SEP b* and was normal including an undetectable HIV viral load in the cerebrospinal fluid. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the cognitive impairment may have been caused by investigational product.
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Protocol Id: ING113086
Investigator Number: 083015
Subject Number: 004700
Treatment Number: 1184
Case Id: Z0016948A
Suspect Drugs: Dolutegravir
Serious Events: Gastroenteritis

This 35-year-old male subject received oral investigational product from 02 FEB 2015. The subject was randomized to receive dolutegravir 50 mg once daily.

Concomitant medications included Kivexa.

On 13 JUL 2017, 527 days after the start of investigational product, the subject developed grade 3 or severe gastroenteritis. The subject suffered from lower abdominal pain without diarrhoea or dysuria and consulted the clinic three days later. The subject was hospitalised for two days. Examination of the body and the ultrasound of the abdomen were without pathologic findings. Laboratory test showed a mild elevation of leucocytes and CRP. The subject was treated with cefuroxime sodium, metronidazole and paracetamol. Treatment with blinded trial medication was continued. The event resolved on 15 JUL 2017 and the subject was discharged. The investigator considered that there was no reasonable possibility that the gastroenteritis may have been caused by investigational product.

Protocol Id: ING113086
Investigator Number: 082955
Subject Number: 004713
Treatment Number: 3321
Case Id: Z0017314A
Suspect Drugs: Dolutegravir
Serious Events: Peritonsillar abscess

This 35-year-old male subject received oral investigational product from 09 FEB 2015. The subject was randomized to receive dolutegravir 50 mg once daily.

Concomitant medications included Truvada.

On 12 OCT 2015, 611 days after the start of investigational product, the subject developed grade 2 or moderate tonsillar abscess and was hospitalised for a planned tonsillectomy. The procedure was performed on 12 Oct 2015 under general anaesthesia without any complications. No further treatment was given. Treatment with investigational product was continued. The event resolved on 15 OCT 2015 and the subject was discharged.

b*: Following year

* 新薬承認情報提供時に置き換え
subject was discharged. The investigator considered that there was no reasonable possibility that the tonsillar abscess may have been caused by investigational product.

This 21-year-old female subject received oral investigational product from 02 FEB *. The subject was randomised to receive dolutegravir 50 mg once daily.

Concomitant medications included Truvada, Alesse and ferrous sulfate. The subject's partner was HIV positive and receiving Atripla.

On 26 JUN *, the subject's beta hCG Quant was 52354 IU/l (normal range 0 - 4.9) and the subject was confirmed as experiencing drug exposure during pregnancy. The subject's last menstrual period was an unspecified date in MAY *. The estimated date of delivery was not provided. Treatment with investigational product was stopped on 27 JUN *. On 03 JUL * 517 days after the start of investigational product, the subject underwent an elective termination at a gestational age of seven weeks. The subject experienced moderate abdominal cramps post elective abortion. She was treated with doxycycline, ibuprofen and acetaminophen.

Follow-up information received 11 JUL *:

The elective termination of pregnancy was for socioeconomic reasons. The foetus was at 7 weeks and no evident defects were noted.

This 21-year-old female subject received oral investigational product from 17 DEC *. This subject was randomised to receive oral dolutegravir 50 mg once daily.

*: Following year
Concomitant medications included Kivexa. The subject had had one previous pregnancy, which resulted in an elective abortion.

On an unspecified date after the start of investigational product, the subject was found to be pregnant; a urine pregnancy test was positive. Her last menstrual period occurred on 17 SEP c*. Treatment with the investigational product was stopped on 19 OCT c*. The subject was exposed to the investigational product before conception and during the first trimester. At the time of reporting, the outcome of the pregnancy was ongoing. The estimated date of delivery is 01 JUL d*.

This female subject received oral investigational product from 14 FEB b* to 09 JUL b*.

Concomitant medications included Kivexa.

On 02 JUL b*, 504 days after the start of investigational product, the subject was found to be pregnant. Her last menstrual period occurred on 03 JUN b*. The pregnancy was confirmed by a serum pregnancy test which was positive. The subject was using a male condom as a form of contraception and conceived normally. Treatment with the investigational product was discontinued on the 09 JUL b* and the subject withdrawn from the study. The subject was exposed to the investigational product before conception and during the first trimester. At the time of reporting, the outcome of the pregnancy was unknown. The estimated date of delivery is MAR c*.

9.6.3. ING114467 SAE and Pregnancy Case Narratives

9.6.3.1. Cases Reported up to 04 June

The narratives included in this section correspond to the SAEs and Pregnancy cases included in both the ING114467 Week 48 CSR (with a data lock point of 04 June for safety data), which is included in m5.3.5.1, and the ISO outputs. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.
This 37-year-old female subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 31 March.

Medical conditions at the time of the event included seizure. Concomitant medications included tramadol hydrochloride, amitriptyline and sumatriptan succinate.

On 26 June a*, 87 days after the start of investigational product, the subject developed grade 1 or mild seizure-recurrent. The subject was admitted to ER on 26 June a* after the seizure but not hospitalized. Whilst still at hospital on 27 June a* the subject had a second seizure and was hospitalised. Head CT was within normal limits and EEG was normal and showed no seizure activity. The subject was started on levetiracetam. Treatment with blinded trial medication-viiiv was continued. The event resolved with sequelae on 28 June a*.

Follow-up information received on 12 March b*:

Sequelae is seizures requiring medication tx.

Follow up information received on 27 April b* via deletions report:

The concomitant medications amitriptyline and sumatriptan succinate were deleted.

Diagnostics:

Ct of Head EEG

Investigator text:

Subject was admitted to ER 6-26-a* after seizure, was not admitted to hosp. Has history of seizures but had stopped taking medication unknown date, site not aware of seizure history---while still at hospital on 6-27-a* had a second seizure and is now admitted for testing and medication adjustment Subject discharged home, started on Keppra, no further seizures. CT of head within normal limits. EEG normal, no seizure activity. Sequelae is seizures now under treatment.
The subject's past medical history included alcohol abuse. Medical conditions at the time of the event included family and emotional stress. Concomitant medications included tramadol hydrochloride and levetiracetam.

On 23 February b*, 329 days after the start of investigational product, the subject developed grade 4 suicide gesture and grade 4 intermittent alcohol abuse. The subject was taken to the ER by the police after calling in a suicide attempt. The subject was intoxicated and cut herself in the wrist area. Lacerations were shallow and she called as soon as it happened. The subject reported severe emotional stress at home. The subject was hospitalised in a psychiatric hospital for evaluation and treatment for alcohol dependence. The subject denied alcohol abuse. The subject was treated with lorazepam, diphenhydramine, zolpidem, paracetamol and gabapentin (Neurontin). The subject also reported treatment with Librium (unconfirmed). Treatment with blinded trial medication-viiv was interrupted from 23 to 27 February b*. The event resolved with sequelae on 27 February b*, described as alcohol abuse, and continued family/emotional stress. The investigator considered that there was no reasonable possibility that the suicide gesture and intermittent alcohol abuse may have been caused by investigational product.

Follow-up information received on 08 March b* via query response:

Have no proof of Librium use at this time. Subject stated took Librium. Neurontin entered

Investigator text:

Suicide gesture, alcohol abuse. Patient seen in clinic on 3/1/b*. Stated that she had been in "detox" for 5 days. Currently known info. patient was admitted to a local ER by the police after calling in a suicide attempt. Patient was intoxicated and cut herself in the wrist area. Lacerations were shallow and she called as soon as it happened. The patient was sent from the ER to a local psychiatric hospital for evaluation and treatment for alcohol dependence. The patient received librium and neurotin during her stay. The incident ran from 2/23/b* thru 2/27/b*. The study medications were held during that time. The patient reports severe emotional distress at home during this interval. The patient has a PMH of substance abuse. She continues to deny alcohol abuse. Records from psychiatric hospital requested. Further information pending. Investigator does not think this is related to study medication. Further information pending. Consider event resolved with sequelae, the sequelae alcohol abuse, and continued family/emotional stress.
This 51-year-old male subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received investigational product from 14 March.

Medical conditions at the time of the event included depression and methamphetamine abuse. Concomitant medications included temazepam.

On 25 September a*, 195 days after the start of investigational product, the subject developed grade 3 or severe attempted suicide. The subject had broken up with his partner and claimed to have taken three 50 mg tablets of Benadryl in an attempted suicide gesture last night. Relevant laboratory results included salicylate level equal to or less than 3.4 mg/dL and acetaminophen level equal to or less than 6 mg/dL. The subject showed persistent suicidal ideation. The subject was hospitalised and the event was life-threatening. Treatment with investigational product was continued. The event resolved on 27 September a*. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by investigational product.

Investigator text:

Pt broke up with his boyfriend yesterday. Came to clinic very distraught this morning. Claims he took three 50 mg tablets of Benadryl in an attempted suicide gesture last night. Spoke with Dr. and our staff therapist. It was decided that he would be transferred to the Emergency Department for 5150 placement and possible transfer to our psychiatric facility due to persistent suicidal ideation. In ER, staff psychiatrist interviews patient and the 5150 is upheld. Pt will be transferred to psych facility for a 72 hour hold. In ER, salicilate and acetaminophen levels were unremarkable. No meds administered. Pt given 1 bottle of each of his 3 study medications (Emergency Resupply), by PI, to bring with him to psych facility as he had not brought his own to clinic that morning. Follow/Up Info: Pt was transferred to psychiatric facility and stayed overnight (discharged on 9/27/a*). 5150 dropped. Emergency resupply of study medication returned, when pt came into clinic to talk with therapist on 10/3/a*. Difficulty getting mental health records. No relevant commeds administered other than restoril x 1. Emotional support provided. Pt reports that immigration has decided not to deport him. Pt smiling in clinic.
This 27-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 10 March 2023.

Medical conditions at the time of the event included methicillin resistant staphylococcus aureus skin infection. Concomitant medications included Septra DS.

On 05 December a*, 270 days after the start of investigational product, the subject developed grade 2 or moderate facial abscess MRSA. The subject came to clinic on 08 December a* complaining of 3-day history of facial infection. The subject reported he may have scratched his face. The subject was referred to the ER. Wound culture taken on 08 December a* showed light staphyloccocus aureus and also one colony of beta hemolytic streptococcus. The subject received 2 IV infusions of vancomycin 1 GM. The subject denied fever, chills, nausea, vomiting. Vitals were normal. The subject was hospitalised for IV antibiotics on 09 December a* at 04:13. The subject was treated with vancomycin and doxycycline. Later that day the infection was noted to have receded a bit. The subject stated he felt better and wanted to go home. The subject was discharged on 09 December a* around 17:00 with prescription for doxycycline. Treatment with blinded trial medication-viiv was continued. The event resolved on 26 December a*. The investigator considered that there was no reasonable possibility that the facial abscess MRSA may have been caused by investigational product.

Investigator text:

Pt came to the clinic on 12/8/a*, to see Dr. ❄❄❄❄❄❄❄. Complained of facial skin infection x 3days. Currently finishing treatment for MRSA skin infection diagnosed in Aug a*. States he may have scratched his face. Pt came in to clinic late in day so was sent to the ER to be checked out. ER record states he got 2 IV infusions of vancomycin 1 GM starting 12/8/a* ending 12/9/a*. Pt denied fever, chills, nausea, vomiting, etc. Vitals were normal. Pt was admitted for IV antibiotics at 12/9/a* at 04:13. Later that day, it is noted that his infection had receded a bit. Pt stated he felt better and wanted to go home. Pt discharged on 12/9/a* around 17:00. Discharge medications unknown at this time. Pt will be in our clinic in 2 hours for his Week 40 visit. Will obtain more info then.
Per patient's discharge summary, wound culture shows resistance to septra. Pt discharged with prescription for doxycycline. Pt came to his regularly scheduled appointment on 12DEC a*. It was noted at that time that his facial abscess was still healing. Pt stopped Septra at this visit. Will continue doxycycline. Recheck at next visit.

Protocol Id: ING114467
Investigator Number: 081186
Subject Number: 005117
Treatment Number: 2441
Case Id: Z0015398A
Suspect Drugs: Atripla
Serious Events: Mania

This 34-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 03 May.

Medical conditions at the time of the event included bipolar disorder.

On 04 May b*, 367 days after the start of investigational product, the subject developed grade 3 or severe manic episode. The subject was hospitalised. The subject was discharged then re-admitted. Treatment with blinded trial medication-viiv was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the manic episode may have been caused by investigational product.

Follow-up information received on 15 June b* via answered query response:

The investigator confirmed the subject had stopped taking his regular bipolar conmeds Zyprexa in March b*.

Investigator text:

No information other than phone contact from psych unit at community hospital. Awaiting records for additional information re: hospitalization. Pt was discharged then readmitted; no information available as no ROI obtained. SAE ongoing, not resolved, at time of study withdrawal.

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*a*: The year
*b*: Following year

*新薬承認情報提供時に置き換え*
This 47-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 02 March.

Medical conditions at the time of the event included hypertension and non insulin dependent diabetes mellitus.

On 01 May, 426 days after the start of investigational product, the subject developed grade 3 or severe congestive heart failure. The subject developed shortness of breath, cough with white phlegm, left-sided pleuritic chest pain and ankle swelling on 01 May. The subject was hospitalised on 04 May. The subject was treated with carvedilol, frusemide and spironolactone. Treatment with investigational product was continued. The event resolved on 06 May and the subject was discharged. The investigator considered that there was no reasonable possibility that the congestive heart failure may have been caused by investigational product.

Diagnostics:

04-MAY-b* B-type Natriuretic Peptide (BNP) 611, units are unknown. Normal ranges: 0-100. 2D echocardiogram performed 05-MAY-b*: showed systolic Ejection Fraction (EF) of 35-40. Per discharge summary, pt was given oral medications to treat Congestive Heart Failure (CHF)

Investigator text:

hospital records still pending. Pt was hospitalized 04-May b* and discharged 06-May-b* Symptoms developed 01-May-b* Signs and symptoms experienced include: Shortness of Breath, cough w/ white phlegm, left-sided pleuritic chest pain and ankle swelling. As noted, s/s were noticed by subject on 01-May-b* -

b*: Following year
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Protocol Id: ING114467
Investigator Number: 081243
Subject Number: 005146
Treatment Number: 1036
Case Id: Z0010779A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Road traffic accident

This 21-year-old female subject was enrolled in a Viiv-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 03 May 2019.

On 17 July 2019, 75 days after the start of investigational product, the subject developed grade 3 or severe motorcycle accident. The subject was hospitalised for two days after surgery to remove debris and gravel from elbow. The subject was treated with cephalaxin, Percocet and hydrocodone. Treatment with blinded trial medication-viiiv was continued. The event resolved on 20 September 2019. The investigator considered that there was no reasonable possibility that the motorcycle accident may have been caused by investigational product.

Follow up information received on 31 October 2019 via AQR:

The subject had no relevant medical history.

Investigator text:

patient was in a serious motorcycle accident and was hospitalized for 2 days after a surgery to remove debris and gravel from elbow. Discharge summary has been requested by myself and by patient in person repeatedly. It is unobtainable. -

Protocol Id: ING114467
Investigator Number: 081243
Subject Number: 005149
Treatment Number: 2470, 2470
Case Id: Z0009610A, Z0009610E
Suspect Drugs: Atripla
Serious Events: Atrial fibrillation, Atrial flutter, Atrial flutter

This 55-year-old male subject was enrolled in a Viiv-sponsored, blinded study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected

a*: The year
antiretroviral therapy naïve adult subjects. The subject received oral investigational product from 12 May.

The subject's past medical history included upper respiratory infection (with fever). Medical conditions at the time of the event included cocaine abuse and hypertensive cardiomyopathy. The subject had a relapse of cocaine usage. The subject had episodes of atrial dysrhythmia previously secondary to prior cocaine use.

On 18 May, six days after the start of investigational product, the subject developed grade 3 or severe atrial flutter and grade 3 or severe atrial fibr. The subject was hospitalised. The subject had heart rate of 93 and a flutter but with rates up to 160 in ER with chest pain and shortness of breath at that time. He was placed on IV diltiazem, oxygen and Heparin for planned cardioversion in am after Echo to rule out clot. The subject was treated with nitroglycerine and warfarin sodium. Treatment with blinded trial medication-viiv was continued. The events resolved on 19 May. The investigator considered that there was no reasonable possibility that the atrial flutter and atrial fibr may have been caused by investigational product and that the events were subsequent to relapse in cocaine usage.

Follow up information received via deletion report on 20 October:

The investigator deleted the treatment medication heparin.

Investigator text:

He was in ER 5/18/a being admitted HR 93 aflutter but with rates up to 160 in ER with chest pain and shortness of breath at that time. Nitroglycerin give and pain resolved shortly. He was placed on IV diltiazem, O2 and Heparin for planned cardioversion in am after echo to assure no clot.

also h/o recent URI with fever 5/10/a so he did not start study meds until 5/12/a. On 5/16 he came to clinic for URI and was given Robitussin AC, and he picked up the Azithromycin 250 mg 2 tabs first day, then 1 tab daily. He also saw urology for pre-existing problem and was given samples of vesicare and flomax.

Subject had a relapse of his cocaine usage, and subsequently developed symptomatic atrial fibrillation / flutter, with shortness of breath. He is hospitalized, and hence has an SAE, thought by you to be unrelated to study drug (IP).

He has had episodes of atrial dysrhythmia previously, secondary to prior cocaine use, which lead you to consider this current cardiac event to be related to cocaine use, and not IP.

Current plan is to continue him in the SINGLE study.

Medical conditions at the time of the event included cocaine abuse.

*a: The year
On 28 September a*, 139 days after the start of investigational product, the subject developed grade 2 or moderate atrial flutter with rapid ventricular response. The subject presented in ER with epigastric pain which was found to be atrial flutter. The event was life-threatening. The subject was initially rate-controlled on diltiazem, this was discontinued as it was discovered he is on a HIV study and diltiazem is a contraindication for the study. Therefore, diltiazem was discontinued and his rate-controlled was attempted with Coreg. This medication was chosen because of his alpha-blocking capacity as well given his ongoing cocaine abuse. This was unsuccessful and he remained tachycardic in the 130s from his atrial flutter. Subsequently, digoxin was added and he spontaneously converted to normal sinus rhythm and therefore, his tachycardia also resolved. The subject's chest pain also abated. Again, given concern of the onset of heart failure, the subject had an echocardiogram done, which was not consistent with, only mild-to-moderate decrease in ejection fraction. Treatment with blinded trial medication-viiv was continued. The event resolved on 30 September a* and the subject was discharged in an improved condition. Medications at discharge included Lisinopril 80 mg once daily, Pradaxa 150 mg twice daily, aspirin 81 mg once daily. He was instructed to stop taking atenolol and was started on carvedilol 25 mg twice daily and Lasix 40 mg once daily. The subject was instructed to continue a low sodium diet. No activity restrictions were recommended, exercise was encouraged. The investigator considered that there was no reasonable possibility that the atrial flutter with rapid ventricular response may have been caused by investigational product.

Diagnostics:

Chest x-ray in 9/29/a*, demonstrated unchanged cardiomegaly. There is no pulmonary pathology. Haemoglobin of 14.9, creatinine unchanged at 1.03 to 1.24. LDL is 77, HDL 54, triglycerides 85 and cholesterol 148. Troponins were negative at less 0.0 times 2. TSH was 0.76. BNP was elevated at 771.

Investigator text:

Initial EKG in emergency department revealed atrial flutter with rapid ventricular rate. The patient was, therefore, started on diltiazem drip and subsequently converted to atrial fibrillation with fairly well-controlled rate and the cardiology team was called to evaluate the patient and admit him for further care. The patient was initially rate-controlled on diltiazem, this was discontinued as it was discovered he is on a HIV study and diltiazem is a contraindication for the study. Therefore, diltiazem was discontinued and his rate-controlled was attempted with Coreg. This medication was chosen because of his alpha-blocking capacity as well given his ongoing cocaine abuse. This was unsuccessful and he remained tachycardic in the 130s from his atrial flutter. Subsequently, digoxin was added and he spontaneously converted to normal sinus rhythm and therefore, his tachycardia also resolved. The patient’s chest pain also abated. Again, given concern of the onset of heart failure, the patient had an echocardiogram done, which is not consistent with, only mild-to-moderate decrease in ejection fraction. The patient was discharged on September 30, a* in improved condition and will have close follow-up with heart failure, electrophysiology and his HIV clinic, which is his primary care clinic. Discharge
medications: Lisinopril 80 mg once daily, Pradaxa 150 mg twice daily, aspirin 81 mg once daily. He was instructed to stop taking atenolol. He was started on carvedilol 25 mg twice daily and Lasix 40 mg once daily. The patient was instructed to continue a low sodium diet. No activity restrictions were recommended. In fact, exercises were encouraged. Patient presented in ER with epigastric pain. It was found to be atrial flutter.

Protocol Id: ING114467
Investigator Number: 081267
Subject Number: 005293
Treatment Number: 1034
Case Id: Z0015490A
Suspect Drugs: Atripla
Serious Events: Abortion spontaneous

This 36-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 28 April 2018.

Concomitant medications included Bactrim DS.

The subject used condoms and spermicide as contraception. She had no previous pregnancies and the type of conception was normal. The subject's HIV positive status was considered to be an additional factor that could have an impact on the pregnancy. The subject's male partner (the father) was reported to be healthy with no relevant medical history and was not taking any medication at the time of conception.

At an unknown time after the start of investigational product, the subject was reported to be pregnant. Her last menstrual period was 22 February and her estimated date of delivery was reported to be 29 November. Treatment with blinded trial medication-viiv was discontinued on 28 March and the subject was withdrawn from the study.

On 28 April, 366 days after the start of investigational product and 32 days after the last dose, the subject developed grade 2 or moderate spontaneous abortion. The event was clinically significant (or requiring intervention). The event resolved on 01 May. The investigator considered that there was no reasonable possibility that the spontaneous abortion may have been caused by investigational product.

Follow-up received on 15 May from investigator via study team:

The investigator commented there was a strong likelihood the subject had electively terminated the pregnancy as at one point she told the investigator that she had an appointment at a clinic but insisted she was not planning to terminate. The site personnel have given her every opportunity to tell them but she has continued to deny terminating.
Diagnostic Results:

Urine Pregnancy Test negative done on 14MAY b*

Investigator Text:

Subject had spontaneous abortion on 28APR b*. She seeked medical care in ER on 02MAY b* but was never seen by gynaecologist. She left before being evaluated. Will request medical records. Urine pregnancy test done at site on 30 day follow-up visit was negative. Subject had approximately 9 gestational weeks per Last menstrual period when the spontaneous abortion occurred. Subject did not receive any treatment for the SAE. Relevant data was added to Section 4, Section 5 and Section 9.

Protocol Id: ING114467
Investigator Number: 081268
Subject Number: 005315
Treatment Number: 3032
Case Id: Z0013364A
Suspect Drugs: Atripla
Serious Events: Renal failure, Respiratory failure, Septic shock, Systemic candida, Vascular pseudoaneurysm

This 33-year-old male subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 31 March.

Medical conditions at the time of the event included alcohol abuse, pulmonary aspergilloma and invasive aspergillosis. Concomitant medications included multivitamins, nicotine, ocular lubricants, thiamine, pantoprazole, paracetamol, cephazolin sodium, diphenhydramine hydrochloride and haloperidol.

On 18 December a*, 262 days after the start of investigational product, the subject developed grade 4 septic shock, grade 4 renal failure and grade 4 candidemia. On 20 December a*, the subject developed grade 4 respiratory failure. On 21 December a*, the subject developed grade 4 pseudoaneurysm of lung vessel branch. The subject was hospitalised and the events were life-threatening. Subject had approximately 7 days of vomiting and diarrhoea prior to admission, denied dysuria and urinary frequency. Subject presented with severe weakness and shortness of breath. On admission the subjects mental status was lethargic and subject was difficult to understand. Results from blood cultures from 18 December a* showed Candidemia. On 21 December a*, subject had interventional radiology procedure; bronchial artery embolization resulting in greatly decreased bleeding to left upper lung. Several failed attempts to remove subject from ventilator occurred over the course of the hospitalization. On 04 January a*, subject had tracheotomy preformed. The subject was treated with vancomycin, paracetamol, liposomal amphotericin B, sodium citrate, ceftriaxone, fentanyl, lignocaine

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
hydrochloride, lorazepam, noradrenaline acid tartrate, piperacillin sodium and Bactrim and the subject was withdrawn from the study. On 09 January a*, subject was discharged from the hospital and released to hospice. The subject died on 16 January b*, due to renal failure and respiratory failure. The investigator considered that there was no reasonable possibility that the septic shock, candidemia, pseudoaneurysm of lung vessel branch and respiratory failure may have been caused by investigational product. The investigator considered that there was a reasonable possibility that the renal failure may have been caused by investigational product.

Follow-up information received on 19 December and 22 December a* from clinical study team:

This subject has had a very complicated medical course over the past few months, despite responding very well to therapy in the study. This year old male was enrolled in SINGLE on 31Mar a*, and at study entry, he had a HIV-1 RNA of 135,515 cp/mL and a CD4 cell count of 219 (21%) cells/mm3. By week 24 (13Sept), the HIV-1 RNA was <50 and CD4 cell count was 668(275%). Despite the robust immunologic recovery, he has had the following OIs in September and October. In September, he was diagnosed with candidal esophagitis, and in October, he was diagnosed with PCP and has been on Bactrim since late September. Of note, he had cystic lesions in his lung resulting from the PCP. In November, this subject was diagnosed with pyelonephritis and treated with Ciprofloxacin. Ultrasound examination of the kidneys confirmed pyelonephritis. The creatinine at that time is currently unknown. The last creatinine in study was performed in Sept a*, at which point it was stable (about 0.5 mg/dL). The Week 32 labs in November were haemolysed, so creatinine was not performed. Per your records, the subject had a stable creatinine in late Oct, prior to the pyelonephritis. For his current presentation - this subject is currently in the ICU and is on Levophed (norepinephrine). He had a pulmonary haemorrhage, which was preceded by haemoptysis as an outpatient, likely related to invasive aspergillosis.

Prior to admission:

"He has another problem for which I had him scheduled to see me this week: Probable fungal ball in lung cavity (presumptive aspergilloma). His sputum and BAL did not reveal fungal elements by stain or culture. Repeat culture from this admission is pending. Until recently, he was asymptomatic. In recent week, he has developed cough with some trace haemoptysis. Was planning on taking him off study and beginning voriconozole with different HIV RX." As discussed today, he presented to the local ER prior to implementation of this plan.

Subject had approximately 7 days of nausea, vomiting, and diarrhoea prior to admission. Denies dysuria or urinary frequency, but didn't have these symptoms when he had E. coli pyelonephritis in November. In November, he had CT findings of bladder wall thickening with partial obstruction of ureter. Awaiting urology consultation to evaluate. F/u UA with cytology okay. Per discussion today, renal ultrasound performed in the last couple of
days (this admission), the subject did not have obstruction and no evidence of invasive fungal disease on renal ultrasound.

18DEC a* - Seen in local ER & transferred/admitted to Hospital MICU with shock.

Presented with hypotension, leukocytosis, metabolic acidosis (Anion Gap), and acute kidney failure. Afebrile. Given IV fluid and low dose pressor (levophed). FIO2 given PNC (not intubated or ventilated). Given empiric antibiotics - IV vancomycin and piperacillin/tazobactam in MICU. Urine, stool, and blood cultures pending. C.diff PCR negative. HIV meds held. Bactrim prophylaxis continued. Had not been taking on regular basis in recent weeks.

The investigator contacted the subject's mother (with whom the subject lives) and she said that subject was taking IP up to 17DEC a* - last dose day before initial SAE 'hospitalization for shock'. Family will visit on Saturday & will bring pill bottles with them.

The anuric acute renal failure was present at time hospitalization on 18DEC a*. He is receiving dialysis; metabolics look better today.

The investigator could not exclude possibility that HIV meds have contributed to renal failure (sepsis acute renal injury/low GFR - elevated drug levels - etc). Therefore, it is possible that IP may have contributed to anuric acute renal failure (added injury to insult).

Interim history is remarkable for:

20DEC a* - Pulmonary haemorrhage requiring intubation, mechanical ventilation (FIO2 40), transfusion of RBC and PLT. Unsuccessful attempt a locating and coiling vessel responsible for bleeding. Note: he was having coughing and haemoptysis before he developed nausea, vomiting, and diarrhoea.

21DEC a* - Interventional radiology identified pseudoaneursym and bleed in LUL. Branch of pulmonary artery with aneurysm coiled. Bleeding into LUL greatly decreased. Pseudoaneursym probably caused by aspergillus.

20DEC a* - Candidemia. Yeast grew from blood culture drawn 18DEC a*. May explain initial sepsis syndrome.

Contribution of IP cannot be ruled out. All HIV therapy/study drugs has been stopped as of admission to the hospital on 18Dec. The subject continues on Levophed and continues in the ICU. The metabolic acidosis is improving, but the situation is still tenuous, as dialysis is still required and additional bleeding could occur in the lungs. Surgery would likely not an option for this subject due to his poor post-surgical survival rate.

Follow-up information received on 23 December a* from clinical study team:

a*: The year
At week two visit the subject had a Grade 3 value was AST/SGOT at 240. His Day 1 AST value was 153 (Grade 2), and the screening value was 142 (also a Grade 2). He also has a Grade 2 elevated ALT/SGPT of 184. The Day 1 and screening values were grade 1 elevations at 135 and 111. Bilirubin remains within normal limits.

Alk phos has been grade 1 (low level) elevated since screening. Lipase was slightly elevated at Screening and Day 1 as well. His HBV and HCV screening labs were non-reactive.

The investigator comment to the prior investigational product administration laboratory test results "Alcohol use indiscretion likely played a major role. Subject's mother called me 5 d prior to visit and said that her son was drinking more alcohol and appeared intoxicated at the time. I talked to subject later during the call & he acknowledged that he had been drinking too much and assured me that he would adhere to the study requirement. He lives with his mother and she will be monitoring him. The con med of Keppra was started in Feb a* - it's possible that this med may be adding to problem. There have been no con med changes while he has been on Single study. I will call him to check on OTC acetominophen use. I had talked to the subject during his study visit (when these labs were obtained) & he was not symptomatic."

Follow up information received on 06 January b* from medical monitor:

The subject was smoking 0.1 packs/day for 5 years.

The subject had abdominal pain. His diarrhoea was watery and non bloody. He had severe weakness, poor appetite and shortness of breath. He does not have any chest pain, headache, swelling of the legs and fever. At the hospital he was found to have creatinine of 6.3, BUN of 49 and AG of 16. He also had hyponatremia with sodium of 103 but the duration of hyponatremia is not clear from the records. He was transferred here for rise in creatinine and hypotension. An US done at the hospital showed increased echogenicity and no hydrenephrosis. He did not have any uap since the arrival. Since the admission here, he was given 6-7 litres of NS for volume repletion, one dose of vancomycin and he is also started on zosyn. His BP did not respond well to fluids and he was started on levophed. He is maintaining his sats and is not intubated. He did not have any history of NSAIDs intake or recent contrast exposure.

Impression from consultation nephrology attended on 19 December a*:

"Pt has severe volume depletion probably from diarrhoea. Many other medical problems including AIDS (we" treated with low viral load), aspergillus, pneumocystis c; and now anuric acute renal failure. Hx of possible urinary obstruction, but my review of the renal US does not show much obstruction. Foley catheter flushes well and there is no urine in bladder. Mental status seems lethargic and he is difficult to understand. Sentences are incomplete, but he is awake, moves a* extremities and can indicate discomfort. He is on pressors and also has hyponatremia -probably chronic (many days). He also has a
profound metabolic acidosis (nl gap) probably from diarrhoea. Agree to give hypotonic NaHCO3 to help replace."

Hospital course was as follows:

The subject was admitted to [deleted] Medical Centre, placed on Levophed and broad spectrum antibiotics, including vancomycin (per Dr. [deleted], not in available hospital records). Pulmonary haemorrhage requiring intubation, mechanical ventilation (FiO2 40), transfusion of RBC and PLT developed on 20 December a*. Unsuccessful attempt at locating and coiling vessel responsible for bleeding. Note: he was having coughing and haemoptysis before he developed nausea, vomiting, and diarrhoea. On 21 December a*, interventional radiology identified pseudoaneursym and bleed in LUL after lengthy evaluation (including significant contrast use). A branch of the pulmonary artery with an aneurysm coiled, and the bleeding into LUL greatly decreased. The pseudoaneursym was probably caused by aspergillus. No recurrence of the pulmonary haemorrhage has been noted up to 03 January b*.

The subject also was noted to have 1 blood culture and 1 urine culture with Candida albicans growth and was subsequently placed on voriconazole for treatment of the Candida albicans fungemia/UTI and invasive pulmonary aspergillosis. Broad spectrum antibiotics were discontinued after isolation of the Candida in blood culture at the outside hospital (from 18 December culture).

With regards to the renal failure, an ultrasound was obtained on 22 December a* with the following results: 1) Increased echogenicity of the bilateral kidneys suggests HIV nephropathy and 2) thickened bladder wall more than expected with existing Foley catheter in place, which may suggest cystitis or inflammatory change. The subject was initially placed on CVVHDF (sometime between 20 December to 22 December) but was switched to haemodialysis when pressors were no longer required (date unknown). After dialysis, the creatinine dropped to 1.2 mg/dL and remained between 0.6-0.9 mg/dL until 02 January b* when creatinine was 3.4 mg/dL. Hospital notes on that day reference plans for HD on 02 January b*. Per review of creatinine and discussions with Dr. [deleted], subject was likely receiving CVVHD until ~30 December a*, as creatinine noted to be 0.7 mg/dL on that date. Electrolytes and acid-base disturbance were corrected with haemodialysis and treatment of underlying sepsis.

Current plans - per discussion on 03 January with Dr. [deleted], the subject was beginning to have spontaneous urine output, up to ~250 mL. Additionally, he was more alert with removal of sedation. As he had poor conditioning prior to admission and was intubated for an extended time with multiple failed attempts to extubate, the subject was to have a tracheotomy by 06 January b* to allow long term attempts to take him off the ventilator. Further plans from Dr. [deleted] include resuming HIV medications with raltegravir and possibly abacavir and renally adjusted lamivudine dosing. The study medication has not been unblinded at this time. Dr. [deleted] also felt that the acute illness/renal injury was likely related to the sepsis (secondary to candidemia).

a*: The year
b*: Following year
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Module 2.7.4 Summary of Clinical Safety

Follow-up information from answered query received 23 January b*:

Investigator Text: We cannot exclude possibility that HIV meds contributed to renal failure (sepsis acute renal injury/low GFR-elevated drug levels/etc). Therefore, it is possible that IP may have contributed to anuric acute renal failure (added injury to insult).

Investigator Text:

Subject had approximately 7 days of vomiting and diarrhoea prior to admission, denied dysuria and urinary frequency. Subject presented with severe weakness and shortness of breath. Subject has history of AIDS pneumocystis pneumonia and a pulmonary aspergilloma. 18DEC a*-Admitted to hospital with septic shock. Mental status was lethargic and patient was difficult to understand. 20DEC a*-Pulmonary haemorrhage required intubation and mechanical ventilation. Results from blood cultures from 18DEC a* showed Candidemia. 21DEC a*-Subject had interventional radiology procedure; bronchial artery embolization resulting in greatly decreased bleeding to left upper lung. Several failed attempts to remove patient from ventilator occurred over the course of the hospitalization. On 04JAN a* patient had tracheotomy preformed. 09JAN a*- Patient was discharged from the hospital and released to hospice. 16JAN a* - Patient died.

Protocol Id: ING114467
Investigator Number: 081272
Subject Number: 005337
Treatment Number: 4116, 4116
Case Id: Z0012902A, Z0012902B
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Postoperative wound infection, Type 2 diabetes mellitus

This [redacted]-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 08 April [redacted].

Medical conditions at the time of the event included type II diabetes. Concomitant medications included metformin hydrochloride.

On 29 September a*, 174 days after the start of investigational product, the subject developed grade 2 or moderate worsening of diabetes type II following an elective cosmetic surgery. During and after the operation, the subject's glucose began to spike (no glucose results were received). The subject was hospitalised. The subject was treated with insulin. Treatment with blinded trial medication-viiv was continued. The event resolved on 01 October a*. The investigator considered that there was no reasonable

a*: The year
b*: Following year
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Module 2.7.4 Summary of Clinical Safety

possibility that the worsening of diabetes type ii may have been caused by investigational product and that the event was secondary to elective surgery.

Investigator text:

Patient reports an unanticipated hospital stay on the night of 29SEP a*, followed by two nights in after-care facility on 30SEP a* and 01OCT a*, following an elective cosmetic surgery. During and after the operation, the patient's glucose began to spike. Patient has a history of type II diabetes. Patient was administered insulin intramuscularly PRN 29SEP a*-01OCT a* (see con meds). -

The subject's past medical history included elective cosmetic surgery.

On 25 October a*, 200 days after the start of investigational product, the subject developed grade 3 or severe infection of cheek wound site secondary to elective surgery. The subject underwent cosmetic procedure on 29 September a*, and began to notice discharge on 25 October a*, which drained through the mouth (the surgery operated through her mouth). The subject was hospitalised. The subject had her right cheek implant removed on 08 November a*. The subject was treated with cephalexin and cefaclor. Treatment with blinded trial medication-vii was continued. The event resolved on 15 November a*. The investigator considered that there was no reasonable possibility that the infection of cheek wound site secondary to elective surgery may have been caused by investigational product.

Follow-up information received on 01 December a* via query response:

Medical records do not reveal the organism that caused the infection.

Investigator text:

Patient reports post-surgical infection of left cheek implant. Began to notice discharge on 25OCT a*, which drained through the mouth (the surgery operated through her mouth). Patient underwent cosmetic procedure initially 29SEP a*. Patient had R cheek implant removed on 08NOV a*. Patient was administered antibiotic at that time. Patient was unsure of the name of one of the two antibiotics today, and will call the clinic with that name. Patient continuing follow-up with surgeon with regard to this condition. Patient took Cephalexin from 11NOV a* to 15NOV a*.

Protocol Id: ING114467
Investigator Number: 081273
Subject Number: 005340
Treatment Number: 1024, 1024
Case Id: Z0009660A, Z0009660B
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Homicidal ideation, Jaw fracture, Suicidal ideation

*a*: The year
This 39-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 08 April.

The subject's past medical history included suicidal ideation without attempt and history of childhood sexual abuse. Medical conditions at the time of the event included depression, schizophrenia and substance dependence. Concomitant medications included risperidone, benztropine mesylate, citalopram hydrobromide, haloperidol and non-gsk propranolol hydrochloride.

On 20 May a*, 42 days after the start of investigational product, the subject developed grade 4 suicidal ideation without attempt and grade 4 homicidal ideation without attempt. The subject discontinued psychiatric medication "weeks prior" to 20 May a* and had since relapsed on cocaine. The subject was hospitalised and the events were life-threatening. The psychiatrist described the subject "presented initially intoxicated on cocaine and thereafter experienced the extreme dysphoria that accompanies stimulant withdrawal". Treatment with blinded trial medication-viiv was interrupted on 21 May a* and re-started on 26 May a*. The events resolved on 31 May a*. The investigator considered that there was no reasonable possibility that the suicidal ideation without attempt and homicidal ideation without attempt may have been caused by investigational product and that the events were possibly due to heavy consumption of cocaine.

Investigator text:

site was contacted on 21may a* by medical staff at local inpatient drug and alcohol facility. the patient presented to a local ER on 20may a* stating suicidal ideation and homicidal ideation without attempt. patient had stated he self discontinued psychiatric medication "weeks prior" to 20may a* and had since relapsed on cocaine. It was determined that the patient was not a current threat and was transferred to Kirkbride Drug and alcohol inpatient on 21may a* in the early morning. the patient reported he had not discontinued his blinded study medication and did have the medication with him at inpatient. a decision was made to hold his medication until a full psychiatric and medical evaluation was completed. site spoke with psychiatrist on 25/may/a* regarding the health of the patient. the psychiatrist states the patient "presented initially intoxicated on cocaine and thereafter experienced the extreme dysphoria that accompanies stimulant withdrawal. in addition, he was sexually abused as a child and has had to suffer with this traumatic experience since that time. As the childhood trauma occurred far before his starting the investigational medication, and his psychiatric presentation occurred directly following heavy consumption of cocaine, it is highly unlikely the investigational HIV medication contributed in any part to his mental status". --on 31may a*, pt returned to office. Stated he restarted IP on 26 may a* without problems. pt feels much better being back on psychiatric medication. denies suicidal and homicidal ideations. Says he feels in control.

*a*: The year
now will resume psychiatric medication, discontinuing haldol and changing to risperdol. referred patient back to psychiatrist.

On 12 December a*, 248 days after the start of investigational product, the subject was mugged and developed grade 3 or severe fractured jaw. The subject presented to the ER and was found to have two fractures of left jaw with dislocation. The subject was hospitalised and has his jaw wired shut on 13 December a*. The subject was instructed he'd be on a liquid diet via straw for several weeks. Treatment with investigational product-viiv was therefore discontinued on 12 December a* and the subject was withdrawn from the study. The subject left the hospital against medical advice on 14 December a*. The subject consequently presented to the site and was started on abacavir liquid 600 mg once daily, epivir liquid 300 mg once daily and intencence 400 mg once daily dispersed in water. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the fractured jaw may have been caused by investigational product.

Investigator text:

Patient was mugged early this morning. Presented to emergency room at XX Hospital. Found to have two fractures of left jaw with dislocation. Awaiting surgical repair with wiring. Patient was instructed that he will be on liquid diet via straw for several weeks. -- Due to the patient having his jaw wired shut, the study team along with site decided he would have to crush the medication, which was radically different than the original intent of dosage, he would have to permanently discontinue study drug. -- Subject walked into the clinic on 14Dec a* after leaving the hospital against medical advice. Subject sated his jaw was wired shut on 13Dec a*. He had no scheduled follow up with the surgeon. He had been off his study medication since 12Dec a* and has not been able to resume. He was started on abacavir liquid 600 mg once daily, epivir liquid 300 mg once daily and intencence 400 mg once daily dispersed in water. First dose of new ARVs witnessed in office. Subject was told to return the following day for evaluation. -- Patient seen in office on 28Dec a* for follow up. On 21Dec a*, the patient cut jaw wires out on own. Went to YY Hospital ER to have any remaining wires removed. ER refused removal since they did not put in went to Hospital ER on 22Dec a* for same and was referred back to Hospital. Patient went to ER on 23Dec a* where the remaining wires were removed and x-ray taken. ENT stated he did not need wires put back in and did not have to follow-up. As of 23Dec b*, SAE resolved as patient has no more follow-ups with specialists.
This 39-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 22 March 2013.

Medical conditions at the time of the event included childhood asthma. Concomitant medications included salbutamol sulphate.

On 21 May b*, 426 days after the start of investigational product, the subject developed grade 3 or severe acute bronchitis. The subject presented to the ER with shortness of breath on exertion x 1 day. The subject reported using Albuterol every 10 minutes. The subject was hospitalised on 22 May b* after complaints of worsening of shortness of breath and wheezing x2 days. Chest x-ray disclosed left lower lobe atelectasis with no consolidation. The subject was treated with methylprednisolone sodium succinate and levofloxacin. Treatment with blinded trial medication-viiv was continued. The subject was discharged on 24 May b*. The investigator considered that there was no reasonable possibility that the acute bronchitis may have been caused by investigational product.

Follow-up information received on 09 August b*:

Acute bronchitis is considered the SAE. The acute asthma exacerbation is considered a symptom of the acute bronchitis.

Investigator text:

Subject was admitted for acute asthma exacerbation on 21 May b*. He has a history of childhood asthma; medication list includes Albuterol PRN. Medical records not available at this time. Subject presented to [deleted] ED with shortness of breath on exertion x 1 day; using his Albuterol every 10 mins. He reported that he has continued dosing IP while inpatient. Limited information available at this time. Discharge summary received. Subject was admitted on 22 May b* after c/o worsening of shortness of breath and wheezing x2 days. He was started on IV Levaquin as well as a nebulizer and Solu-medrol. Final diagnoses: acute exacerbation of asthma with acute bronchitis. He was discharged to home on 24 May b* with scripts for Solu-medrol and Levaquin. -

Protocol Id: ING114467
Investigator Number: 081266
Subject Number: 005407
Treatment Number: 2245
Case Id: Z0014533A
Suspect Drugs: Abacavir sulphate + lamivudine, Diazepam, Dolutegravir, Fluoxetine hydrochloride, Hydrocodone
Serious Events: Intentional overdose, Suicide attempt

b*: Following year
This 21-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 01 April.

The subject has a family history of suicide (paternal mother's sister as well as paternal father's sister committed suicide). The subject has a diagnosis of post traumatic stress disorder from childhood. Medical conditions at the time of the event included anxiety, depression and manic-depressive disorder. Concomitant medications included hydrocodone, fluoxetine hydrochloride and diazepam.

On 26 February b*, 331 days after the start of investigational product, the subject developed grade 4 attempted suicide and grade 4 intentional drug overdose. The subject was found unconscious after taking an overdose with hydrocodone, Prozac and Valium. The length of unconsciousness was unknown. The subject was hospitalised and the event was life-threatening. The subject was discharged from hospital on 29 February b* and admitted to an inpatient psychiatric hospital for further evaluation. Treatment with blinded trial medication-viiv was continued. The subject was discharged on 03 March b*. The intentional drug overdose resolved on 26 February b*. The attempted suicide resolved on 06 March b*. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by investigational product and that the event was possibly due to the concomitant medication, hydrocodone, fluoxetine hydrochloride and diazepam.

Follow-up information received on 27 March b* via query response:

Duration of unconsciousness: unknown.

Investigator text:

Subject's Mother called 911 when she found subject unconscious. Subject was admitted to Hospital and it had been found that he overdosed on hydrocodone, Prozac, and Valium. the amount taken is unknown at this time. Subject was discharged from the hospital on 02/29/b* and admitted to an Inpatient Psychiatric Hospital to further evaluation. Subject was then discharged on 03/03/b* to follow Psychiatric treatment as Outpatient. Patient suffers from depression, and Anxiety. Paternal Mothers sister committed suicide as well as paternal Fathers sister as well committed suicide. The subject has a DX of Post traumatic Stress Disorder from childhood.
This 41-year-old male subject was enrolled in a ViiV-sponsored, randomized, double-blind study for the treatment of human immunodeficiency virus infection. The subject received oral IP at 1 tablet per day from 01 APR to 12 APR.

The subject was randomized to Atripla once daily. Medical conditions at the time of the event included penicillin allergy.

On 11 APR, 10 days after the start of IP, the subject developed grade 3 or severe generalized rash (allergic reaction). The event was clinically significant (or requiring intervention). The subject presented on 12 APR with a 1 day history of rash over the whole body as well as fever, chills and nausea. The subject also experienced pruritus and diarrhoea at onset but these symptoms had settled. The subject further experienced confluent rash, fever, chills, tachycardia, sore eyes and a general feeling of malaise. There were no swallowing or breathing issues and no blisters, no mucus membrane involvement except conjunctival involvement. The subject was treated with prednisone. Treatment with IP was discontinued on 12 APR and the subject was withdrawn from the study. The event resolved on 03 MAY.

The investigator considered that there was a reasonable possibility that the generalized rash (allergic reaction) may have been caused by IP.

Follow up received from the clinical team on 14 APR: The subject was a 41-year-old Caucasian male with HIV disease. The subject had no co-morbidities. Concomitant medications included: Zantac, Benadryl for a recent rash, Imovane (a hypnotic started on 01 APR), multivitamins and selenium. The subject had a history of sulphur allergies with an unknown reaction. The subject started IP on 31 March. He contacted the research manager on 09 APR with complaints of a rash. He started on Benadryl and Claritin at home. The subject was sent for an office visit on 04 APR and was found to be afebrile, with a maculopapular rash. He denied any other complaints. The IP was continued and the subject was followed daily. The investigator noted rash progression and confluence but there was no mucosal involvement, vesiculations or bullae. The subject felt feverish but the site stated he was afebrile on examination. He also did not complain of gastrointestinal, or respiratory symptoms, although he admitted to mild fatigue. Worse with dosing phenomenon was not elicited as the subject took study medications at night and went to bed. Local laboratory tests were done on 11 APR and LFTs and U/A were normal. A complete blood count (CBC) was performed (results pending).

Follow up received from the Clinical team on 13 APR:

* 新薬承認情報提供時に置き換え
Telephone contact was made on 12 APR a*. Screen values obtained on 08 March a*- CD4 = 251 c/mm³, viral load = 36,553 copies/ml. The subject had a history of PCN allergy (rash). He started IP on 01 APR a*. On 12 April (day 11), he presented to the investigator with complain of an onset of pruritic skin rash, which began on day 10 of the study regimen. He also complained of a bout of loose stools which resolved by the time of the office visit. He denied other complaints of fever, respiratory symptoms, however he did complain of mild chills. The rash had progressed slightly today, but was otherwise asymptomatic. The doctor examined the subject and reported a body temperature of 37.5, with Grade 1-2 erythematous maculopapular rash on the upper trunk, and legs, but no palmar or mucosal involvement. The subject appeared clinically stable. After review of the subject's signs and symptoms, the investigator decided to continue study medications and the subject was to receive a short tapering course of steroids. No study medications were interrupted.

The subject returned for a follow up on 13 APR a*:

He was complaining of malaise, had more extensive confluence of rash when he woke up in the morning. Upon examination in the office, he also had bilateral conjunctivitis. His temperature was 38.0 degrees Celsius, pulse = 120 and blood pressure 120/80. His last dose of study medication was on 12 APR a* in the afternoon. Due to symptom progression with fever, grade 3 rash and constitutional complaints, the investigator decided to discontinue the study regime and withdrew the subject. The differential diagnosis includes suspected ABC HSR, allergic reaction to Sustiva with a rash and fever.

Follow-up information received 23 FEB b*:

The subject was HLA-B 5701 negative at screening.

Investigator text:

Systemic allergic reaction. Subject presented, on April 12th with a one day history of rash over whole body as well as fever, chills and nausea. The pruritus and diarrhoea that were there at onset had already settled. He was started on Prednisone 50 mg once daily and is continuing on this. Subject presented again today with severe confluent rash, fever, chills, tachycardia, sore eyes and a general feeling of malaise. There are no swallowing or breathing issues and no blisters. There is no mucus membrane involvement except conjunctival involvement. Subject took his last dose of IP on April 12. Was seen by Principal Investigator on April 13, 14, 18 and 26 for follow-ups. He was also seen on May 3rd when it was noted that his hypersensitivity reaction had resolved.

*a*: The year
*b*: Following year
This 54-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 25 February 2015.

The subject's past medical history included fistulectomy. Concomitant medications included multivitamins, tdap vaccine (non-GSK) and zolpidem.

On 24 May a*, 88 days after the start of investigational product, the subject developed grade 2 or moderate bacteraemia. The subject complained of chills and achiness beginning the morning of 24 May a*. The subject was hospitalised. The subject had a body temperature 102.9 F and normal blood pressure. Laboratory test results dated 24 May a* included CD4 lymphocytes 198 cells/uL (normal range 174-490) and CD8 lymphocytes 359 cells/uL (normal range 180-1170). The subject was treated with ceftriaxone sodium, paracetamol, ascorbic acid, vancomycin, diphenhydramine hydrochloride, heparin sodium, morphine, mupirocin, ondansetron hydrochloride, Bactrim DS, zinc sulfate and levofloxacin. Treatment with blinded trial medication-viiv was continued. The subject was discharged on 27 May a*. The event resolved on 14 June a*. The investigator considered that there was no reasonable possibility that the bacteraemia may have been caused by investigational product.

Follow-up information received on 02 August a* via query response:

PI and Sub-I believed, at the time of admission that the symptoms were possibly related to the fistulectomy. Awaiting labs and final report from hospital to determine final relationship to SAE.

Follow up information received on 22 September a* via answer query report:

The investigator confirmed that the fistulectomy was a relevant risk factor for the onset of the bacteremia.

Diagnostics:

24May a*: Buttock - Left Complete Gram Stain - Final, Wound Culture Final: Klebsiella Pneumoniae, Escherichia Coli, Staphylococcus Aureus

Investigator text:

*a*: The year
Subject presented to study clinic for week 12 and c/o chills, achiness beginning this morning on waking. Fever of 102.9. BP normal. Patient transferred to Emergency Room after receiving 1Gm rocephin and 650 mg Tylenol for fever. Subject evaluated at E.R. and admitted to hospital for treatment of bacteraemia. Further details will be provided when available. Subject discharged on 27May a* from hospital. -

Protocol Id: ING114467
Investigator Number: 081279
Subject Number: 005544
Treatment Number: 2094
Case Id: Z0008758A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Food poisoning

This 39-year-old male subject was enrolled in a ViiV-sponsored, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product from 15 March.

On 28 March a*, 13 days after the start of investigational product, the subject developed grade 2 or moderate food poisoning. On day 12 of dosing, the subject complained of abdominal pain, nausea, vomiting and myalgia. The event was disabling and clinically significant (or requiring intervention). The subject was hospitalized. The subject was treated with ciprofloxacin and metronidazole. Treatment with investigational product was interrupted on 27 March a*. The event resolved on 01 April a*. The subject was re-started on the investigational product on 01 April a* in the office and observed for 3 hours to rule out hypersensitivity reaction to abacavir. No reaction occurred and the subject was sent home. Vital signs collected pre-dose: BP 110/72, PR 78, post-dose 15 min BP 118/78, PR 80, 30 minutes post-dose BP 118/72 PR 74, 60 minutes post- dose BP 120/78 PR 78, 90 minutes post- dose BP 118/78 PR 80, 120 minutes post- dose BP 118/76, PR 78. The investigator considered that there was no reasonable possibility that the food poisoning may have been caused by investigational product.

Diagnostic test results:
Abdominal sonogram 30 March a*- impression: mild hepatomegaly, otherwise normal study; Chest- X-ray PA/Lat 28 March a* - impression: Normal chest; C-difficile Toxin A and B 28 March a* - negative; occult blood stool 30 March a*- negative

Investigator text:
Patient presented to the office on 04/01/a* after being discharged from local Hospital. Patient states he was admitted for food poisoning and was hospitalized from 03/28-04/01.
On day 12 of dosing he complained of food abdominal pain, nausea, vomiting and myalgia. His medications was interrupted while hospitalized. He was started back on medication on 04/01/a* in the office and observed for 3 hours to rule out hypersensitivity reaction to abacavir. Patient did not have a reaction to medication and was sent home. Pt predose bp 110/72, pr 78, post dose 15 min 118/78, 80, 30 minutes post dose 118/72 pr 74, 60 minutes post dose 120/78 pr 78, 90 minutes post dose 118/78 pr 80, 120 minutes post dose 118/76, pr 78

Follow up received from medical monitor on 04 April a*:

The subject was initiated into the study regimen on 15 March a*. His baseline CD4=390, and viral load=5945. He had a history of chronic back pain and the only con med was Percoset 5/325. He had no history of allergies. On Day 12, he noted the onset of mild nausea which became progressively worse on Day 13, and was associated with vomiting and myalgias. He went to the Hospital on 28 March a*, where he was admitted for 2-3 days. His last dose of study regimen was the night of 27 March a*. The subject apparently denied fever, rash or other symptoms. According to the investigator, the subject, who was considered to be reliable, gave history that the hospital diagnosis was possible food intoxication. The subject was clinically stable and willing to re-initiate study regimen in the office. The subject did subsequently re-initiate study regimen at approximately 2:13 pm on 01 April a*, as he did not believe that the subject's symptoms was consistent with ABC HSR. The subject was monitored for 2 ½ hours with vital signs being takes Q 15 minutes. The subject tolerated IP with no adverse events.

The site made a phone contact to the subject on 02 April a*, who continued to be asymptomatic. The visit to the office on 01 April a* coincided with the 2 week visit and so 2 week labs were obtained, which are still pending. The next OV for the subject is approximately on 12 April a*.

This 400-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 13 June.

The subject was randomized to receive Atripla once daily.
The subject's past medical history included attempted suicide and overdose. Medical conditions at the time of the event included depression and substance abuse. The subject admitted to prostitution for drug money and prior episodes of suicide attempts by cutting her wrists and taking pills. Concomitant medications included cocaine.

On 02 December a*, 172 days after the start of investigational product, the subject developed grade 3 or severe suicidal ideation and grade 3 or severe homicidal ideation. On 03 December a*, the subject developed grade 3 or severe worsened depression. The subject presented to the ER stating she had thoughts of wanting to stab her roommate and also to kill herself. The subject stated she had never had thoughts of hurting someone else. The subject stopped taking her antiretrovirals approximately 4 months prior to admission due to disinterest (inaccurate time period due to non-detectable viral load in October a*). The subject was hospitalised with one to one supervision. The subject was treated with hydroxyzine. The subject also attended groups and requested to be discharged. The subject self-discontinued treatment with blinded trial medication-viiv 2-4 months prior to admission, approximately on 20 November a*. The suicidal ideation and homicidal ideation resolved on 05 December a*. The worsened depression resolved on 19 January b*. Investigational product was restarted on 19 January b*. The investigator considered that there was a reasonable possibility that the worsened depression, suicidal ideation and homicidal ideation may have been caused by investigational product because depression can lead to suicidal ideation and/or homicidal ideation and these symptoms can be related to efavirenz and it's unknown if the subject was taking efavirenz as the treatment is blinded.

Investigator text:

Patient presented to ED stating that she had thoughts of wanting to stab her roommate and also to kill herself. Stated she had never had thoughts of hurting someone else. Admits to prior episodes of suicide attempts by cutting her wrists and taking pills. She had been smoking crack cocaine over the past 4 months and was having arguments with her roommate over money and drugs. She had also been prostituting herself for drug money. She did have a plan for suicide- Jumping off a bridge. She admitted to stopping her antiretrovirals 4 months prior to admission because of disinterest. This time period is likely inaccurate as she had a non-detectable viral load October a*. She was admitted with one on one supervision. While inpatient, she attended groups and requested to be discharged. She was referred to an outpatient psychiatric facility for follow up. This event may have been related to Sustiva- treatment blinded. Of note, the patient self-discontinued her study medication 2-4 months prior to the admission. Also, patient admits to 4 prior suicide attempts in the past dates unknown- will estimate f* -
This 40-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 02 March 2023.

The subject had no relevant prior medical history or risk factors.

On 31 July 2023, 151 days after the start of investigational product, the subject developed grade 4 low-flow priapism. The subject was hospitalised and the event was clinically significant (or requiring intervention). The subject underwent surgical treatment under general anaesthetic, and was treated with cephazolin sodium and bupivacaine hydrochloride. Treatment with blinded trial medication-viiv was continued. The event resolved on 02 August 2023 and the subject was discharged. The investigator considered that there was no reasonable possibility that the low-flow priapism may have been caused by investigational product.

Diagnostic text:

Diagnostic was made through clinical observation in the Emergency Room

Investigator text:

Subject first presented in the Emergency Room on July 31st, 2023 with a ring around the base of his penis and scrotum. He had also used crystal meth three days prior as well as Viagra. The ring was removed by the emergency physician, however he still have a persistent erection. He was then sent home. He presented to the Emergency Room again on August 1st, 2023 with priapism which, at this point, at been ongoing for more than 24 hours. He was given a penile block and attempts were made for aspiration as well as a phenylephrine injection through the gland to the corpora. This did not have satisfactory results. He was then brought to the operating room where a formal distal corporal glandular shunt was performed under general anaesthetic. He was also given intravenous Ancef as an infection prophylaxis. The operation was successful. The wound was dressed and the patient was kept under observation until August 2nd, 2023. Patient has been made aware of the potential risk of erectile dysfunction given the lengthy duration of his low-flow ischemic priapism. With this prolonged period of priapism, there is significant fibrosis and scarring that is high-risk for long-term erectile dysfunction. Subject did not
have any relevant prior medical history and/or risk factors. Subject subsequently developed cellulitis at the site of his penile surgery; which is captured in the adverse events log.

Protocol Id: ING114467
Investigator Number: 083637
Subject Number: 005679
Treatment Number: 2458
Case Id: Z0010829A
Suspect Drugs: Atripla
Serious Events: Paranoia, Suicidal ideation

This 59-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 05 May.

The subject was randomized to receive Atripla.

The subject's past medical history included suicidal ideation. Medical conditions at the time of the event included depression.

On 03 July, 59 days after the start of investigational product, the subject developed grade 4 suicidal ideation and grade 4 paranoia. The subject was hospitalised. The subject was treated with clonazepam, lorazepam and olanzapine. Treatment with investigational product was discontinued on 27 July and the subject was withdrawn from the study. The events resolved on 04 August. The investigator considered that there was a reasonable possibility that the suicidal ideation and paranoia may have been caused by investigational product.

Follow-up information received on 12 September via query response:

Based on PI's experience with Sustiva, he feels that there is a possibility that this patient's SAE could be related to Sustiva IF he had been randomized to the group receiving that medication.

Follow-up information received on 03 October via query response:

PI feels that it is related to the study medication. Because it remains blinded, PI was unable to confirm if that was the exact cause. Even if it was not Sustiva, still they cannot rule out they were related to study medication.

Follow-up information received 03 November:

The investigator updated the events as not related to study participation.

Diagnostic Results:

a*: The year

* 新薬承認情報提供時に置き換え
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Module 2.7.4 Summary of Clinical Safety

Toxicology Results: Alcohol <2.0 mmol/L  All other lab results normal

Investigator Text:

Patient travelled to Trinidad and returned on July 3rd. Increasing paranoid thoughts and suicidal ideation. Parents report erratic behaviour and took patient to [deleted] Hospital on July 10th. Was admitted by ER doctor for involuntary psychiatric evaluation. Remains in hospital but was allowed a day pass to come to clinic to be evaluation by PI. Remains confused and paranoid. PI decided to withdraw patient b/c he suspects this may be Sustiva-related, but remains unblinded. Patient came into the clinic for Follow Up and was events are still ongoing although he had been released from the hospital. Patient still heavily medicated on anti-psychotics and anti-depressants. He did report feeling less paranoid since stopping the study medication. Patient with rtc on 01Sep a* for further follow up. (01-Sep-a*) At follow up appointment, patient remains off of ARV’s and was seeing a psychiatrist regularly. No other changes. -

Protocol Id:  ING114467
Investigator Number: 084143
Subject Number: 005726
Treatment Number: 2516
Case Id: Z0010026A
Suspect Drugs:  Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Bronchitis

This 35-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 30 May .

Medical conditions at the time of the event included asthma. Concomitant medications included lorazepam and salbutamol sulphate.

On 03 June a*, four days after the start of investigational product, the subject developed grade 3 or severe bronchitis. The subject experienced progressive cough and shortness of breath with a low-grade fever from 03 June a*. The subject presented to the ER on 10 June a* and was hospitalised due to shortness of breath. Chest x-ray performed on 10 June a* showed no discrete lung infiltrates and no pleural effusions; normal cardiomiastinal and hilar contours; lung volumes appeared normal. Laboratory test results dated 10 June a* included ESR 32 mm/h (NR 1-20), haemoglobin 102 g/l (NR 115-155), RBC count 3.60 tera/L (NR 3.8-5.2) and WBC count 11.6 giga/L (NR 4-11). Liver and renal function tests were normal. The subject was treated with moxifloxacin hydrochloride. Treatment with blinded trial medication-viiv was continued. The subject left the hospital on 13 June a*. In clinic on 13 June a*, she had a low-grade fever (37.4), with BP 135/80, P71, R10. She was not short of breath but had some right chest pain and decreased air entry in this area. The investigator made a diagnosis of bronchitis and started her on a one week course of moxifloxacin 400 mg.
daily for one week. The event resolved on 19 June a*. The investigator considered that there was no reasonable possibility that the bronchitis may have been caused by investigational product.

Follow up received from the Clinical team on 14 June a*:

The subject had progressive cough, shortness of breath with low grade fever beginning 03 June a*. The subject presented to ER for evaluation on 10 June a*. She was admitted to hospital based on shortness of breath. A chest x-ray was normal but her WBC was a bit elevated at 11.6 (neutrophils 7.7). Her ESR was 32 and haemoglobin was 102 (a bit low for her). Liver and renal function tests were normal. She was admitted and shortness of breath improved and the subject chose to leave hospital on 11 June a*. On 13 June a*, in the clinic she had a low grade fever (37.4), with blood pressure (BP) 135/80, P71 and R10. The subject was not short of breath but had some right chest pain and decreased air entry in this area. There a diagnosis of bronchitis was made.

Follow up received from the clinical team on 08 August a*:

It was confirmed that subject's baseline ongoing respiratory condition was asthma. The subject does not recall when she was first prescribed Ventolin (1 puff QH6) but known it was many years ago. The furthest back her usage can be confirmed is 17 November e*.

Investigator text:

Patient called from the ER to inform coordinator of respiratory distress. Patient had progressive cough and shortness of breath with a low-grade fever beginning on June 3, a*. She presented to ER for evaluation on June 10. She was admitted to hospital based on the shortness of breath she was experiencing. A CXR was normal, but her WBC was a bit elevated at 11.6 (neutrophils 7.7). Her ESR was 32. Hgb was 102 (a bit low for her). Liver and renal function tests were normal. She was admitted and her SOB improved markedly and she chose to leave hospital June 11. In clinic June 13, she had a low-grade fever (37.4), with BP 135/80, P71, R10. She was not SOB but had some right chest pain and decreased air entry in this area. The investigator made a diagnosis of bronchitis and started her on a one week course of moxifloxacin 400 mg daily for one week. -

<table>
<thead>
<tr>
<th>Protocol Id:</th>
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<tr>
<td>Investigator Number:</td>
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<td>Subject Number:</td>
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<td>Treatment Number:</td>
<td>4105</td>
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<tr>
<td>Case Id:</td>
<td>Z0012451A</td>
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<tr>
<td>Suspect Drugs:</td>
<td>Abacavir sulphate + lamivudine, Dolutegravir</td>
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<tr>
<td>Serious Events:</td>
<td>Bartholin's cyst</td>
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This 25-year-old female subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 05 April 2019.

The subject's past medical history included endovaginal tumefaction.

On 24 August 2019, 141 days after the start of investigational product, the subject developed grade 2 or moderate Bartholin cyst. The subject was hospitalised and treated by puncture of Bartholin cyst (30 cc) on 24 August 2019. Liquid was brown but without suspected anomaly. The subject was then treated with pristinamycin. Treatment with investigational product was continued. The event resolved on 25 August 2019. The investigator considered that there was no reasonable possibility that the Bartholin cyst may have been caused by investigational product.

Investigator text:

- Endovaginal tumefaction of 20 mm of diameter (29 Jun 2019), old from many years, increasing. Treated by puncture of Bartholin cyst (30 cc) on 24 Aug 2019. Liquid was brown but without suspected anomaly. Treated by pyostacin 2 g/daily for 15 days. If the cyst comes back, surgery will be scheduled.

Protocol Id: ING114467
Investigator Number: 087426
Subject Number: 005753
Treatment Number: 3054
Case Id: Z0012452A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Osteoarthritis, Tendon disorder

This 25-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 19 April 2019.

The subject's past medical history included septic arthritis of knee. Medical conditions at the time of the event included high blood pressure, knee arthrosis, knee pain and shoulder pain. Concomitant medications included atenolol and tramadol hydrochloride.

MRI performed in December 2018 showed an aspect of chondropathy of external rotula side and X-ray found right femoro-patellar arthrosis. The subject's knee pains increased since the septic arthritis episode.

On 29 July 2019, 101 days after the start of investigational product, the subject developed grade 2 or moderate shoulder tendinopathy and grade 2 or moderate worsening knee
arthrosis. The subject was hospitalised on 29 July a*. The subject was treated with Diprostene, ketoprofen, sodium hyaluronate and esomeprazole. Treatment with blinded trial medication-viiv was continued. The shoulder tendinopathy resolved on 03 August a* and the subject was discharged. The worsening knee arthrosis was (and will remain) unresolved. The investigator considered that there was no reasonable possibility that the shoulder tendinopathy and worsening knee arthrosis may have been caused by investigational product.

Follow-up information received on 10 November a* via query response:

I confirm this (=knee arthrosis) will be never resolved

Investigator text:

SEPTIC ARTHRITIS OF RIGHT KNEE COMPLICATED BY SEVERE SEPSIS(Hospitalized from 24feb a* to 07apr a*). RMI from December e* shown an aspect of chondropathy of external rotula side and RX found right femoro patellar arthrosis. Knee pains increased since the septic arthritis episod. This septic arthritis episod was totally finished. Shoulder pains for ten years and recent RX permits to diagnosticate a shoulder tendinopathy. Hospitalisation required for treatment of articular pains (shoulder and knee) from 29jul a* to 3aug a*.

Protocol Id: ING114467
Investigator Number: 085422
Subject Number: 005771
Treatment Number: 4123
Case Id: Z0009086A
Suspect Drugs: Atripla
Serious Events: Hypersensitivity

This 38-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 11 April a*.

The subject was randomized to receive Atripla once daily.

On 20 April a*, nine days after the start of investigational product, the subject developed grade 3 or severe possible hypersensitivity. The event was clinically significant (or requiring intervention). He also experienced rash on skin, oedema of skin, nausea, fever and creatine phosphokinase increased. The subject was treated with desloratadine. Treatment with investigational product was discontinued on 20 April a* and the subject was withdrawn from the study. The event resolved on 03 May a*. The investigator considered that there was a reasonable possibility that the possible hypersensitivity may have been caused by investigational product.
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Follow-up information via Clinical team received on 21 April a*:

The subject had no allergies or concomitant pathology. There were no other concomitant medications except for vitamin complement which the subject has taken for several years.

Follow-up information received on 03 May a*:

The site confirmed that the subject had a suspected Abacavir hypersensitivity reaction (HSR).

Follow-up information received 23 February b*:

The subject's HLA-B*5701 status was negative at screening (17 March a*).

Investigator Text:

extended cutaneous rash with oedema.

with nausea, fever (38C) and feeling of malaise

with increase of CPK -

Protocol Id: ING114467
Investigator Number: 084229
Subject Number: 005793
Treatment Number: 2409, 2409, 2409
Case Id: Z0010696A, Z0010696B, Z0010696C
Suspect Drugs: Atripla
Serious Events: Bronchitis, Depression, Depression, Respiratory distress

This [year]-year-old female subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 28 April [year].

Medical conditions at the time of the event included depression. Concomitant medications included esomeprazole and folic acid.

On 19 July a*, 82 days after the start of investigational product, the subject developed grade 3 or severe worsened depression. The subject experienced sadness, exhaustion and conflict with her husband. The subject was hospitalised. No tests or investigations were performed. The subject was treated with oxazepam, venlafaxine hydrochloride and methotrimeprazine. Treatment with blinded trial medication-viiv was continued. The event resolved on 29 July a*. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by investigational product.

* a*: The year
* b*: Following year
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Investigator text:

sadness, exhaustion, conflict with her husband at home

Hospitalization is necessary to keep far -

Medical conditions at the time of the event included depression. Concomitant medications included etoricoxib, loperamide oxide monohydrate, paracetamol, esomeprazole and tramadol hydrochloride.

On 08 October a*, 163 days after the start of investigational product, the subject developed grade 3 or severe worsened depression. The subject experienced sadness, exhaustion and conflict with her husband. The subject was hospitalised. Relevant diagnostic tests performed showed a fracture of the tenth rib which was treated by strapping. The subject was treated with methotrimепразине, oxazepam and venlafaxine hydrochloride. Treatment with blinded trial medication-viiv was continued. The event resolved on 17 October a*. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by investigational product.

Investigator text:

sadness, exhaustion, conflict with her husband at home

Hospitalization is necessary to keep far -

On 27 November a*, 213 days after the start of investigational product, the subject developed grade 3 or severe respiratory distress syndrome and grade 3 or severe bronchitis infection. On the same day, the subject also experienced fever. The subject was hospitalised. Investigations revealed new moderate chronic lung obstruction disease. The subject was treated with Augmentin, methylprednisolone sodium succinate, terbutaline sulphate, ipratropium bromide, salbutamol sulphate and pristinamycin. Treatment with investigational product was continued. The events resolved on 07 December a*. The investigator considered that there was no reasonable possibility that the respiratory distress syndrome and bronchitis infection may have been caused by investigational product.

Diagnostic text:

MODERATE CHRONIC OBSTRUCTIVE LUNG DISEASER

Investigational text:

FEVER HAS ITS ARRIVAL ON 27/11/a* -
This 41-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 01 June 2020.

No medical history was reported.

On 01 April 2021, 305 days after the start of investigational product, the subject developed grade 2 or moderate hodgkin's disease. The subject did not experience any fever, pain or other symptoms. The subject was hospitalised on 21 May 2021. Histology from biopsy performed on 30 May 2021 showed Hodgkin disease. Treatment with blinded trial medication-viiv was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the laterocervical lymphadenomegaly may have been caused by investigational product.

Follow-up information received on 31 May 2021 via query response:

The cause of SAE was not known.

The subject was withdrawn on 24 July 2021, as per protocol, as the subject required prohibited medicines to treat his Hodgkin’s disease.

Diagnostic Assessments:

Histologic sample: Hodgkin disease.

Investigator Text:

Onset on April of left latero-cervical lymphoadenomegaly, no fever no pain o other symptoms. On 21/05/2021 patient was hospitalised to obtain a diagnosis:TAC is ongoing and biopsy On 30/05/2021 biopsy was done, the histologic sample shown: Hodgkin disease. Patient is treated with chemotherapy. -
This 35-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 16 March.

The subject had no relevant medical history.

On 06 September, 174 days after the start of investigational product, the subject developed grade 1 or mild carpal tunnel syndrome. The subject was hospitalised. Treatment with investigational product was continued. The event resolved on 12 October. The investigator considered that there was no reasonable possibility that the carpal tunnel syndrome may have been caused by investigational product.

Diagnostic Results:

electromyography was performed on 7 September.

Investigator Text:

patient was hospitalized on 12 Oct, at the same day the neurolysis was done, subject discharged from hospital on 13 Oct.

This 35-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 14 March.

a*: The year
On 18 April a*, 35 days after the start of investigational product, the subject developed grade 2 or moderate shoulder impingement syndrome. The subject was hospitalised and underwent a therapeutic shoulder-arthroscopy. The subject was treated with dipyrrone, omeprazole, enoxaparin and ibuprofen. Treatment with blinded trial medication-viiV was continued. The event resolved on 21 April a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the shoulder impingement syndrome may have been caused by investigational product.

Investigator text:

Patient was admitted to hospital on 18.Apr.a*. For treatment of the subacromial impingement syndrome a therapeutic shoulder-arthroscopy was performed. Patient was discharged on 21.Apr.a*.

Protocol Id: ING114467
Investigator Number: 084007
Subject Number: 005913
Treatment Number: 3024
Case Id: Z0009017A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Toxoplasmosis

This -year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 25 March .

The subject was randomised to GSK1349572+Epzicom/Kivexa once daily

On 10 April a*, 16 days after the start of investigational product, the subject developed grade 2 or moderate central nervous system toxoplasmosis. The subject was hospitalised. The subject was treated with pyrimethamine, sulphadiazine, gabapentin and calcium folinate. Treatment with investigational product was continued. The event resolved on 05 May a*. The investigator considered that there was no reasonable possibility that the central nervous system toxoplasmosis may have been caused by investigational product.

Follow up received on 18 April a*:

The investigator reported that the event occurred first on 11 April a*, the subject entirely lost consciousness. The subject's partner described symptoms of typical epileptic seizure. The subject was taken to the emergency room but left the hospital against doctor's orders. A second epileptic episode occurred on 14 April a*. The subject again lost consciousness and fell face first. Upon arrival to the emergency unit a third seizure was observed by the paramedics. No antiepileptic drugs were given and the seizures resolved. The subject fully recovered and did not have any further episodes since 14
April. No imaging or further diagnostics were performed. The subject was hospitalised to rule out concomitant pathology to explain the symptoms.

Follow up received from Clinical team on 18 April a*:

The subject's past medical history revealed some dermatological infections (mostly furuncles on his trunk) which were merely scars or dried. No prior CNS or head trauma history. The subject had no known history of illicit drug use, alcohol use or herbal remedies. The subject is a [blank] year old male with viral load >500 000, CD4 (absolute) 63.

On 11 April, the subject experienced a 10-15 second generalised seizure tonic/clonic type seizure. The subject was taken to the emergency room (ER) where he signed an out AMA. The subject could not remember the 20 minutes immediately after the event and had no postictal symptoms and no reported loss of body functions/controls. A similar event occurred on 14 April, and the subject went to ER and signed an AMA form. The subject had lost consciousness and fell on his face. No testing was done.

Diagnostics:

CT skull: Mass left temporoparietal, MRT skull: multiple lesions in the supratentorial white matter inflammatory lesions of toxoplasmosis in accordance

Investigator text:

On 04/18/a* informed us the family doctor on seizures of the patient. Patients visit us on 04/18/a* to visit Week4. We referred the patient to a hospital for evaluation. There, on 04/20/a* conducted a CT scan of the skull. Findings: CLAIM AREA LINKS TEMOROPARIETAL There, on 4/21/a* implementation of an MRT. Findings: multiple lesions in the white matter on both sides. Determination toxoplasmosis. Upfront of seizures by toxoplasmosis. No relationship to study-medication. Start with the treatment of toxoplasmosis on 04/23/a*.

a*: The year
This 38-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 24 March.

The subject has no relevant medical history.

On 29 December, 280 days after the start of investigational product, the subject developed grade 2 or moderate muscle pain. The subject was hospitalised. No movement restriction was reported. Chest X-ray, laboratory test results and physical examination were all negative. No event treatment was given. Treatment with blinded trial medication-viiiv was continued. The event resolved on 30 December and the subject was discharged in a stable general condition. The investigator considered that there was no reasonable possibility that the muscle pain may have been caused by investigational product.

Follow-up information received on 17 February via query response:

The hospital report confirmed ambiguous muscle pain. Event outcome is not in subject record.

Follow-up information received on 02 March via query response:

No medical history. No treatment.

Diagnostics:

X-ray thorax negative, Laboratory results negative, physical examination negative

Investigator text:

X-ray thorax negative, Lab results negative, physical examination negative, no movement restriction. stable general condition and dismissal from the hospital on 30-DEC-a* -
This 21-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 15 March.

Medical conditions at the time of the event included alcohol abuse relapse. The subject has no history of epilepsy.

On 20 November a*, 250 days after the start of investigational product, the subject developed grade 2 or moderate grand mal seizure. The subject was hospitalised. Neurological examination was without pathological results; psychiatric examination without pathological results; general examination without pathological results; elevated prolactin level as a marker for epileptic seizure. No event treatment was given. Treatment with blinded trial medication-viiv was continued. The event resolved on 21 November a* and the subject was discharged at own risk and without completion of diagnostic. The investigator considered that there was no reasonable possibility that the grand mal seizure may have been caused by investigational product and that the event was possibly due to alcohol consumption and lack of sleep.

Follow-up information received on 19 January b* via query response:

The patient has not a history of epilepsy. The possible reason was consumption of alcohol and lack of sleep. There was no treatment initiated.

Diagnostics:

CCT 20.11.a* no pathological results /ECG 20.11.a* sinus rhythm, tachycardia 137/min, hypertrophia of LV, lab results unknown

Investigator text:

the patient has been admitted to the hospital due to grand mal seizure, neurological examination without pathological results, psychiatric examination without pathological results, general examination without pathological results, elevated prolactin level as a marker for epileptic seizure. Patient has been discharged on 21.nov.a* at own risk, without completion of diagnostic. -

Protocol Id: ING114467
Investigator Number: 084009

a*: The year
b*: Following year
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Module 2.7.4 Summary of Clinical Safety

Subject Number: 005921
Treatment Number: 4048
Case Id: Z0013169A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Infected dermal cyst

This 39-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 15 March.

On 06 December a*, 266 days after the start of investigational product, the subject developed grade 3 or severe infected atheroma. The subject was hospitalised. Admission laboratory test results included CRP 3.5 mg/dl (normal range <0.5 mg/dl) and leukocyte 14.10 /nl (normal range 3.6-9.2 /nl). The subject underwent surgical treatment on 06 December a* and was also treated with ceftriaxone. Treatment with blinded trial medication-viiv was continued. The event resolved on 15 December a*. The investigator considered that there was no reasonable possibility that the infected atheroma may have been caused by investigational product.

Follow-up information received on 07 February b*:

Doxycycline was deleted as a treatment med.

Investigator text:

surgery of abscess 06.dec.a* -

Protocol Id: ING114467
Investigator Number: 084009
Subject Number: 005923
Treatment Number: 2148, 2148
Case Id: Z0010365A, Z0010365B
Suspect Drugs: Atripla
Serious Events: Coronary artery disease, Sciatica

This 39-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 22 March.

Medical conditions at the time of the event included lumbar ischialgia.

*a*: The year
*b*: Following year
On 19 June a*, 89 days after the start of investigational product, the subject developed grade 3 or severe worsening lumboischialgia. The subject was hospitalised on 24 June a* due to pain increase. The subject was treated with ibuprofen. On 28 June a*, the subject underwent sequester nucleotomy of L4/5. Treatment with blinded trial medication-viiv was continued. The event resolved with sequelae on 05 July a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the worsening lumboischialgia may have been caused by investigational product.

Investigator text:

Since 19.jun.a* serious lumbar ischialgie. Analgesia first with Ibuprofen( house doctor)Due to increase of pain hospitalisation 24.Jun a* for diagnostic and treatment. Further details unknown at the moment. Information will be provided asap. on 28.Jun a* patient get a Sequesternucleotomia L4/5.Discharge date was 05.Jul a*.

Medical conditions at the time of the event included smoking.

On 17 November a*, 240 days after the start of investigational product, the subject developed grade 2 or moderate coronary heart disease. The subject was hospitalised on 17 November a* due to left thoracic pain emanating into the left arm. By 150 Watt in stress ECG dyspnoea and angina pectoris symptoms have been verified. Coronary angiography performed on 22 November a* showed a coronary heart disease without high-grade stenosis but elevated left ventricular pressure. The subject was treated with amlodipine and aspirin. Treatment with blinded trial medication-viiv was continued. The event resolved on 23 November a*. The investigator considered that there was no reasonable possibility that the coronary heart disease may have been caused by investigational product.

Follow-up information received on 19 January b* via query response:

The diagnosis of CHD could not be considered in the following two cardiological consultations. The cardiologists suspected spine problems are the reason for thoracic pain.

Investigator text:

the patient has been admitted on17 Nov a* to a hospital due to left thoracic pain emanating into the left arm. By 150 Watt in stress ECG dyspnoea and angina pectoris symptoms have been verified. Coronary angiography on 22 Nov a* showed a coronary heart disease without high-grade stenosis but elevated left ventricular pressure.
Module 2.7.4 Summary of Clinical Safety

Case Id: Z0013412A
Suspect Drugs: Atripla
Serious Events: Cholelithiasis

This 32-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 12 April 2019.

The subject's past medical history included gallstone. The subject was known to have recurring complaints of pressure pain in the upper abdomen after eating, abdominal fullness and flatulence since e*.

On 01 September a*, 142 days after the start of investigational product, the subject developed grade 2 or moderate cholecystolithiasis. The subject was hospitalised. Sonography performed on 29 November a* abdomen showed cholecystolithiasis. The subject was treated with dipyrone and scheduled to undergo a cholecystectomy. Treatment with blinded trial medication-viiv was continued. The event resolved on 02 December a*. The investigator considered that there was no reasonable possibility that the cholecystolithiasis may have been caused by investigational product.

Investigator text:

since g* known gallstones since e* recurring complaints. Since September a* lasting discomfort, therefore operation required cholecystectomy is performed.

Protocol Id: ING114467
Investigator Number: 086924
Subject Number: 006029
Treatment Number: 2116
Case Id: Z0011576A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Foot fracture

This 32-year-old male subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 17 March 2019.

On 05 August a*, 141 days after the start of investigational product, the subject developed grade 1 or mild calcaneal tuber fracture. The subject had a work accidents resulting in a right leg entrapment. The subject was taken to the ER and his right leg was...
immobilized. The subject returned to the ER on 09 August a* due to severe pain and was hospitalised. The subject was given prophylaxis with anticoagulant treatment and pain treatment. The immobilisation was removed due to oedema and equimosis in the right foot with pain. Treatment with blinded trial medication-viiv was continued. The subject was discharged on 12 August a* and was scheduled for physiotherapy. The event resolved on 20 December a*. The investigator considered that there was no reasonable possibility that the calcaneal tuber fracture may have been caused by investigational product.

Follow-up information received on 19 September a* via query response:

Hospitalization report is not available. Treatment data not available. It is confirmed that patient received anticoagulation therapy and painkillers, however the name, doses and dates are not available.

Diagnostics:

Calcaneous CT: diagnosis right calcaneal tuber fracture and oedema. Discarded subastragaline articulation event

Investigator text:

The patient suffered a working accident on the 5th of August a* resulting with a right leg entrapment. Consulting to ER was diagnosed with right calcaneal tuber fracture. Right leg was immobilized. Referring severe pain few days later, on the 9th aug a* visited ER again and hospitalization was performed. During the hospitalization patient was given prophylaxis with anticoagulant treatment and the immobilization was removed observing oedema, and equimosis in the right foot with pain. Patient was discharged on the 12th of August. Patient will start next week the rehabilitation.

Protocol Id: ING114467
Investigator Number: 086916
Subject Number: 006044
Treatment Number: 4070
Case Id: Z0008990A
Suspect Drugs: Atripla
Serious Events: Cerebrovascular accident

This __-year-old male subject was enrolled in a blinded study for the treatment of hiv-1 infection. The subject received investigational product from 23 March a* to 06 April a*.

The subject was randomised to Atripla once daily.

Concomitant medications included omeprazole and prednisone.
On 06 April \(^{a*}\), 14 days after the start of investigational product, the subject developed grade 4 stroke. The subject was hospitalised. The subject was treated with aspirin and prednisone. Treatment with Atripla was discontinued on 06 April \(^{a*}\) and the subject was withdrawn from the study. The event resolved with sequelae on 23 May \(^{a*}\). The investigator considered that there was a reasonable possibility that the stroke may have been caused by investigational product.

Diagnostic assessment:

General status preserved. BP 110/70. HR 90. Mild dysphasia. Several patches of folliculitis, predominantly in thighs and lower abdomen with some thoracic involvement. Skin biopsy folliculitis. MR vascular Willis circle (April 18th) Ay segment hypoplasia of right anterior cerebral artery and single anterior cerebral artery (normal variant). Lung sounds: normal

Abdomen: nil Reduced strength of right upper limb of distal predominance. Lab test nothing of note. Normal thorax. MR (April 14th) elongated lesion affecting left frontal lobe with free-water restriction in diffusion frames, compatible with acute infarction. Small hyperintense lesion in T2 FLAIR frames affecting the right lateral portion of pons with free-water restriction in diffusion frames, compatible with an acute ischemic lesion. Brain vessels inflammatory vasculopathy without stenosis.

Follow up received from the Clinical team on 19 April \(^{a*}\): No risk factors were report at the time of this report. The subject was withdrawn from the study on 07 April \(^{a*}\). The subject had a loss of strength and sensibility in the right hand and had slurred speech. At the time of this report the subject was still hospitalised. The subject had only taken aspirin as treatment. Serology for the subject was negative and an ultrasound did not show any signs of arteriosclerosis but there was minimal arterial wall inflammation.

Follow up received from the clinical team on 20 April \(^{a*}\): An MRI was suggestive of injuries on left parietal due to cerebral stroke. Some cutaneous lesions were found before this episode. The skin lesions were not considered to be related. Anti aggregation treatment with aspirin was continued.

Follow up received from Clinical team on 06 May \(^{a*}\): The subject's relevant medical history included: HIV infection/A2, CD4 368, viral load 2,900. Primo - infection in August \(^{h*}\).

The subject was admitted to hospital on 14 April \(^{a*}\) with right hand clumsiness and speech disorder. Four or five days after starting the investigational product the subject experienced a macular popular rash affecting the limb predominantly. Two - three days later, the subject experienced hyperaesthesia in the fingers of the right hand loss of dexterity. Three days later the subject suffered a sudden a sudden episode of monosparesis in the right upper limb and dysphasia with intense improvement over 15-20
minutes although without complete recovery. On 10 April a*, the subject suffered a similar episode lasting 15 minutes.

MRI on 14 April a*, showed an elongated lesion affecting the left frontal lobe with free-water restriction in diffusion frames, compatible with acute infarction. Small hyperintense lesion in T2 FLAIR frames affecting the right lateral portion of pons with free-water restriction in diffusion frames, compatible with an acute ischemic lesion. CSF cytology showed no malignant cells and a skin biopsy showed folliculitis.

Follow up information received on 30 June a* via answer query report:

The investigator reported that the sequelae were disartria and bad coordination.

Investigator text:

Lose of strength and sensibility in the right hand and slurred speech. This episode occur 3 times between 20-30 min without a complete recovered. -

Protocol Id: ING114467
Investigator Number: 086942
Subject Number: 006055
Treatment Number: 2101
Case Id: Z0008834A
Suspect Drugs: Atripla
Serious Events: Hallucination, visual

This 1-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product from 16 March.

The subject was randomized to Atripla once daily

Medical conditions at the time of the event included paranoid schizophrenia. Concomitant medications included risperidone and pravastatin.

On 02 April a*, 17 days after the start of investigational product, the subject developed grade 3 or severe visual hallucination. At site visit on 31 March a* the subject reported suffering from non-serious insomnia and received treatment with Orfidal. The subject presented at the ER on 03 April a* and was hospitalised. The subject was treated with olanzapine. Treatment with investigational product-viiv was discontinued on 03 April a* and the subject was withdrawn from the study. The subject was discharged on 03 April a*. The subject failed to present to a site visit on 07 April a* due to readmission. The event resolved on 06 May a*. The investigator considered

*a*: The year
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Module 2.7.4 Summary of Clinical Safety

that there was a reasonable possibility that the visual hallucination may have been caused by investigational product.

Follow-up information received on 24 May a* via query response:

[Event outcome is not available] as the patient is still hospitalized. The study team is trying to contact him or patient's family without success until the moment.

Investigator text:

Probable intensification of patient psychiatric affection by the investigational product. Patient has psychiatric history and is receiving treatment with Risperdal due to a diagnosis of Schizophrenia paranoid. A planned visit at site was performed on 31st March. Insomnia was the symptom referred by patient and Orfidal was prescribed (this does not meet SAE criteria). On 2nd Apr hallucinations started and patient went at emergency room on 3rd Apr. He came back at home same day. A new visit at site was performed on 7th Apr but the patient didn't go because he was admitted to a different site (admission date: 07 Apr a*) Study medication has been stopped on 3 Apr a* it hasn't been started again. More information is requested to another hospital. Patient is withdrawn from the study and an EW visit will be performed when possible.)

Protocol Id: ING114467
Investigator Number: 086942
Subject Number: 006056
Treatment Number: 3015, 3015, 3015
Case Id: Z0011577A, Z0011577B, Z0011577C
Suspect Drugs: Atripla
Serious Events: Anaemia, Pneumococcal sepsis, Renal failure chronic

This 22-year-old female subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 16 March.

Medical conditions at the time of the event included hiv infection CDC category C3. Concomitant medications included folic acid, omeprazole, paracetamol, Septrin, Kaletra, Kivexa and metamizole magnesium.

On 31 August a*, 168 days after the start of investigational product and 47 days after the last dose, the subject developed grade 3 or severe streptococcus pneumoniae bacteraemia. The subject was hospitalised on 05 September a*. The subject was treated with ceftriaxone. The event resolved on 18 October a*. The investigator considered that there was no reasonable possibility that the streptococcus pneumoniae bacteraemia may have been caused by investigational product.

Diagnostics:

a*: The year

* 新薬承認情報提供時に置き換え
On study at Nephrology Dept due to a Renal Impairment by an unknown cause from 05/Aug/.

Anaemia Normochromic/Normocytic under study from Dec/.

Follow up received from the Clinical team on 06 September:
The subject had anaemia (haemoglobin=8.6) since 15 December.
The first episode of pneumonia was on 13 December before inclusion.

The subject was in the Nephrology department since 05 August. No invasive procedures were found to have been performed so far and a diagnosis of renal disease was not made. Laboratory and diagnostic data on 05 August included:

- Urinanalysis: Proteins 200 mg/dL, >150 RBC/mcL, hyaline-granulous casts in the sediment.
- Blood chemistry: Creatinine 1.09 mg/dL, TGF (MDRD) 59.39 mol/min, Na 130 mmol/L, Potassium 4.1 mmol/L and C1 96 mmol/L.
- Cryoglobulin positive in blood, CPK 1636 u/l, GOT (AST) 141 u/l, GPT and ALT 86 u/l.

The subject was admitted for evaluation of acute febrile syndrome with no clear focal signs. There was no recurrence of pneumonia and moxifloxacin was discontinued on 14 July.

Follow up received on 05 October via email from investigator:
The subject was still in the hospital. It has been confirmed the subject has cryoglobulinemia, but the primary underlying disease has not yet been diagnosed. Kidney function has improved but she has developed lymph node enlargement and splenomegaly.

Results of a lymph node biopsy was still pending. It seems likely that the disorder was present before the subject was included in the clinical trial.

On 07 July after the start of investigational product, the subject developed grade 3 or severe worsening of chronic anaemia. The subject was hospitalised on 05 September. No treatment was given since the anaemia was not caused by iron deficiency. On 12 July subject's haemoglobin level was at 8.4 g/dl (normal range 12-16). The subject's haemoglobin level was checked on 06 Sep. on 14 Sep she had fever again (38.2°C). High fever disappeared on 06 Sep. On 14 Sep. she had fever again (38.2°C). High fever disappeared on 06 Sep. On 14 Sep. she had fever again (38.2°C).

Follow-up information received on 14 November via query response:

Investigator text:

After the patient finished the Moxifloxacin treatment that was prescribed on 05 August, No invasive procedures were found to have been performed so far and a diagnosis of renal disease was not made. Laboratory and diagnostic data on 05/Aug were:

- Proteins 200 mg/dL, >150 RBC/mcL in the sediment.
- Blood chemistry: Creatinine 1.09 mg/dL, TGF (MDRD) 59.39 mol/min, Na 130 mmol/L, Potassium 4.1 mmol/L, Cryoglobulin positive in blood, CPK 1636 u/l, GOT (AST) 141 u/l, GPT and ALT 86 u/l.

The subject was admitted for evaluation of acute febrile syndrome with no clear focal signs. There was no recurrence of pneumonia and moxifloxacin was discontinued on 14 July.

Follow up received on 05 October via email from investigator:

The subject was still in the hospital. It has been confirmed the subject has cryoglobulinemia, but the primary underlying disease has not yet been diagnosed. Kidney function has improved but she has developed lymph node enlargement and splenomegaly. Results of a lymph node biopsy was still pending. It seems likely that the disorder was present before the subject was included in the clinical trial.
18). Treatment with blinded trial medication-viiv was discontinued on 15 July a* and the subject was withdrawn from the study. The event resolved on 18 October a* and the subject was discharged with haemoglobin of 7.8 mg/dl. The investigator considered that there was no reasonable possibility that the worsening of chronic anaemia may have been caused by investigational product.

Medical conditions at the time of the event included HIV infection CDC category C3. Concomitant medications included folic acid, omeprazole, paracetamol, Septrin, Kaletra and Kivexa.

Follow-up information received on 03 November a* via query response:

No, cryoglobulinemia is not another SAE; the patient had cryoglobulinemia before starting study drug.

Diagnostics:

On study at Nephrology Dpt due to Renal Impairment by an unknown cause from 05/Aug/a* Anaemia Normochromic/Normocytic under study from Dec/e*

Investigator text:

After the patient finished the Moxifloxacin treatment that was prescribed on Jul/a* because a second episode of Bacterial Pneumoniae was diagnosed she was admitted on 5/Sep/a* for study of febrile syndrome with worsening of previously mentioned worsening of chronic anaemia and renal impairment (of undetermined origin) Patient has been discharged on 18Oct a*. She will be under study due to Chronic Anaemia, Chronic Kidney Failure and Cryoglobulinemia polyclonal IgM. Haemoglobin value 7.8 mg/dL at the day of discharge. Since Anaemia is not due to Iron deficiency no treatment has been given. Cryoglobulinemia should be the cause of renal failure and anaemia, although these could develop later in the course of the disease and not seen until ART was initiated (coincidence?, some kind of IRIS?). No clear cause has been found as an explanation to the cryoglobulinemia, as frequently happens. Our current feeling is that cryoglobuleniema was present before initiating antiretroviral therapy, and neither the anaemia nor the renal failure are drug-related, whatever the patient is receiving. (Hb value 12/Jul/a* 8.4 g/dl -Normal Range 12.0-18.0-) -

Medical conditions at the time of the event included HIV-1 infection CDC classification C3. Concomitant medications included folic acid, omeprazole, paracetamol, Septrin, Kaletra and Kivexa.

On 07 July a*, 113 days after the start of investigational product, the subject developed grade 3 or severe worsening of chronic renal failure. The subject was hospitalised. Treatment with blinded trial medication-viiv was discontinued on 15 July a* and the subject was withdrawn from the study. The event resolved on 28 September a*. The
investigator considered that there was no reasonable possibility that the worsening of chronic renal failure may have been caused by investigational product.

Follow-up information received on 03 November a* via query response:

Normal range: Creatinine: 0.30-1.10 mg/dl; MDRD: >60 ml/min. No medication was administered since the cause for chronic renal failure has not been yet determined. The patient remains under study at the Nephrology department. No change in event outcome.

Follow-up information received on 10 January b* via query response:

IP discontinued on 15 July a* due to both worsening of chronic anaemia and worsening of chronic kidney disease.

Diagnostic Results:

On study at Nephrology Dpt due to renal impairment by an unknown cause from 05/Aug/a* Anaemia Normochromic/Normocytic under study from Dec/a*

Protocol Id: ING114467
Investigator Number: 086942
Subject Number: 006059
Treatment Number: 4074
Case Id: Z0010469A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Tuberculosis

This 37-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 24 March a*.

Concomitant medications included Atripla.

On 30 May a*, 67 days after the start of investigational product, the subject developed grade 3 or severe tuberculosis. The subject presented at the hospital with fever and thoracic pain on 30 May a*. The diagnosis was probable right lung pneumonia with pleural effusion (ruled out). The subject received treatment with 14-day course of levofloxacin and the symptoms disappeared. The subject then presented at the ER 13 days later with the same symptoms and was hospitalised. Results from pleural puncture obtained on 06 July a* showed that the subject suffered from tuberculosis. The subject was treated with Rimstar, Benexol, ceftriaxone, clarithromycin, paracetamol, Cotrimoxazol, ibuprofen and Rifinah. Treatment with blinded trial medication-viiv was discontinued on 05 July a* and the subject was withdrawn from the study. The event resolved on 11 July a* and the subject was discharged. The investigator considered
that there was no reasonable possibility that the tuberculosis may have been caused by investigational product.

Follow-up information received on 18 August a* via query response:

Initially the doctors thought the patient was suffering from pneumonia. Subsequent tests were performed and a diagnosis of TB was given, and so the pneumonia was discarded.

Investigator text:

The patient came to the hospital with fever and thoracic pain on 30-may-a*. The diagnostic was a probable right lung pneumonia with pleural effusion. After treatment with levofloxacin during 14 days the symptoms disappeared and the patient status at week 12 visit was fine. 13 days later the patient comes to the ER with the same symptoms and so he was hospitalized. Several medical tests were performed and finally a pleural puncture indicated a diagnostic of Tuberculosis on 06-Jul-a*. That day TBC treatment was started and will be kept for about 8 months. Hospitalization finished on 11-Jul-a*. The patient is currently taking Atripla since 06-Jul-a* when the study drug was discontinued. In summary: Initially the doctors thought the patient was suffering from pneumonia. Subsequent tests were performed and a diagnosis of TB was given, and so the pneumonia was discarded -

Protocol Id: ING114467
Investigator Number: 086925
Subject Number: 006081
Treatment Number: 2144
Case Id: Z0015415A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Neurosyphilis, Syphilis

This 31-year-old male subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 22 March .

Concomitant medications included clotrimazole.

On 18 April b*, 393 days after the start of investigational product, the subject developed grade 3 or severe syphilis. The subject presented an ulcer in lips and exanthema in trunk, hands and feet. On 03 May b*, the subject developed grade 3 or severe syphilitic meningitis. The subject was hospitalised on 08 May b*. The subject was treated with phenoxyemethylpenicillin potassium and benzylpenicillin. Treatment with blinded trial medication-viiv was continued. The events resolved on 18 May b* and the subject was discharged. The investigator considered that there was no reasonable
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possibility that the syphilitic meningitis and syphilis may have been caused by investigational product.

Follow-up information received on 17 May b* via query response:

Syphilis considered serious event due to it causes the meningitis.

Follow-up information received on 22 May b* via query response:

Candidal balanitis not considered as SAE. It will be recorded as AE in AE pages

Investigator text:

On the 18th of April b* patient presents an ulcer in lips and exantema in trunk, hands and feet. Diagnosis: syphilis. RPR 1/64. On the 3rd of May results for patient were: PL: cell: 15(90% linfios), prot 50 mg/dL, RPR negative, FTA-Abs positive, Ac T. Pallidium: low limit. Considered as Syphilitic meningitis. Patient entered in hospital on the 8th of May b* were he was treated with penicillin until 18th of May. On the 14th of May patient was diagnosed with candidal balanitis and is treated with clotrimazol until the 18th when he is discharge from hospital.

Protocol Id: ING114467
Investigator Number: 086919
Subject Number: 006106
Treatment Number: 2145
Case Id: Z0008732A
Suspect Drugs: Atripla
Serious Events: Bipolar I disorder

This 21-year-old female subject was enrolled in a ViiV-sponsored, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 22 March a* to 29 March a*.

The subject was randomized to receive Atripla once daily.

On 27 March a*, five days after the start of investigational product, the subject developed grade 3 or severe manic-depressive reaction. The subject presented at the hospital on 29 March a* due to insomnia and maniac episode. Treatment with blinded trial medication-viiiv was therefore discontinued on 29 March a* and the subject was withdrawn from the study. X-ray computed tomography showed that the subject did not have any lesions. On 31 March a*, the subject returned to the hospital and was admitted for psychiatric evaluation and treatment of symptoms. The subject was treated with olanzapine and lorazepam. The event resolved on 08 April a* and was

a*: The year
b*: Following year
discharged on the same day. The investigator considered that there was a reasonable possibility that the manic-depressive reaction may have been caused by investigational product.

Investigator text:

On 29/Mar/a* the patient came to the hospital because she had insomnia and a maniac episode, as a result the investigational products were withdrawn. On 31/03/a* the patient came again to the hospital and she is admitted to psychiatric evaluation and treatment of the symptoms. Follow-up: The patient was diagnosed with manic episode secondary to antiretroviral medication by psychiatrist. Zyprexa treatment was started on 31/03/a* and he was discharged on 08/04/a* for outpatient follow-up due to improvement.

Protocol Id: ING114467
Investigator Number: 086905
Subject Number: 006133
Treatment Number: 2064
Case Id: Z0013268A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Syphilis

This 26-year-old male subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product per day from 11 March 2021.

The subject's past medical history included latent syphilis.

On 25 August a*, 167 days after the start of investigational product, the subject developed grade 2 or moderate syphilis reinfection. The subject was hospitalised. The subject's lumbar puncture was negative for neurosyphilis. The subject was treated with benzylpenicillin. Treatment with blinded trial medication-viiv was continued. The event resolved on 05 September a*. The investigator considered that there was no reasonable possibility that the syphilis reinfection may have been caused by investigational product.

Follow-up information received on 08 February b* via query response:

Patient was treated for syphilis. There were a re-infection on august a* with RPR 1/128. HIV treatment guidelines recommend a lumbar function for the patient

Follow-up information received on 24 February b* via query response:

Syphilis was suspected by symptoms (anal fissure). We confirmed diagnosis by a RPR test (1/128)
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Diagnostics:

Rapid plasma reagin (RPR) positive 1/128 performed on 19 AUG a*

Investigator text:

Patient was admitted at hospital to study possible neurosyphilis by lumbar puncture. It was negative.

Protocol Id: ING114467
Investigator Number: 086937
Subject Number: 006171
Treatment Number: 2150
Case Id: Z0013365A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Tonsillar disorder

This 38-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 22 March a.

Concomitant medications included ibuprofen, Amoxycillin-clavulanic acid and anesthetic. The subject had no relevant medical history.

On 10 November a*, 233 days after the start of investigational product, the subject developed grade 3 or severe tonsillar dysplasia. The subject was hospitalised. The subject presented with mild pain and enlargement of tonsils. Tonsillar biopsy performed in left tonsil revealed high degree tonsillar dysplasia. Surgery of both tonsils was performed on 12 December a*. Treatment with blinded trial medication-viiv was continued. The event resolved on 16 December a*. The investigator considered that there was no reasonable possibility that the tonsillar dysplasia may have been caused by investigational product.

Investigator text:

PATIENT PRESENTED WITH MILD PAIN AND ENLARGEMENT OF TONSILLS. A TONSILLAR BIOPSY WAS MADE IN LEFT TONSILL THAT REVEALED TONSILLAR DYSPLASIA, AND SURGERY OF BOTH TONSILLS WAS INDICATED AND PERFORMED ON DEC.12.a*.
This 31-year-old male subject was enrolled in a ViiV-sponsored, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 14 April.

On 26 April a*, 12 days after the start of investigational product, the subject developed grade 3 or severe renal cyst. The subject was hospitalised on 26 April a* due to kidney pain. CT scan of kidneys showed cyst right kidney. The subject was treated with diclofenac. Treatment with blinded trial medication-viiv was continued. The event resolved on 27 April a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the renal cyst may have been caused by investigational product.

Diagnostic assessment:

CT scan of kidneys. Result: cyst right kidney

Investigator text:

The patient was hospitalised 26 April a* due to kidney pain. Was CT scanned and discharged from hospital 27 April a*.

On 22 April b*, 374 days after the start of investigational product, the subject developed grade 3 or severe infected perianal hematoma, following haemorrhoids surgery on 16 April b*. The subject was hospitalised. The infected perirectal haematoma was evacuated. No medication was given. Treatment with blinded trial medication-viiv was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the infected perianal hematoma may have been caused by investigational product.

Diagnostics:

Proctoscopy in general anaesthesia

Investigator text:

The patient had a planned operation for haemorrhoids 16 April b*. He was hospitalized due to infection in the operated area. It turned out to be an infected perirectal haematoma which was evacuated. No medication given.
This 33-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 19 April 2016.

On 29 September 2016, 163 days after the start of investigational product, the subject was involved in a bicycle accident and developed grade 3 or severe head injury, described as concussion and minor cranial fractures. The subject was hospitalised. CT scan showed small parenchymatous haemorrhage in the right frontal lobe, orbital fracture, zygomatic arch fracture and maxilla fracture. The subject was treated with ondansetron hydrochloride and ibuprofen. Treatment with investigational product was continued. The subject was discharged on 30 September 2016. The event resolved with sequelae on 29 November 2016. The investigator considered that there was no reasonable possibility that the head injury may have been caused by investigational product.

Follow up information received 17 November 2016 via answered query report:

No relevant medical history and no relevant concomitant medications related to the fall.

Investigator text:

Subject was involved in a bicycle accident. Brought to emergency care by ambulance (29 SEP 2016). Diagnosis: Concussion and minor cranial fractures. Stays overnight at hospital. Subject discharged from hospital on 30 SEP 2016.

PROTOCOL ID: ING114467
INVESTIGATOR NUMBER: 083764
SUBJECT NUMBER: 006279
TREATMENT NUMBER: 2353
CASE ID: Z0012070A
SUSPECT DRUGS: Abacavir sulfate + lamivudine, Dolutegravir
SERIOUS EVENTS: Head injury

**a*: The year

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PROTOCOL ID: ING114467
INVESTIGATOR NUMBER: 086586
SUBJECT NUMBER: 006391
TREATMENT NUMBER: 2433
CASE ID: Z0009442A
SUSPECT DRUGS: Atripla
SERIOUS EVENTS: Ovarian cancer

**a*: The year
This female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product at 1 tablet per day from 02 May to 10 May.

On 05 May, three days after the start of investigational product, the subject developed grade 3 or severe pelvic tumour (ovarian cancer). The subject was hospitalised on 10 May due to nausea, diarrhoea and anorexia, which started on 05 May, followed by malaise, fatigue, watery stools and chills. Treatment with blinded trial medication-viiv was discontinued on 10 May and the subject was withdrawn from the study. Laboratory test results dated 10 May included ALT 91 U/L (NR 0-49), AST 212 U/L (NR 0-46), ESR 120 mm/h (NR 6-12), GGT 135 U/L (NR 1-24), and haemoglobin 8.6 g/dl (NR 11-15). Laboratory test results dated 11 May included ALT 77 U/L, AST 124 U/L, bilirubin direct 0.36 mg/dl (NR 0-0.2), BP 80 mmHg, GGT 109 U/L, hematocrit 22.6 (NR 37-48), haemoglobin 7.5 mg/dl, MCV 74.5 (NR 82-95), potassium 2.8 mEq/L, prothrombin time 18.8 sec (NR 11-15), red blood cell count 3.05 (NR 3.5-5), sodium 129 mEq/L. Abdominal and pelvic ultrasound performed on 12 May revealed a pelvic tumour, retroperitoneal and abdominal lymphadenopathy and ascites. The tumour marker was specific for ovarian cancer, CA 125, has abnormal value 177.2 U (normal range <35). The subject was treated with Voluven, metoclopramide, Arginine sorbitol, blood and pantoprazole. On 13 May the subject had a body temperature of 38.4 degrees centigrade. The subject refused CT scan and gynaecological examination scheduled on 13 May. The subject decided to leave the hospital and discontinue study medication. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the pelvic tumour (ovarian cancer) may have been caused by investigational product.

Follow up received on 11 May:

The subject had an initial emesis beginning the 05 May which continued until 11 May. The subject had developed fever, chills as of the 09 May. The subject took the last dose of the investigational product on 10 May. The subject was not given oral medications or food due to the emesis. The subject denied taking any ethanol, over the counter drugs, new medicines, exposure to bad foods or sick relatives. The subject's screening and baseline AST and ALT were within normal limits. Laboratory data collected on 10 May (during hospitalization) included: AST 212 and ALT 91. The doctor noted that the subject's haemoglobin level decreased from 10 to 7.6/8.7. Platelet levels were normal and the subject had no rash. The subject is suspected to be having a toxic reaction with haemolysis and liver enzyme elevation. The doctor did not suspect a HCV reactivation flare.

Follow-up information received on 19 May:

I can confirm the patient has no any cancer treatment, she refused.

Diagnostics:
Abdominal Ultrasound- pelvic tumour with abdominal and retroperitoneal lymphadenopathy, ascites CA 125 177.2 U (normal value <35)

Protocol Id: ING114467
Investigator Number: 083760
Subject Number: 006417
Treatment Number: 2312, 2312
Case Id: Z0009661B, Z0009661C
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir, Paracetamol
Serious Events: Intentional overdose, Pyrexia

This 26-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 12 April 2019.

Medical conditions at the time of the event included type 1 diabetes.

On 16 May a*, 34 days after the start of investigational product, the subject developed grade 3 or severe fever of undetermined origin. The subject was hospitalised. Blood cultures MC&S showed no growth. The subject was treated with ceftriaxone, metronidazole and doxycycline. Treatment with blinded trial medication-viiv was continued. The investigator reported "Origin of fever unspecified in subjects notes". The event resolved on 23 May a*. The investigator considered that there was no reasonable possibility that the fever of undetermined origin may have been caused by investigational product.

Investigator text:

Patient discharged 23/0/a*, no formal diagnosis given.

Medical conditions at the time of the event included type1 diabetes. Concomitant medications included paracetamol.

On 12 August a*, 122 days after the start of investigational product, the subject experienced grade 2 or moderate intentional overdose of paracetamol tablet. The subject was hospitalised and the event was life-threatening. The subject intentionally took 64 paracetamol tablets due to social pressures. Treatment with blinded trial medication-viiv was continued. The event resolved on 15 August a*. The investigator considered that there was no reasonable possibility that the intentional overdose of paracetamol tablet may have been caused by investigational product and that the event was possibly due to the concomitant medication, paracetamol.

Investigator text:
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tried to contact patient 12 August following grade 3 alert blood glucose of 18.8mmols. Patient did not respond to phone contact or e-mails till this morning. Patient was admitted to hospital 12/8/a*, discharged 15/08/a* at 23.00hrs, he will phone tomorrow with details. No further information at the moment. patient reports due to social pressures he took overdose of paracetamol and this precipitated his admission to hospital. Discharged following unspecified care and has now returned to work under continuing care of mental health outreach workers. Patient has agreed to attend centre for follow up safety bloods later this week.

<table>
<thead>
<tr>
<th>Protocol Id:</th>
<th>ING114467</th>
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<tbody>
<tr>
<td>Investigator Number:</td>
<td>084698</td>
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<tr>
<td>Subject Number:</td>
<td>006452</td>
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<tr>
<td>Treatment Number:</td>
<td>2315</td>
</tr>
<tr>
<td>Case Id:</td>
<td>Z0010546A</td>
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<tr>
<td>Suspect Drugs:</td>
<td>Atripla, Codeine phosphate + paracetamol</td>
</tr>
<tr>
<td>Serious Events:</td>
<td>Overdose</td>
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</tbody>
</table>

This [num] year-old male subject was enrolled in a ViV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/ lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 12 April [num].

Concomitant medications included Co-codamol.

On 01 May [num], 19 days after the start of investigational product, the subject developed grade 3 or severe overdose of cocodamol. The subject was hospitalised after taking 32 cocodamol tablets. Treatment with blinded trial medication-viiv was continued. The event resolved on 02 May [num]. The investigator considered that there was no reasonable possibility that the overdose of cocodamol may have been caused by investigational product and that the event was possibly due to the concomitant medication, Co-codamol. No further information was available.

Follow-up information received outside Inform on 13 July [num]:

Subject was treated at another hospital possibly with N-acetylcysteine for acetaminophen overdose.

Follow up information received on 11 August [num] via answer query report:

The investigator reported that treatment with N-acetylcystine for the SAE was not in the subjects records, nor was there any other signs symptoms or clinical sequelae noted as a result of the overdose.

Follow-up information received on 11 August [num]:

*a*: The year
This episode meets SAE criteria as patient was admitted to hospital overnight. The inpatient conmeds have not been confirmed. There have not been further AEs as a result of this event.

Investigator text:

The subject reported that he had been admitted into [deleted] General Hospital in May due to a deliberate overdose of 32 cocodamol tablets. He can not remember the date but his admission was for one night.

Investigator Text:

admitted to ER with complaints of pleuritic chest pain and shortness of breath. No recent infective symptoms. If the effusion is persistent or recurs alternate diagnosis such as KS will need to be considered.

This 21-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 10 March.

On 31 December a*, 296 days after the start of investigational product, the subject developed grade 3 or severe pleural effusion. The subject was hospitalised. The subject was treated with amoxicillin trihydrate. Treatment with investigational product was continued. The event resolved on 07 January b*. The investigator considered that there was no reasonable possibility that the pleural effusion may have been caused by investigational product.

Investigator Text:

* a*: The year
* b*: Following year
This 43-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 30 March.

On 22 June a*, 84 days after the start of investigational product, the subject developed grade 2 or moderate humerus fracture after being hit from behind by a motor vehicle whilst riding his bicycle. There was no loss of consciousness. The subject was hospitalised. Head, neck and spine were cleared and there was no thoracoabdominal injury. His pelvis and lower extremities suffered no injuries. X-ray demonstrated a comminuted fracture through the mid-shaft of the left humerus. The subject had a

The subject has no relevant medical history or risk factors.

Investigator text:

Patient was decorating bathroom on 15 June a*, locked himself in the bathroom and therefore climbed out of the bathroom window and fell resulting in a fractured left heel. Visited emergency room on 15 June a* and discharged. Repair was attended on 27 June a* when the swelling had decreased. No nil effects. Discharge from hospital 1 July a* Patient recovered well no nil effects.

Protocol Id: ING114467
Investigator Number: 083535
Subject Number: 006622
Treatment Number: 4090
Case Id: Z0010501A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Humerus fracture

* a*: The year
posterior splint in place. The subject was moderately diffusely swollen about the left upper arm down to the elbow and complained of numbness over the dorsum of the thumb but otherwise was neurovascularly intact. The subject was treated with Tylenol #3, hydromorphone hydrochloride, tramadol hydrochloride, dimenhydrinate, paracetamol, celecoxib and lorazepam. Treatment with blinded trial medication-viiv was continued. The subject was fitted with a Sarmiento brace and collar and cuff sling and was discharged on 24 June a*. Repeat X-ray showed no significant improvement. Open reduction and internal fixation as an out-patient was performed on 15 July a*. Repeat x-ray performed on 30 November a* showed periosteal new bone formation which suggested interval healing when compared to the previous exam. The latest x-ray taken on 03 August b* showed an ongoing radiographic union of the mid humeral shaft fracture. The fracture lines were now less visible; the internal plate appeared intact and alignment was satisfactory. The event resolved on 03 August b*. The investigator considered that there was no reasonable possibility that the humerus fracture may have been caused by investigational product.

Diagnostics:

Chest and cervical spine x-rays done on June 22nd, a*. Normal. Left humerus x-ray: Acute transverse fracture through the midshaft of the humerus with half a bony width of anterior displacement with no significant angulation deformity.

Repeat x-ray of left humerus on June 23rd, a*; alignment across the mid diaphyseal fracture is worse. Repeat x-ray done on July 4th, a*: distal fracture remains displaced medially and anteriorly by 4.5 cm. X-ray done on July 11th shows no change. X-ray done July 15th post open reduction and internal fixation shows plate and screws used to transfix the mid-shaft fracture of the humerus in satisfactory position. Repeat x-ray done on November 30th, a* shows that there is periosteal new bone formation which suggest interval healing when compared to the previous exam. The latest x-ray taken on August 3rd, b* shows an ongoing radiographic union of the mid humeral shaft fracture. The fracture lines are now less visible. The internal plate appears intact. Alignment is satisfactory. This fracture is considered healed.

Protocol Id: ING114467
Investigator Number: 083535
Subject Number: 006625
Treatment Number: 2260
Case Id: Z0014686A
Suspect Drugs: Atripla
Serious Events: Deep vein thrombosis

This -year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected
antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 05 April.

The subject's past medical history included torn hamstring (repaired in day-surgery on 16 January b*). The subject was seen for post-surgical follow-up on 08 March b* where it was found his right calf was quite swollen. Ultrasound performed on 09 March b* showed multiple sub acute deep vein thrombosis.

On 09 March b*, 339 days after the start of investigational product, the subject developed grade 3 or severe multiple sub acute deep vein thromboses on calf. The event was clinically significant (or requiring intervention). The subject was admitted to hospital on 09 March b* and was seen daily in ER for anti-coagulation therapy with dalteparin sodium and warfarin sodium until 15 March b*. The subject did not stay as an inpatient during this time. Laboratory test results dated 14 and 15 March b* showed INR of 2.0 (normal range 0.9-1.2). The subject is to complete a 6-month course of treatment with warfarin sodium. Treatment with blinded trial medication-viiv was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the multiple subacute deep vein thromboses on calf may have been caused by investigational product.

Follow-up information received on 26 April b* via query response:

The swelling did not go down and no new symptoms appeared. This was a condition that should have gotten better but had not. The specialist's opinion is what prompted further investigations which in turn showed the DVT. Start date remains 9 March b*.

Investigator text:

Subject suffered a tear to his right hamstring on December 19th, a*, which was repaired in day-surgery on January 16th, b*. He was seen in follow-up by his surgeon on March 8th, when it was found that his right calf was still quite swollen. The surgeon organized an ultrasound for the day after. Multiple sub acute deep vein thrombosis were seen on ultrasound. Subject was admitted to the hospital on the 9th of March, and seen daily in Emergency for anti-coagulation therapy from then until March 15th. He did not stay in the hospital during that period; he went in only for his treatment. He is currently taking Warfarin as a treatment and will be followed by his GP. Subject will continue on Warfarin for a total of six months after which time he will be considered as having recovered from this SAE, unless more symptoms develop. -

Protocol Id: ING114467
Investigator Number: 083535
Subject Number: 006627
Treatment Number: 2302
Case Id: Z0010073A
Suspect Drugs: Atripla
Serious Events: Pneumonia

a*: The year
b*: Following year
This 43-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product at 1 tablet per day from 11 April.

The subject's past medical history included pulmonary embolism, sinusitis and upper gastrointestinal haemorrhage. Medical conditions at the time of the event included compartment syndrome of leg, depression, dyslipidemia and eczematous dermatitis. The subject is a current smoker. Concomitant medications included warfarin sodium.

On 10 June a*, 60 days after the start of investigational product, the subject developed grade 3 or severe pneumonia. On 13 June a*, the subject presented at the site with a 3-5 day history of back and chest pain, headache, shortness of breath, fever and chills. The subject was hospitalised and was febrile for the first couple of days with temperature up to 38.5°C. Chest x-ray showed a left anterior upper lobe consolidation which was likely the source of his fevers and chest pain. Blood cultures were negative. Laboratory test results dated 13 June a* included ALT 85 U/L (NR 15-55), AST 80 U/L (NR 15-45), INR 5.0 (NR 0.9-1.2), neutrophils 6.1 giga/L (NR 2-8), sodium 128 mmol/L (NR 135-148), WBC count 8.1 giga/L (NR 4-11). On 15 June a*, sodium was 132 mmol/L (NR 135-148). The subject was treated with cefuroxime sodium, azithromycin, ceftriaxone and morphine. Treatment with blinded trial medication-viiv was continued. The subject was discharged on 16 June a*. The subject was reviewed on 04 July a*. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by investigational product.

Diagnostics:

On June 13th, subject had a chest x-ray that showed "right upper lobe pneumonia". He also had an ECG that showed "sinus tachycardia", which is not considered serious per protocol, with otherwise normal results. The hospital also performed a CT of the chest (pulmonary angiogram protocol) to confirm pneumonia. The CT also ruled out central or lobar pulmonary embolism.

Investigator text:

Subject presented in our office on June 13th, a* with a 3-5 day history of back and chest pain, headache, shortness of breath and fever/chills. He currently smokes one half pack per day. He was transported by ambulance to the local hospital. Febrile over the first couple of days of admission with temperatures up to 38.5 degrees Celsius. Chest x-ray showed a left anterior upper lobe consolidation which is likely the source of his fevers and chest pain. Blood cultures were negative. Did quite well over the course of his admission and was stepped down to oral antibiotics on the 15th of June. He remained afebrile and off oxygen and was discharged from hospital on June 16th, a*.

a*: The year
Dr. [deleted] on July 4th, a*. No complaints of chest pain, shortness of breath, cough or malaise. Chest clear with normal breath sounds and air entry bilaterally. -

Protocol Id: ING114467
Investigator Number: 086977
Subject Number: 006687
Treatment Number: 2189
Case Id: Z0015432A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir, Fluoxetine
Serious Events: Suicide attempt

This  [●] -year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 25 March [●].

Medical conditions at the time of the event included depression. Concomitant medications included fluoxetine, citalopram, bromazepam and lorazepam.

On 07 May b*, 409 days after the start of investigational product, the subject attempted (grade 1 or mild) attempted suicide. The subject had taken 20 tablets of fluoxetine. The subject was hospitalised. The subject underwent a gastric lavage, an EGC and blood extraction. All results were within normal limits. The subject was treated with ipecac. Treatment with blinded trial medication-viiv was continued (subject missed one dose due to vomiting caused by SAE treatment; re-started IP on 08 May b*). The event resolved on 08 May b* and the subject was discharged in good condition. The investigator considered that there was no reasonable possibility that the attempted suicide may have been caused by investigational product and that the event was possibly due to the concomitant medication, fluoxetine.

Follow-up information received on 22 May b* via query response:

The treatment of the SAE causes vomiting, so the subject skipped one dose. The criterion to register any change in the dosage of the IP is to skip 3 days. The subject only missed one day due to treatment of the SAE.

Follow up information received from clinical on 21 May b*:

The subject's recent medical history included no suicidal intent, no psychological disorders and no psychotic disorders during the study.

Three years ago, the subject was fired and from that point onwards the subject started to abuse alcohol. The subject felt guilty, frustrated, anxious, depressed and "a loser". Three months ago, the subject started to attend an [●] Centre.

a*: The year
b*: Following year
Investigator text:

The patient was admitted with attempt suicide diagnosis on 7/May b*. During the hospitalization was performed a gastric lavage, an EGC and blood extraction. All results were within normals limits. The patient was discharged on 8/May b* at good condition. The patient restarted taking blinded trial medication on 8/may/b*.

Protocol Id: ING114467
Investigator Number: 081249
Subject Number: 006739
Treatment Number: 2442
Case Id: Z0013256A
Suspect Drugs: Atripla
Serious Events: Cellulitis

This 34-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 03 May.

The subject's past medical history included cellulitis.

On 06 December a*, 217 days after the start of investigational product, the subject developed grade 2 or moderate cellulitis aggravated. The subject presented to the hospital with right thigh erythema and complaining of feeling faint the night before at the end of his shift, also lethargic with malaise. The subject took motrin and but still developed fevers to 102 degrees Fahrenheit. The subject was hospitalised on 07 December a*. A CT scan of the right thigh performed on 08 December a* ruled out abscess. The subject was treated with sodium chloride, azithromycin, cephalixin, docusate, gabapentin, Hydrocodone + acetaminophen, hydromorphone hydrochloride, ketorolac trometamol, lactobacillus rhamnosus, levofloxacin, metoclopramide, ondansetron hydrochloride, polyethylene glycol, pravastatin, ranitidine hydrochloride, Theragran-M, tramadol hydrochloride, zolpidem, acetylcysteine, Clavera, clindamycin, paracetamol and diphenhydramine hydrochloride. Treatment with blinded trial medication-viiv was continued. The event resolved with sequelae (residual pain and swelling at site) on 26 December a*. The investigator considered that there was no reasonable possibility that the cellulitis aggravated may have been caused by investigational product.

Follow-up information received on 13 January b* via query response:

Date of admission is 07dec a*

Follow-up information received on 17 April b* via query response:
Sequelae: Residual pain and swelling at site

Diagnostics:

Blood Culture from 2 sites on 07dec a*: No growth as of 12dec a*

Investigator text:

Patient presented to the hospital with right thigh erythema complaining of feeling faint the night before at the end of his shift, also lethargic with malaise. Subject took motrin and but still developed fevers to 102 degrees farenheit. Further evaluation a recurrence of cellulitis of the right thigh area. A CT scan of the right thigh was performed on 12/8/a* that ruled out abscess.

Medical conditions at the time of the event included emphysema. Concomitant medications included morphine, barium sulfate, iohexol and iopamidol.

On 02 August a*, 81 days after the start of investigational product, the subject developed grade 3 or severe respiratory distress secondary to narcotic administration. On 09 August a*, the subject developed grade 3 or severe intubation requirement secondary to aspiration pneumonia. On 11 August a*, the subject developed grade 3 or severe disseminated intravascular coagulopathy. The subject presented to the ER on 02 August a* with a several day history of abdominal pain and was hospitalised. The subject was given intravenous morphine for pain resulting in a respiratory depression, requiring intubation. CT of the abdomen and pelvis showed dilatation of the pancreatic duct. Laboratory test results dated 03 August a* included amylase of 1200 units/L (normal range 25-115). The subject was treated with salbutamol sulphate, enoxaparin, lactulose, pantoprazole, sodium chloride, D5 + NS + KCl, midazolam, piperacillin sodium, vancomycin, lorazepam, etomidate, naloxone, ondansetron hydrochloride and suxamethonium. Treatment with blinded trial medication-viiv was discontinued on 08 August a* and the subject was withdrawn from the study. The subject died on 12 August a* due to disseminated intravascular coagulopathy, secondary to aspiration pneumonia and respiratory distress secondary to narcotic administration. An autopsy was not performed. The investigator considered that there was no reasonable possibility that
the respiratory distress secondary to narcotic administration, intubation secondary to aspiration pneumonia and disseminated intravascular coagulopathy may have been caused by investigational product and that the respiratory distress secondary to narcotic administration was possibly due to the concomitant medication, morphine.

Follow up received from the Clinical team on 02 August a*:

The year old subject was randomised on 13 May a* with a CD4 count of 301 and a HIV RNA of 26,695. The subject had baseline concomitant medications that included proventil, megace and symbicort and had reported AEs of constipation and poor appetite.

As the subject developed abdominal pain on 01 August a*, the subject received Zosyn, vancomycin and was on ventilator support.

Follow up received from the Medical team on 26 August a*: The subject was doing well in the Single study. At day 1 - her CD4 cell count was 301 (47%; screening 323, 29%) and her viral load was 26695 c/mL. She was noted to have a low albumin at 2.2 mg/dL and elevated lipase at 78 U/L. Her platelets were also low at screening - 81,000/mm3 but were not evaluated at Day 1 due to severe platelet clumping. The subject had an adequate viral load response by week 8 (08 July) with a viral load of 70 cp/mL but the CD4 cell count was relatively stable - 305 (28%). At week 8, the platelets had improved to 110 000/mm3 (after reaching a peak of 131 000).

On 01 August a*, the subject presented to a local emergency room (ER) with complaints of abdominal pain for 1 week. She was given morphine 4 mg IV and developed respiratory distress, requiring intubation. She stayed in ER till 02 August a*, when she was admitted to the ICU. A CT scan of the brain on 02 August a* showed no haemorrhage or mass effect but did not show age related involutional change.

The subject's abdominal/pelvic CT from 02 August a* revealed left pleural effusion, atelectasis within the right lung base with abnormal appearance of the right lower lobe posteriorly (honeycombing, bronchiectasis or atelectasis), emphysematous changes within the lingual, right middle lobe, right renal cyst, dilatation of pancreatic abnormalities), leiomyomatous uterus, central canal stenosis (L2-L3,L3-L4). Small focus of air anterior to heart (significance unknown), fatty infiltration of liver considered. After consultation with surgery and repeat abdominal examinations, it was felt that she did not have free air in her peritoneum (which was suspected based on the abdominal CT).

The corresponding amylase on 01 August a* was 95 U/L (NR: 25-115), then 1088 U/L and 1200 on 03 August a*, 1143 and 1216 on 04 August a*, 537 on 06 August a*, 274, on 07 August a* 95 on 09 August a*. The study medications were stopped on 08 August a*. Lipase on 01 August a* was 287 and did not become elevated.

Admission laboratory data (as per admission note) on 01 August a*: Na 141, K 4.6, Cl 103, bicarbonate 38, BUN 14, creatinine 1.0, glucose 88, total protein 7.7, albumin

a*: The year

* 新薬承認情報提供時に置き換え
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2.5, calcium 8.9, total bilirubin 0.3, AST 28, ALT 21, alkaline phos 112, amylase 92, CRP 34.5, lipase 287, troponin-I <0.04. Urinalysis: mild cloudy urine, nitrate negative, LE negative.

Prior to admission the subject's medical history included: chronically abnormal chest x-ray, pleural effusion, weight loss, chronic shortness of breath, functional decline, pulmonary embolus, moderate-sized pleural effusion, however there was no significant pleural fluid was found on ultrasound, chronic lobar parenchymal changes on CT scan of the chest and HIV.

The doctor noted that the subject was not receiving oxygen supplementation. The admission labs were consistent with alkalosis and in light of her respiratory disease, seems consistent with emphysema and chronic carbon dioxide retention, which abated with ventilation.

A CT scan of the chest on 02 August a*, showed no acute abnormality, periventricular white matter microangiopathic ischemic changes in cavernous segment, internal carotid artery and atherosclerotic calcification.

On 12 August a*, the subject died due to cardiopulmonary arrest. There were multiple potential causes for her decompensation (also likely due to small size), respiratory decompensation (also unlikely due to ease of ventilation). She did not have evidence for an acute intra-abdominal process and had a thorough work up. The abdominal wall hemorrhage likely contributed significantly to the underlying condition leading to hypotension and need for pressors.

Follow up information received via answer query report on 21 October a*: The investigator confirmed that an autopsy was not performed and that they could not get a copy of the death certificate.

Follow up information received via answer query report on 21 March b*: The investigator confirmed that the events that occurred were on 02 August a*, 81 days after the start of investigational product, the subject developed severe respiratory distress secondary to narcotic administration. On 09 August a*, the subject developed severe intubation secondary to aspiration pneumonia. On 11 August a*, the subject developed severe disseminated intravascular coagulopathy. The investigator removed the events deep vein thrombosis secondary to prolonged hospitalisation, abdominal wall hematoma secondary to surgical insertion of gastrostomy tube and treatment with morphine due to abdominal pain.

Investigator text:

Pt was brought in to the ER for abd pain x several days. She was given morphine IV for the pain but developed respiratory depression because of it, hence, she was intubated. Pt
now in ICU. Pt is withdrawn from the study as of 08Aug a*, per PI's discretion. Pt's condition worsened (this happened after the IP was stopped). Pt developed complications, the family did not want her to be resuscitated on her second code, she then expired on the 12th of August. -

Protocol Id: ING114467
Investigator Number: 088550
Subject Number: 006772
Treatment Number: 3058
Case Id: Z0009709A
Suspect Drugs: Atripla
Serious Events: Meningitis cryptococcal

This 42-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product per day from 25 April 2006.

Medical conditions at the time of the event included acquired immune deficiency syndrome (AIDS). The subject has been experiencing some signs and symptoms of immune reconstitution syndrome since investigational product was started (investigator confirmed this did not meet SAE criteria). Concomitant medications included sodium chloride and vancomycin.

On 24 May a*, 29 days after the start of investigational product, the subject developed grade 2 or moderate cryptococcal meningitis. On 23 May a*, the subject experienced headache, nausea/vomiting, high blood pressure secondary to pain and was started on Phenergan suppositories without any improvement. Cryptococcal antigen test performed on 25 May a* was positive. The subject was hospitalised. The subject was treated with fluconazole and amphotericin. The subject presented to the ER on 19 June a* with recurrent signs and symptoms of cryptococcal meningitis (headache, nausea/vomiting, high blood pressure secondary to pain) and was admitted to hospital for management of symptoms. The subject was discharged on 21 June a*. The subject presented at the ER again on 06 July a* with headache and altered mental status, and was re-admitted. Head CT performed on 06 July a* revealed area of low density in left anterior frontal lobe. MRI performed on 07 July a* showed "scattered areas of oedema with associated parenchymal and meningeal enhancement and lack of diffusion restriction most consistent with cerebritis and meningitis. The largest enhancing lesion is in the left posterior temporal lobe with 1.5 cm rim enhancement, possibly early abscess formation. The greatest degree of oedema and meningeal enhancement is in the medial left frontal lobe which corresponds to the CT abnormal". The subject was treated with further fluconazole. Treatment with blinded trial medication-viiv was continued. The event resolved on 03 November a*. The investigator considered that there was no

a*: The year
reasonable possibility that the cryptococcal meningitis may have been caused by investigational product.

Follow-up information received on 14 July a*:

Subject remains in hospital for IV diflucan. Clinically improving. Repeat head CT/MRI pending.

Follow-up information received on 02 August a*:

Subject remains in hospital for IV diflucan. Clinically improving. Repeat head CT/MRI pending. RESULTS: MRI 28JUL a*-marked improvement in the areas of cerebritis compared to 7/17.

Follow-up information received on 05 December a*:

MRSA and renal failure occurred during the hospitalization and were treated

Follow-up information received on 01 February b* via query response:

MRSA and renal failure do not meet seriousness criteria. Normal saline was given to treat the renal failure, however it's primary indication was as a pre-med for the amphotericin.

Diagnostics:

Cryptococcal antigen test 05/25/a* - + CT brain 06JUL a* MRI brain 07JUL a*

Investigator text:

pt has been experiencing some s/s of immune reconstitution syndrome since meds started. on may23, reported that vomiting had started, and headache continues, started phenergan suppositories and asked pt to call next day. call from pt reveals no improvement in s/s. Dr. [deleted] sent pt to have crypto test done since s/s not resolving. Test results=+. Had pt present to research centre this morning for assessment. Pt admitted for further workup and treatment of cryptococcal meningitis. pt presented to ER on 19JUN a* with recurrent s/s of cryptococcal meningitis (headache, nausea/vomiting, high blood pressure secondary to pain) admitted to hospital for management of symptoms. subject was dc'd 21JUN a*. This will not be reported separately as the SAE has already been reported. If htn persists after resolution of headache, we will add a new ae at that time. discussed with Dr. [deleted]. Pt presented to the ER again on 6JUL a*, with headache, altered mental status. re-admitted. Head CT reveals area of low density in left anterior frontal lobe. MRI done. "Scattered areas of edema with associated parenchymal and meningeal enhancement and lack of diffusion restriction most consistent with cerebritis and meningitis. the largest enhancing lesion is in the left posterior temporal lobe with 1.5 cm rim enhancement, possibly early abscess formation. The greatest degree of edema and
meningeal enhancement is in the medial left frontal lobe which corresponds to the CT abnormal -

Protocol Id: ING114467
Investigator Number: 088550
Subject Number: 006775
Treatment Number: 3072
Case Id: Z0010288A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Mycobacterium avium complex infection, Pneumonia

This [21]-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product per day from 27 May 

On 27 June a*, 31 days after the start of investigational product, the subject developed grade 2 or moderate cavitation pneumonia and grade 2 or moderate mycobacterium avium infection. On 28 June a*, the subject reported fever, cough, back pain and aches. Chest X-ray showed pneumonia and the subject was given prescription for antibiotics. He worsened that day and was hospitalised. Chest X-ray showed 4 cm right lung opacity. The subject was treated with levofloxacin and ceftriaxone sodium. Treatment with blinded trial medication-viiv was continued. The cavitary pneumonia resolved on 31 July a*. On follow-up on 08 July a* the subject was afebrile with a persistent cough. Per the investigator's exam, MTB PCR negative; the investigator strongly suspected immune reconstitution syndrome and atypical mycobacterium causing cavitary pneumonia/mediastinal LAD. On 31 December a*, the mycobacterium avium complex infection had resolved.

The investigator considered that there was no reasonable possibility that the cavitation pneumonia and mycobacterium avium infection may have been caused by investigational product.

Follow-up information received from Clinical team on 01 July a*:

The patient called the research centre on the 2nd July with complaints of cough back ache and fever. He presented to the clinic on the morning of the 28th June for a chest X-ray. The intent was to treat the patient on an outpatient basis for pneumonia. Patient called investigator again that afternoon with complaint of feeling worse, and getting no better, very worried. He was admitted on that evening.

Patient is a known Type II diabetic with poor glycemic control. Patient reports a history of: seasonal allergies, headaches, diabetes, constipation, right leg pain, oral thrush and an appendectomy in u*.

a*: The year
u*: 21 years ago
The investigator ordered additional sputum tests, and will defer a treatment decision until next week when those are received. In the interim, patient will be continued on bactrim ds, azithromycin and diflucan. He will return to research next Friday for follow up, review of pending sputum results, and a decision about removing him from the study so he can receive treatment for TB.

Follow-up information received on 25 July a* via query response:

Yes he will continue [in the study], TB has been ruled out, so treatment will not be initiated.

Follow-up information received 21 May b* via answered query report response:

The investigator confirmed the event immune reconstruction syndrome was not a serious adverse event.

Diagnostics:

Chest x-ray 06/28 a*=pneumonia; 30JUN a* Sputum AFB=+ ; 01JUL a* Sputum AFB=+ ; 01JUL a* Sputum MTB = negative; 28JUL a* Histoplasma AG =<2.0= negative. 29JUN a* Blood AFB= negative no other relevant labs

Investigator text:

28JUN a* pt reported that he has had fever, cough, back pain and aches. sent for CXR, + pneumonia, given prescription for antibiotics. Worsened that day, presented to hospital per Dr. [deleted] order for admission. CXR reveals 4cm Right lung opacity. H&P states question of immune reconstitution syndrome. Pt with hx of diabetes. Sputum cultures done. AFB present. TB precautions instituted. Additional more specific cultures obtained and sent. Pt. improved and was discharged home to await further culture results. 07JUL a*, results received, MTB negative in sputum. Blood cultures negative. Pt was seen at the Research Center on 08JUL a* in follow up. Afebrile, persistent cough. Per Dr. [deleted] exam. "MTB PCR negative. Strongly suspect immune reconstitution syndrome and atypical mycobacterium causing cavitary pneumonia/mediastinal LAD" -
This 21-year-old male subject was enrolled in an open-label study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 29 March.

On 17 May, 49 days after the start of investigational product, the subject developed grade 3 or severe acute appendicitis. The subject was hospitalised. The subject was treated with morphine, ondansetron hydrochloride and ertapenem sodium. Treatment with blinded trial medication-viiv was continued. The event resolved on 18 May. The investigator considered that there was no reasonable possibility that the acute appendicitis may have been caused by investigational product.

Diagnostic assessment:

CT Abdomen & Pelvis diagnosis acute appendicitis

Investigator text:

Patient admitted to Baylor ER 3:15 am May 17, a* with nausea, vomiting and abdominal pain that had worsened over the past several hours of the day. Diagnostic testing revealed Acute Appendicitis. Surgical removal without complications. Patient discharged from Baylor at 10:20 am May 18, a* No relevant past medical history indicating problems with appendix.

- Protocol Id: ING114467
- Investigator Number: 088551
- Subject Number: 006780
- Treatment Number: 2246
- Case Id: Z0009103A
- Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
- Serious Events: Viral infection

This 21-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 01 April.

The subject was randomized to receive GSK1349572+Epzicom/Kivexa once daily.

Concomitant medications included Maalox and metoprolol.

On 20 April, 19 days after the start of investigational product, the subject developed grade 1 or mild viral illness. The subject presented to the ER on 20 April a* with a fever of undetermined origin, vomiting, nausea, hypotension and volume depletion. The subject was hospitalised. Laboratory test results dated 20 April a* included ALT 41

a*: The year
U/L (NR 10-40), AST 85 IU/L (NR 13-40), blood pressure 111/68 mmHg, haemoglobin 11.6 g/dl (NR 12-15), lymphocytes 0.4 k/ul (NR 1.1-3.9), MCHC 32.5 g/dl (NR 33-35), MCH 26.1 pg (NR 27-33) and platelets 140 K/ul (NR 150-450). The subject was treated with ondansetron hydrochloride, ceftriaxone sodium, paracetamol, sodium chloride and tramadol hydrochloride. Treatment with blinded trial medication-viiv was continued. The event resolved on 22 April a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the viral illness may have been caused by investigational product.

Diagnostics:

Chest X-ray result normal, Abdominal Ultrasound result normal. UA reported as "somewhat dirty but asymptomatic". Culture not reported in Hospital records but sb. not treated for UTI. Ultrasound reported "contracted gallbladder" due to non fasting status. Subject has not had a repeat abdominal sono.

Investigator text:

Patient presented to ER 4-20-a* with fever of unknown origin, vomiting, nausea, hypotension and volume depletion. Admitted to hospital and given IV fluids, Odansetron, Rocephin and Acetaminophen. Improved and released 4/22/a*.

This 21-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product at 1 tablet per day from 24 March 2018.

On 09 July a*, 107 days after the start of investigational product, the subject developed grade 2 or moderate facial abscess. The subject reported his face started to hurt and swelling gradually increased from 09 July a*, and oozing from 11 July a*. At week 16 visit on 12 July a*, physical examination revealed swollen chin, warm to touch, painful and draining. The subject was hospitalised. The subject was treated with vancomycin and Bactrim. Treatment with blinded trial medication-viiv was continued. The event resolved on 15 July a*. The investigator considered that there was no reasonable possibility that the facial abscess may have been caused by investigational product.

Diagnostics:
grams stain reported 2+ gram positive cocci, 1 + wbc's, culture- scanty growth of methicillin resistant staph aureus, blood cultures negative at 3 days

Investigator text:

Patient presented to the office for his routine week 16 visit. on physical exam, chin was swollen, warm to touch, painful and draining. patient being admitted for work up for abscess and have an I&D performed patient stated he face began to hurt and swelling gradually increased from the 09 jul a* to 12 jul a* when the patient was seen. He states it was oozing since 11 jul a* -

Protocol Id: ING114467
Investigator Number: 081279
Subject Number: 006798
Treatment Number: 2317
Case Id: Z0014687A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Cerebrovascular accident

This 45-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 12 April.

The subject was randomized to receive GSK1349572+Epzicom/Kivexa once daily.

On 04 March b*, 327 days after the start of investigational product, the subject developed grade 2 or moderate cerebral vascular accident. The subject was hospitalised. Treatment with blinded trial medication-viiv was continued. The event resolved on 09 March b*. The investigator considered that there was no reasonable possibility that the cerebral vascular accident may have been caused by investigational product.

Follow-up information received on 20 April b* via answered query report:

Subject under a CT scan which confirmed the final diagnosis. Symptoms included left-sided weakness and an episode of sudden loss of vision and dizziness. Positive light-headedness and dizziness without syncope or palpitations. Relevant risk factors include age, hypertension, dislipidemia and hypothyroidism. Treatment included optimize blood pressure, resume diovan, norvasc, atenolol, subject to continue statin. Optimize synthroid.

Investigator text:
Patient presented to office for routine week 48 visit on 03/15/b*. Patient informed us she was admitted to a local hospital for 5 days due to stroke. She states is fully recovered. Patient signed release of medical records. Waiting for hospital chart -

Protocol Id: ING114467
Investigator Number: 081274
Subject Number: 006806
Treatment Number: 4158
Case Id: Z0015587A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Febrile neutropenia

This 26-year-old male subject was enrolled was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 26 April.

The subject was randomised to receive GSK1349572+Epzicom/Kivexa once daily.

The subject has no previous history of neutropenia or any known risk factors. Concomitant medications included paracetamol.

On 19 May a*, 23 days after the start of investigational product, the subject developed grade 3 or severe febrile neutropenia. The subject presented to hospital with fever, body aches, nausea and dizzy spells. The subject was hospitalised. Laboratory test results showed neutrophils 0.13x10^3 (normal range 1.5-8) on 20 May a* and 0.31x10^3 on 22 May a*. The subject was treated with cefepime, vancomycin, oxycodone, Amoxicillin + clavulanate K and ciprofloxacin. Treatment with investigational product was continued. The event resolved on 23 May a*. Blood re-test performed on 25 May a* showed neutrophils of 2.7x10^3 (normal range 1.8-7.7). The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by investigational product.

Diagnostics:

Chest x-ray-no findings, Brain MRI-normal exam, CT of facial bones-no osseous change involving bones of the face or mandible. Absolute neutrophil count 300. Pending tests: EBV, CMV, HHV6, Parvo testing, On 5/22/a* Subject EBV positive(test not listed above). All other tests listed in this comment section negative

Follow-up information received on 22 May a* via email from clinical study team:

The subject had been admitted to hospital for fever w/u and was noted to be neutropenic on admission. The subject's ANC on admission was 40 and that he did not have an

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*a*: The year
*b*: Following year
infiltrate on chest X-ray (was simply atelectasis). His admit blood cultures were negative and he responded to fluids (did not require pressors). The admitting team had decided to hold his antiretrovirals. He was also started on cefepime. The subject had defervesced on the cefepime. It was noted that the subject complained of dizziness prior to admission, which had resolved with IVF. He was noted to have lymphadenopathy in the groin on admission. In the morning of 22 May a*, the subject looks well and his blood cultures remain negative. The neutrophil count is up to 300, but he remains neutropenic. The attending physician was inclined to think that the subject's syndrome may be due to a viral aetiology (ordered EBV, CMV, parvovirus PCRs etc.). Haematology saw the subject this AM and felt that his neutropenia was most likely related to an infection, not a malignancy with drug effect on the differential. They have recommended a bone marrow biopsy. Subject has currently declined.

In reviewing subject's lab results for the SINGLE study - he had a neutrophil count on the low end of normal at 2001 on screening. His most recent neutrophil count was again at the low end of normal at 2260 (this was Week 48 visit on 28 March a*).

Follow-up information received on 31 May a* from investigator via clinical study team email:

The investigator spoke with the subject on 31 May a*, who told the investigator that his bone marrow biopsy was cancelled because his WBC count was back to normal. At the time of reporting the investigator was waiting for verification from the [deleted] system for the WBC and ANC results. The subject assured the investigator that he did not miss a single dose of his antiretrovirals while hospitalized. He stated that he was afebrile and felt fine.

Therefore the event-study drug causality was changed from yes to no by the investigator as he/she believed the event febrile neutropenia was not caused by the subject's study drugs.

Investigator text:

Patient presented to hospital with fever, body aches, nausea and dizzy spells. Was diagnosed with neutropenic fever. No previous episodes of neutropenia or known risk factors -

Protocol Id: ING114467
Investigator Number: 088547
Subject Number: 006854
Treatment Number: 2361
Case Id: Z0013893A
Suspect Drugs: Atripla
Serious Events: Scrotal abscess
This 45-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 19 April.

On 17 January b*, 273 days after the start of investigational product, the subject developed grade 3 or severe scrotal wall abscess. The subject presented with swelling in groin area but no fever or chills. The subject was hospitalised. Laboratory test results dated 24 January b* included hematocrit 38.8% (normal range 40-52), haemoglobin 13 g/dl (normal range 13.5-18), red blood cell count 3.91 M/ul (normal range 4.5-6). The subject had the scrotal abscess drained surgically on 25 January b* with no complications. The subject was treated with vancomycin, linezolide, Senokot, fentanyl, morphine, lorazepam, ondansetron hydrochloride, labetalol hydrochloride, hydralazine, salbutamol sulphate, diphenhydramine hydrochloride, Percocet, paracetamol, piperacillin sodium, enoxaparin, tramadol hydrochloride and tamsulosin hydrochloride. Treatment with blinded trial medication-viiv was continued. The subject was discharged on 27 January b*. The event resolved on 15 February b*. The investigator considered that there was no reasonable possibility that the scrotal wall abscess may have been caused by investigational product.

Follow-up information received via query response on 01 February b*:

Subject was released from hospital on 27Jan b*. PI does not feel SAE is resolved.
Subject is to start wound care 01Feb b*.

Follow-up information received on 22 March b* via query response:

Per PI, the SAE is the only one involved. Some of the things listed at discharge were a contributing issues that led to the SAE including the patients past medical history.

Diagnostics:

Patient was out of town in Dallas and presented to ER on 20Jan b* with complaint of swollen area in groin. It was noted that patient did have swelling in groin area. Patient did not have fever or chills. Patient was positive for erythema. Patient is tachycardic. Exam shows no apparent injury to the area. Abdomen appears normal. Abscess is noted and drainage is not noted. Outpatient treatment with Bactrim and Rifampin is suggested with the patient to return to ER if no changes or increasing changes within 24 hours. Patient returns to ER within 3 hours and wants to be admitted. Patient is admitted. Testicular Sonogram performed on 01/24/b*. Impression- Left scrotal wall abscess, bilateral hydroceles, 0.5 cm benign cyst lower pole right testicle. Patient went into surgery on 01/25/b* for the incision and drainage of the scrotal wall and which time a wound culture was taken which later revealed methicillin-resistant staphylococcus. He was given oral Zyvox for ten days to treat this.

b*: Following year
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Investigator text:

20Jan b* Multiplanar grayscale imaging of scrotum and testicles-findings show inflammatory changes in the base of the scrotum consistent with cellulitis with possible developing abscess. 21Jan b* Pelvis CT with contrast, findings consistent with scrotal cellulitis with small abscess. All other procedures of this type all verified scrotal cellulitis. Patient had scrotal abscess drained surgically on 25Jan b* with no complications and discharged on 27Jan b* with diagnosis of sepsis syndrome, methicillin-resistant Staphylococcus aureus scrotal abscess with cellulitis, transient urinary retention, and HIV and a condition at discharge of stable and improved.

Protocol Id: ING114467
Investigator Number: 088551
Subject Number: 006861
Treatment Number: 1042
Case Id: Z0010978A
Suspect Drugs: Atripla
Serious Events: Pneumonia, Sepsis

This 37-year-old female subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 18 May.

The subject's past medical history included recurrent pneumonia and tuberculosis. Medical conditions at the time of the event included chronic asthma. Concomitant medications included noradrenaline acid tartrate, nicotine, nystatin, levosalbutamol, fluconazole, valaciclovir hydrochloride, pantoprazole, heparin, enoxaparin and cyclobenzaprine hydrochloride.

On 07 August a*, 81 days after the start of investigational product, the subject developed grade 4 pneumonia and grade 4 sepsis. The subject presented at the ER on 07 August a* with fever, tachycardia, pain, nausea, vomiting and cough. Chest x-ray revealed pneumonia. The subject was treated with vancomycin, paracetamol, ondansetron hydrochloride, meropenem, morphine, magnesium hydroxide, bisacodyl, salbutamol sulphate, ipratropium bromide, levofloxacin, Hydrocodone/apap, potassium bicarbonate, potassium chloride, sodium chloride, Bactrim DS and methylprednisolone sodium succinate. Treatment with investigational product was continued. The events resolved on 13 August a* and the subject was discharged in a stable condition on oral antibiotics. The investigator considered that there was no reasonable possibility that the pneumonia and sepsis may have been caused by investigational product.

Additional information from email received 02 December a*:

a*: The year
b*: Following year
Before [the subject] enrolled into the study she had renal problems in January of this year. She had proteinuria 3+ and it was noted that she was probably developing HIV associated nephropathy. She also has a past Hx of drug abuse with crack cocaine.

Diagnostics:

Chest X-ray, indication fever. Diagnosis pneumonia. Urinalysis, normal except Protein Pos 2+; Ketones trace, blood trace. MRSA PCR - Positive. Ultrasound for line placement only.

Investigator text:

The patient arrived in the ER the night of 8/7/a* with 104.5 fever/tachycardia/pain/nausea/vomiting and cough. Chest x-ray revealed pneumonia. Patient was also diagnosed 8/8/a* with Sepsis. Placed on oral and IV antibiotics. On 8/13/a*, the patient was deemed stable and discharged home on oral antibiotics.

Protocol Id: ING114467
Investigator Number: 081203
Subject Number: 006870
Treatment Number: 4196
Case Id: Z0011440A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Subdural haematoma

This 9-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 10 June.

The subject's past medical history included hypertension aggravated, hyponatremia and respiratory failure. Concomitant medications included hydromorphone hydrochloride and ondansetron hydrochloride.

On 27 July a*, 47 days after the start of investigational product, the subject suffered a trauma (was attacked with a pipe) and developed grade 4 subdural hematoma. The subject was hospitalised. The subject was treated with phenytoin. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The event resolved on 26 August a*. The investigator considered that there was no reasonable possibility that the subdural hematoma may have been caused by investigational product.

Diagnostic Results:

CT Head without contrast (26JUL a*): Blunt trauma to head with left acute subdural hematoma, minimal mass effect and minimal right-sided shift. (27JUL a*): increasing...
thickness of left subdural hematoma, increasing subfalcine shift to the right. (28JUL a* and 29JUL a*): No change. (03AUG a*): increasing size of the left-sided subdural hematoma, 12mm subfalcine shift to the right together with left transtentorial herniation. (03AUG a* & 05AUG a*): stable postoperative CT scan of the head. (09AUG a*): reaccumulation of subdural hematoma on the left with worsening subfalcine shift and herniation. (10AUG a*): stable subdural hematoma on the left, subfalcine shift and transtentorial herniation remains the same. (11AUG a*): interval evacuation of left subdural hematoma, decreased subfalcine shift, decreased herniation. (15AUG a*): stable postoperative CT scan of the head with no change or increase in size of extra-axial collection on the left. Subfalcine shift is also stable.

Investigator Text:

Pt was hospitalized on 27 JUL a* after she was assaulted by a stranger while trying to walk to a nearby store. She was repeatedly hit on the head by a metal pole and suffered subdural bleeding. The pt underwent left craniotomy with drainage of the bleed and stayed in the hospital for 4 weeks; she was then transferred to a rehab facility and stayed there for 2 weeks. She was discharged to home today, 26 AUG a*. Pt took her last dose of study medications on 26 JUL a* (day before hospitalization). Subdural evacuating pole system was placed on 03 AUG a*.

Protocol Id: ING114467
Investigator Number: 088625
Subject Number: 006920
Treatment Number: 2515
Case Id: Z0012189A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir, Lisinopril
Serious Events: Angioedema

This 16-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 30 May. Concomitant medications included lisinopril and famotidine.

On 07 October a*, 130 days after the start of investigational product, the subject developed grade 3 or severe angioedema. The subject awoke to right side facial swelling, worsening over a few hours. The subject presented to the ER and was hospitalised. The subject was treated with lorazepam, diphenhydramine, methylprednisolone and racepinephrine. Treatment with blinded trial medication-viiv was continued. The subject was discharged on 09 October a* on oral Benadryl, with swelling almost resolved. The event resolved on 12 October a*. The investigator considered that there was no...
reasonable possibility that the angioedema may have been caused by investigational product and that the event was possibly due to the concomitant medication, lisinopril.

Investigator text:

Awoke to right side facial swelling 07Oct a*, worsening over a few hours, went to the Emergency room. Angioedema felt to be related to lisinopril, which was discontinued. treated with Benadryl, Methylprednisolone, and Famotidine. Discharged, 09Oct a*, with swelling almost resolved, on oral benadryl. To follow-up in clinic in a few days. Subject states did not miss any dose of study medication. -

Protocol Id: ING114467
Investigator Number: 081186
Subject Number: 006927
Treatment Number: 2503
Case Id: Z0011863A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Non-cardiac chest pain

This -year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 23 May.

Medical conditions at the time of the event included coronary artery disease. The subject had visits to ER for chest pain in the past that were due to anxiety. The subject had anxiety attacks in the past.

On 20 September a*, 120 days after the start of investigational product, the subject developed grade 3 or severe non-cardiac related chest pain. The subject presented to ER due to chest pain to the left anterior which was present for about three hours. There was some association with positional changes and severity of pain. The subject denied fevers, vomiting, diaphoresis, cough or shortness of breath. Electrocardiogram did not demonstrate any significant changes; troponins were normal. The subject was hospitalised for further evaluation of pain. The subject was treated with lorazepam. Treatment with blinded trial medication-viiv was continued. The event resolved on 21 September a* and the subject was discharged in a stable condition. The investigator considered that there was no reasonable possibility that the non-cardiac related chest pain may have been caused by investigational product.

Follow-up information received on 29 September a*:

The initially reported SAE Ventricular Thrombus was deleted by investigator on 29 September a*. The physician confirmed that this condition is part of the subject's
medical history. No SAE occurred at this time; no exacerbation. Hospital records were unclear

Diagnostics:

Drug screen positive for THC, opiates. EKG, CXR unchanged. Troponins levels were all normal.

Follow-up information received on 03 October a* from Medical monitor:

Regarding this subject it was felt that the elevated CPK values were not cardiac related. Cardiac enzymes and POC Trophin done in the past since his MI have been negative multiple times. CKMB and Trophin tests done recently were WNL. Several ER visits for chest pain were felt to be due to anxiety which the subject does experience and has had anxiety attacks in the past. He has been seen by a cardiologist and will continue to do so. Unfortunately we do not have any history of past CPK values.

It is possible that the elevated CPK values can be related to statin use as he has been on a statin since his MI on 6/21/f* status post angioplasty and 3 stents placement.

He was on Crestor and is not on Pravastatin. Another area that will be evaluated is his thyroid. A TSH test will be done next week.

The subject does not work out and is not having any muscle problems. He does not take any supplements of any kind or power drinks.

Regarding his past history of MI (6/21/f*), the subject states that he was told contributing factors were, past history of hypertension, and past history of cocaine and alcohol use, and smoking. There is also a family history of father with hypertension and CAD, and a brother and sister both who have had a CVA. Subjects states he no longer uses cocaine. He does still take alcohol socially. He no longer smokes.

Regarding the recent positive tox screen he does admit to intermittent use of marijuana but states he has not used any pain medications/narcotics or social drugs, no cocaine, and had not eaten any foods/drinks with poppy seeds prior to his hospitalization. He did used Valium and Flexeril once or twice for anxiety within the two weeks before his hospital admission.

Investigator text:

- year-old gentleman with a history of coronary artery disease presents to the emergency department because of chest pain to the left anterior, present for about three hours. There is some association with positional changes and severity of pain. Denies fevers, vomiting, diaphoresis, cough, shortness of breath. He is on Coumadin because of a history of intracardiac thrombus. Electrocardiogram did not demonstrate any significant changes. His troponins were all normal. Admitted to the internal medicine service for further evaluation of his pain. Update: Sept. 27, a*. Patient was discharged in stable

a*: The year
f*: 2 years ago

* 新薬承認情報提供時に置き換え

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condition from the hospital on Sept. 21, a* with chest pain resolved and determined non cardiac. Left Ventricular thrombus was resolved. Patient to follow up with cardiology for consideration of AICD placement as outpatient.

Update: Sept. 30, a*: Correcting the information given in the update of Sept. 27, a*. The discharge note to the patient listed the Left ventricular thrombus as resolved, however that was not recent, it was part of the patient's past history. This was confirmed with the patient's PCP. It was therefore deleted from this SAE. Update Oct. 5, a* Patient has had ER visits for chest pain in the past that were felt to be due to anxiety which patient admits to having and has had anxiety attacks in the past. Patient was discharged on Lorazepan for anxiety.

Protocol Id: ING114467
Investigator Number: 081179
Subject Number: 006929
Treatment Number: 2526
Case Id: Z0010132A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Drug hypersensitivity

This [ ]-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product at 1 tablet per day from 03 June [ ] to 14 June a*.

The subject was randomized to GSK1349572+Epzicom/Kivexa once daily.

On 04 June a*, one day after the start of investigational product, the subject developed grade 2 or moderate possible abacavir hypersensitivity reaction. The event was clinically significant (or requiring intervention). The subject developed sore and swollen throat on 04 June a* and stopped investigational product after dose on 05 June a*. She didn't take any investigational product from 06 to 13 June a* and the symptoms resolved. The subject then took another dose on 14 June a* and the symptoms swollen & scratchy throat, diarrhoea, nausea, fatigue, cough and fever reappeared. Treatment with blinded trial medication-viiv was discontinued on 14 June a* and the subject was withdrawn from the study. The event resolved on 14 June a*. The investigator considered that there was a reasonable possibility that the possible abacavir hypersensitivity reaction may have been caused by investigational product and that the event was possibly due to study participation.

Follow up information received 22 July a*:

No antihistamines were taken to resolve symptoms.

Follow-up information received 23 February b*:

The subject's HLA-B* 5701 status was negative at screening.

a*: The year
b*: Following year
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Follow-up information received on 19 March b*:

It is related to the ABC not the dolutegravir.

Follow-up information from answered query received 27 March b*:

The SAE was RELATED to the Abacavir not the Dolutegravir.

Investigator text:

Patient started study medications on 06/03/a*. On 06/04/a* she c/o sore & swollen throat. Pt stopped study medication after dose on 06/05/a*. no study medications taken 06/06/a* - 06/13/a*. symptoms resolved. she then took another dose on 06/14/a* and sxs reappeared (swollen & scratchy throat, diarrhoea, nausea, fatigue, cough, fever (not quantified). Patient did not take any more study medication after that and symptoms resolved. Patient did not call our office during these sxs. she came in to office on 06/16/a* for routine week 2 visit and informed us of these symptoms at that time. Due to multiple sxs - ABC HSR can not be ruled out.

Protocol Id: ING114467
Investigator Number: 086936
Subject Number: 007796
Treatment Number: 2287
Case Id: Z0013942A
Suspect Drugs: Atripla
Serious Events: Gastroenteritis

This □-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 11 April □.

Medical conditions at the time of the event included insulin dependent diabetes mellitus. Concomitant medications included human insulin and insulin.

On 22 January b*, 286 days after the start of investigational product, the subject developed grade 2 or moderate acute gastroenteritis. The subject was hospitalised on 25 January b* with a 3-day history of diarrhoea (10 stools a day) and diagnosed with acute gastroenteritis without microbiological diagnosis. The subject was treated with metoclopramide, paracetamol, pantoprazole, dextrose and physiological electrolyte solution. The subject also experienced symptomatic hypoglycaemic episodes during hospitalization. Treatment with blinded trial medication-viiv was continued. The event resolved on 02 February b*. The investigator considered that there was no reasonable possibility that the acute gastroenteritis may have been caused by investigational product.

*a*: The year
*b*: Following year
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Investigator text:

The patient who is insulin dependent diabetic was admitted with the diagnosis of acute gastroenteritis and during hospitalization for several episodes of hypoglycemia are not justified. alparecer the patient is not put insulin at home and also that these episodes occurred. The patient was diagnosed with insulin dependent diabetes mellitus. She is admitted in hospital on January 25, b* to present 3 days before diarhoea (10 stools a day). While in hospital presents symptomatic hypoglycemic episodes. After asking detailed take insulin means not scheduled in the last year because of poor tolerance.

Protocol Id: ING114467
Investigator Number: 086971
Subject Number: 007817
Treatment Number: 2367
Case Id: Z0015054A
Suspect Drugs: Atripla
Serious Events: Ectopic pregnancy

This -year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 20 April.

On 09 April b*, 355 days after the start of investigational product, the subject developed grade 3 or severe abortion induction due to tubal pregnancy. The subject complained of abdominal pain, vaginal bleeding and delayed menses. Pregnancy test was positive on 09 April b* (previous test on 22 March b* had been negative). The subject suffered potentially lethal tubal pregnancy. The subject was hospitalised and underwent methotrexate-induced abortion on 10 April b*. The subject was also treated with diclofenac, ibuprofen, dipyrone and paracetamol. Treatment with blinded trial medication-viiv was interrupted on 09 April b* and restarted on 13 April b*.

New gonadotropin tests were due on 16 April b*. If levels were increasing, new dose of methotrexate was planned. The event resolved on 17 April b*. The investigator considered that there was no reasonable possibility that the abortion induction due to tubal pregnancy may have been caused by investigational product.

Follow-up information received via email from medical monitor:

The subject was to remain in the study, and not withdrawn. Date of restarting study drug was pending at time of this report.

Follow up information received via paper pregnancy notification form on 18 April b*:

b*: Following year
The subject's medical history included one spontaneous abortion. The subject's last menstrual period was 10 February b*.

Follow up information received via paper pregnancy notification form on 26 April b*:

The subject had no previous pregnancies.

Diagnostics:

Blood beta chorionic gonadotrophin performed in the hospital (ECLIA) 586 mUI/mL (reference range for 5 weeks pregnancy 217-7138. Ultrasound showing adnexal mass. Date of last menses: 8 Feb.b*

Investigator text:

The patient complained abdominal pain, vaginal bleeding and delayed menses. On 9.abril, positive pregnancy test in urine (the blood test of the study drawn on 22.march b* had been negative. Termination with methotrexate is being attempted; new gonadotropin tests are due on 16th April. If increasing, new dose of methotrexate will be administered. -

Protocol Id: ING114467
Investigator Number: 086925
Subject Number: 007835
Treatment Number: 2183
Case Id: Z0013894A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Meningitis

This ■-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 25 March ■.

On 20 January b*, 301 days after the start of dolutegravir and investigational product, the subject developed grade 2 or moderate meningitis. The subject experienced headache and fever. The subject was hospitalised. A lumbar puncture carried out on 20 January b* showed 554 cells with 90% polymonuclear cells and 10% mononuclear cells. Total proteins 189, glycrrrhachia 72.3 for glucose 168. The subject was treated with ampicillin trihydrate, acyclovir, ceftriaxone, amitriptyline, paracetamol and ibuprofen. Treatment with blinded trial medication-viiv was continued. The event resolved on 04 February b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the meningitis may have been caused by investigational product.

Diagnostics:
Cranial computerized tomography: normal. X-Ray: normal. A lumbar puncture was carried out on 20/JAN/b*

Investigator text:

Diagnosis: meningitis. Normal Cranial TC. A Lumbar puncture was carried out. 554 cells with 90% polynuclear cells and 10% mononuclear cells. Total proteins 189, glycorrachia 72.3 for glucose 168. Headache and pyrexia. Patient is going well and is discharge from hospital on 04/Feb/b*

Protocol Id: ING114467
Investigator Number: 086925
Subject Number: 007836
Treatment Number: 2240
Case Id: Z0014235A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Pneumonia

This 52-year-old male subject was enrolled in a Viiv-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 01 April.

Medical conditions at the time of the event included chronic bronchitis. Concomitant medications included salmeterol xinafoate.

On 12 February b*, 317 days after the start of investigational product, the subject developed grade 3 or severe pneumonia. The subject experienced high body temperature (39 degrees Celsius) and chest pain. The subject was hospitalised. Thorax X-ray showed right lower lobe density increased. The subject was treated with methylprednisolone, ceftriaxone, levofloxacin, salbutamol sulphate, paracetamol, cefuroxime sodium, dipyrone, ipratropium bromide and enoxaparin. Treatment with investigational product was continued. The event resolved on 17 February b*. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by investigational product.

Investigator text:

Patient with high temperature, 39°C and pain in torax. X ray with the right lower lobe density increased. Final diagnosis Pneumonia treated with IV antibiotic.
This 32-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from an unspecified date.

The subject previously had one elective abortion.

At an unknown time after the start of investigational product, the subject was found to be pregnant. An HCG test was positive. The method of contraception being used was condoms and the type of conception was normal. The subject's last menstrual period was on 02 February and the estimated date of delivery is on 10 November a*.

Treatment with blinded trial medication-viiv was discontinued on 27 March a* and the subject was withdrawn from the study.

**Protocol Id:** ING114467  
**Investigator Number:** 86924  
**Subject Number:** 6026  
**Treatment Number:** 2096  
**Case Id:** B0792666A  
**Suspect Drugs:** Atripla  
**Pregnancy**

This 32-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 16 March b* to 22 March b*.

The subject's past medical history included 1 previous normal birth. Concomitant medications included isoniazid. Previous medication history included Urbason, Certirizine, Propofol, Ferplex and Flu Vaccine.

At an unknown time after the start of investigational product, the subject was found to be pregnant. It was reported that the subject decided to stop using contraception by her own on an unknown date. The date of the subject's last menstrual period was 11 February b*. Treatment with blinded trial medication-viiv was discontinued on 22 March b*. The subject was exposed to the blinded trial medication-viiv prior to conception and during the first trimester. At the time of reporting the outcome of the pregnancy was unknown.

Follow up information received on 29 March b*:

a*: The year  
**b*: Following year
The investigator confirmed that the estimated date of delivery was November b*.

The subject's last menstrual period was confirmed as 11 February b*, the subject became pregnant the beginning of March b*.

This 34-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 18 March.

The subject's past medical history included two elective abortions and two normal births.

On an unspecified date after the start of investigational product, the subject was found to be pregnant. Her last menstrual period occurred in December a*. Treatment with blinded trial medication-viiv was discontinued on 23 February b* and the subject was withdrawn from the study. The subject was exposed to the investigational product before conception and during the first trimester. At the time of reporting, the outcome of the pregnancy was unknown. The estimated date of delivery was unknown at the time of reporting.

Follow-up information received on 29 March b*:

Pregnancy was confirmed on by blood test on 23 February b*. The investigator reported that the subject became pregnant at the end of December. The subject's last menstrual date occurred at the beginning of December (On 20 January b*, during the visit of week 40, the pregnancy blood test was negative). The estimated delivery date was estimated to be during September b*. At the beginning of March the subject received an echo and everything was normal, therefore the subject decided to continue the pregnancy.

Follow up information received on 02 October b*:

Concomitant medications include d Kaletra and Combivir.

The subject had a C-section on 03 September b* at 39 gestational weeks. The neonate was male and weighed 3.7 kg.
This [269x679]year-old female subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 27 April [204x638].

The subject's pregnancy history included three elective abortions and one normal birth.

On an unspecified date after the start of investigational product, the subject was found to be pregnant. Her last menstrual period occurred on 15 October a*.

Treatment with the investigational product was stopped on 21 November a*. The subject was exposed to the investigational product before conception and during the first trimester. At the time of reporting the pregnancy was ongoing. The estimated date of delivery was not provided.

Follow up information received on 09 December a*:

The pregnancy was confirmed on 23 November a*. The subject decided to have an elective abortion. There were no concomitant medications.

Follow up information received on 24 February b*:

The subject voluntarily aborted the baby in the early weeks of the pregnancy. The subject felt well some days after when she attended the study visit. The subject reported that everything during the intervention was ok. We have no more information about the event.

### 9.6.3.2. Cases Reported Between 05 June to 26 October

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the safety data lock point for both the ING114467 Week 48 CSR and the ISO outputs, through to the final 26 October safety data lock point for the ISS, and includes all initial reports and follow up information received by the company through 26 October. The data included here are not represented in the clinical study report included in m5.3.5.1, nor in the ISO Tables and Figures produced for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials database in preparation of these narratives.

Protocol Id: ING114467
Investigator Number: 081261

*a*: The year
*b*: Following year
This male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product once per day from 13 May.

At an unknown time after the start of investigational product, the subject was hospitalised in the psychiatric ward due to a psychotic break. Treatment with Atripla was interrupted. Outcome was unknown at time of reporting. The investigator considered that there was no reasonable possibility that the psychiatric hospitalization may have been caused by investigational product and was possibly related to crystal methamphetamine use.

Investigator text:

Pt was hospitalized in the psychiatric ward due to a psychotic break, possibly related to crystal methamphetamine use. Currently diagnosis, start and date and outcome are unknown. We are trying to obtain further details.

This [redacted]-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 02 March.

The subject's past medical history included polysubstance abuse.

On 29 August b*, 546 days after the start of investigational product, the subject developed grade 3 or severe congestive heart failure. The subject presented at the ER on 28 August b* with complaint of shortness of breath. The subject was hospitalised on 29 August b*. Treatment with blinded trial medication-viiv was continued. The event resolved on 01 September b*. The investigator considered that there was no
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reasonable possibility that the congestive heart failure may have been caused by investigational product.

Diagnostics:

Hospital records indicate the following: Echocardiogram performed on 28-AUG-b* showed severe cardiomyopathy with left ventricular apical thrombus. ECG performed 28-AUG-b*: sinus rhythm possible left atrial enlargement, poor R- wave progression

Investigator text:

Received message patient is hospitalized for Congestive Heart Failure. Hospital records pending subject presented to local Emergency Dept. on 28-AUG-b* with complaint of Shortness of Breath. He was found to have a positive toxicology screen for cocaine, amphetamine and PCP and was admitted for further work up on 29-AUG-b* -

Protocol Id: ING114467
Investigator Number: 081272
Subject Number: 005332
Treatment Number: 2035
Case Id: Z0015833A
Suspect Drugs: Atripla
Serious Events: Syncope

This 46-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 03 March .

The subject was randomized to receive Atripla once daily.

The subject had experienced an episode of syncope previously on 29 March b* which had been reported as a non serious adverse event.

On 05 June b*, 460 days after the start of investigational product, the subject developed grade 3 or severe syncope aggravated. The subject was hospitalised. Treatment with investigational product was continued. The event was unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the syncope aggravated may have been caused by investigational product and that the event was possibly due to study participation.

Follow-up information received on 06 August b* via query response:

b*: Following year
It is possibly related to study drug. The association with study medication cannot be ruled out. As per the Sub Investigator. The subject has been referred for Cardiology and Neurology assessment.

Follow-up information received on 26 September via answered query:

Subject was not taking any relevant concomitant medications. No details on any corrective therapy were provided.

Investigator text:

Patient was hospitalized for AE condition listed. No other information obtained other than history condition prior to 05 JUN related to study medication. Hospitalisation followed likely phlebotomy related light-headedness and syncopal episode suspicious for vaso-vagal response. Diagnosis will be further narrowed based on review of records being obtained from Neurologist but so far include vasovagal versus cardiogenic versus other neurogenic cause versus medication induced. -

Protocol Id: ING114467
Investigator Number: 081242
Subject Number: 005485
Treatment Number: 2211, 2211
Case Id: Z0016658A, Z0016658B
Suspect Drugs: Atripla
Serious Events: Cellulitis, Subcutaneous abscess

This [●]-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 29 March.

On 04 August, 494 days after the start of investigational product, the subject developed grade 3 or severe upper back cellulitis. The event was clinically significant (or requiring intervention). The subject was hospitalized on 04 August with initial diagnosis of cellulitis of right upper back. An ultrasound on affected area showed an abscess cavity of soft tissues of right upper back. Blood culture showed presence of staphylococcus aureus. The subject was treated with vancomycin, Bactrim, piperacillin sodium and mupirocin. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the upper back cellulitis may have been caused by investigational product.

Follow-up information received on 10 October via query response:
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Final diagnosis per hospital records is Cellulitis of the back

Investigator text:

Subject was hospitalized from August 4, b*, through August 8, b*. Initial diagnosis of cellulitis of right upper back. Subject had ultrasound on affected area and showed an abscess cavity of soft tissues of right upper back. A Blood culture was done and results showed presence of Staphylococcus aureus. We received final medical records that report patient received Vancomycin and Sozyn medication IV. However, no dosage was reported. At discharge pt was sent home with Bactrim DS PO BID for ten days and mupirocin 2% ointment for ten days. -

On 04 August b*, 494 days after the start of investigational product, the subject developed grade 2 or moderate skin abscess on back/trunk. The event was clinically significant (or requiring intervention). Treatment with blinded trial medication-viiiv was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the skin abscess on back/trunk may have been caused by investigational product.

Protocol Id: ING114467
Investigator Number: 087113
Subject Number: 005764
Treatment Number: 4138
Case Id: Z0017224A
Suspect Drugs: Atripla
Serious Events: VIIth nerve paralysis

This 50-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 14 April.

Medical conditions at the time of the event included human immunodeficiency virus.

On 16 August b*, 490 days after the start of investigational product, the subject developed grade 2 or moderate lateral facial paralysis. The subject was hospitalised. Treatment with investigational product was continued. The subject's brain MRI and lumbar puncture were within normal limits. The subject was treated with corticosteroid. The event improved on an unspecified date.

The investigator considered that there was no reasonable possibility that the lateral facial paralysis may have been caused by investigational product.

Follow up information received on 11 October b* via Answered Query Report:
b*: Following year
The subject did not have any relevant medical history.

Investigator text:

Hospitalisation in Germany 3 days for a left facial paralysis. Patient didn't experience fever; brain MRI was normal and so lumbar punction. Patient is currently receiving re-education.

Protocol Id: ING114467
Investigator Number: 084020
Subject Number: 005932
Treatment Number: 2169, 2169
Case Id: Z0016092A, Z0016092B
Suspect Drugs: Atripla
Serious Events: Depression, Depression

This 9-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 23 March.

The subject was randomized to receive Atripla once daily.

Medical conditions at the time of the event included clinical depression. Concomitant medications included citalopram (20 mg/day).

On 26 June b*, 461 days after the start of investigational product, the subject developed grade 3 or severe worsened depression. The subject was hospitalised on 26 June b*. The subject has not expressed feeling suicidal. The subject was treated with citalopram at an increased dose of 30 mg/day. Treatment with blinded trial medication-viiv was continued. The event resolved on 02 July b*. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by investigational product.

Follow-up information was received on 27 June b* via investigator's email:

June, 26th was the day of hospitalization.

June, 06th was the day of onset of signs for worsening of his underlying depression = Start date of AE "worsening of pre-existing ongoing medical history Depression".

He is under continuous concomitant psychiatric and psychological treatment since the start depression m*, and had been stable concerning his psychic condition when we ruled him into the SINGLE trial. Upon the start of worsening of the depression June, 6th...
the concomitant treatment was intensified with visits at both the psychiatrist and the psychologist on a weekly basis.

Signs and symptoms associated are those that are typically associated with worsening of depression: the subject complained that his emotions and feelings got worse, he felt more and more weak and sad all the time, getting up for work got harder and harder, everything looked black, no hope of improvement any more hospitalization had been discussed with the patient previously as we did not see any improvement though very intensive psychic treatment, and so on June, 26th he went for hospitalization. There was no real precipitating event. All he complained of was that he felt more and more incapable of doing his daily routine due to his depression. Upon several thorough request the subject had not expressed being suicidal.

Follow-up information received on 24 September b* via query response:

Subject is still in outpatient treatment, he continues to receive medication, he feels a little better.

Investigator text:

Pt is under concomitant psychiatrical and psychological treatment since the start of depression m*. concomitant treatment was intensified 06 June with visits at both the psychiatrist and the psychologist on a weekly basis. as we did not see any improvement though very intensive psychic treatment, June 26 he went for hospitalization. the subject had not expressed being suicidal. -

Medical conditions at the time of the event included clinical depression. Concomitant medications included venlafaxine hydrochloride, mirtazapine and folic acid.

On 10 July b*, 475 days after the start of investigational product, the subject developed grade 3 or severe worsened depression. The subject was re-hospitalised due to lack of improvement of depression. The subject was treated with citalopram, mirtazapine and venlafaxine hydrochloride. Treatment with blinded trial medication-viiv was continued. The event resolved on 21 September b*. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by investigational product.

Follow-up information received on 08 August b* via clinical study team:

Subject has been in our office today for Study Visit 13 week 72, he is still hospitalized for the reason of his psychiatric disorder.

His therapy regime is as following: Citalopram 40 mg/d Start 18.07.b*- ongoing; Mirtazapin 45 mg/d Start 18.07.b*- ongoing.

Conmeds stop:- Citalopram 30 mg/d Start 27.06.b*- 17.07.b* - Citalopram 20 mg/d Start 25.10.e*- stop: 26.06.b*

b*: Following year
e*: Last year
m*: 9 years ago
Accompanied by psychiatric therapy two times a week.

Physical exam: no findings, no new symptoms.

Follow-up information received on 24 September b* via query response:

Subject feels better, subject is still in outpatient treatment

Investigator text:

re-hospitalization due to lack of improvement of depression Patient is still in the hospital, he gets two times a week psychotherapy

Protocol Id: ING114467
Investigator Number: 084011
Subject Number: 005940
Treatment Number: 002102
Case Id: B0835064B
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Abortion spontaneous

This 31-year old female subject was enrolled in a blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 17 March.

The subject was randomised to the dolutegravir + epzicom/kivexa once daily arm.

On 12 September b*, 545 days after the start of investigational product, the subject experienced grade 2 or moderate spontaneous abortion. The event was clinically significant (or requiring intervention). The event resolved on 14 September b*.

The investigator considered that there was no reasonable possibility that the spontaneous abortion may have been caused by investigational product.

Follow up information received on 11 October b*.

GSK case B0835064B has been identified as a duplicate of B0835064A. All future correspondence will be submitted to B0835064B.

The following information was taken from GSK case B0835064A:

Follow up information received on 04 October b*:

The date of last menstrual period was 29 June b* and the estimated date of delivery was March c*.

b*: Following year

\(c^*\): 2 years later
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Follow-up information received 08October b*: The spontaneous abortion was not considered related to investigational product. Withdrawal status from study was being required. The spontaneous abortion onset on 12 September b*, and was resolved by 14 September b*.

Investigator text:

Subject was pregnant and had an spontaneous abortion before planed abortion

Protocol Id: ING114467
Investigator Number: 084014
Subject Number: 005957
Treatment Number: 2095
Case Id: Z0016516A
Suspect Drugs: Atripla
Serious Events: Subcutaneous abscess

This -year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 16 March .

The subject was randomized to receive Atripla once daily.

Medical conditions at the time of the event included acne inversa. No concomitant medications were reported.

On 24 June b*, 466 days after the start of investigational product, the subject developed grade 2 or moderate axillary abscess. The subject was hospitalised and underwent abscess incision and drainage under anaesthesia. Postoperative course was complication-free. No additional drug therapy was given. Treatment with blinded trial medication-viiv was continued. The event resolved on 25 June b* and the subject was discharged. The investigator considered that there was no reasonable possibility that axillary abscess may have been caused by investigational product.

Follow-up information received on 16 October b* via query response:

No drug therapy given as part of event treatment.

Investigator text:

Patient presented at 24 June with new-onset abscess at the hospital. He has recurrent abscesses (acne inversa) in the medical history. On the evening of admission was

b*: Following year

* 新薬承認情報提供時に置き換え
performed abscess cleavage under anaesthesia. Complication-free postoperative course. The patient was discharged from hospital at 25 June b*.

Protocol Id: ING114467
Investigator Number: 088028
Subject Number: 006068
Treatment Number: 2223
Case Id: Z0016802A
Suspect Drugs: Atripla
Serious Events: Sciatica

This 31-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 30 March.

The subject was randomized to receive Atripla once daily.

The subject underwent lumbar surgery on 23 May b*. Concomitant medications included omeprazole.

On 24 May b*, 421 days after the start of investigational product, the subject developed grade 2 or moderate sciatica. The subject also experienced paresis and hypoesthesia in left leg. The subject was hospitalised. The subject was treated with enoxaparin, ondansetron hydrochloride, dipyrone, morphine hydrochloride, fentanyl, lorazepam, levofloxacin, rifampicin and vancomycin. Treatment with blinded trial medication-iiiv was continued. The event resolved on 06 June b*. The investigator considered that there was no reasonable possibility that the sciatica may have been caused by investigational product.

Diagnostics:

Lumbar CT: Degenerative lumbar hernia at L5-S1 Lumbar Ultrasound: Collection in lumbar zone.

Follow-up information received on 07 September b* via query response:

The lumbar surgery was performed on May 23th.

Investigator text:

The patient was admitted in hospital due to complication after lumbar surgery with paresis and hiposthesia of the leg with complete recovery.
This 47-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 13 April.

The subject was randomized to receive GSK1349572+Epzicom/Kivexa once daily.

Concomitant medications included clarithromycin, ceftriaxone, paracetamol and (unknown drug) Exoheparin.

On 18 September b*, 524 days after the start of investigational product, the subject developed grade 2 or moderate respiratory tract infection. The subject experienced dyspnoea. The subject was hospitalised. Chest X-ray did not show condensations. Outcome was unknown at time of reporting. The investigator considered that there was no reasonable possibility that the respiratory tract infection may have been caused by investigational product.

Investigator text:

The patient attended yesterday due a dyspnoea. The Chest Rx does not show condensations.

This 47-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 28 April.
The subject has no relevant medical history.

On 01 June b*, 400 days after the start of investigational products, the subject developed grade 3 or severe herpes 6 infection. The subject experienced headache, fever, muscular pain, diarrhoea and vomiting. The subject was hospitalised. Virological blood test was positive for HHV6 virus. Serology herpes 6 IgM and IgG positive. The subject was treated with aspirin, paracetamol and alizapride hydrochloride. Treatment with investigational products was continued. The event resolved on 11 June b*. The investigator considered that there was no reasonable possibility that the herpes 6 infection may have been caused by investigational product.

Follow-up information received on 03 July b* via query response:

Virological blood test positive for the HHV6 virus

Follow-up information received on 07 August b* via query response:

Diagnosis of hepatitis not yet confirmed. Subject needed to return for blood sample confirmation.

Follow-up information received on 16 August b*:

Serology herpes 6 IgM and IgG positive

Follow-up information received from investigator's site on 22 August b*:

Laboratory results demonstrate hepatitis:

TGO (ASAT) + 125 UI/L (14 - 40) on 08/06/b* 12:00 (C)
TGP (ALAT) + 212 UI/L (6 - 40) on 08/06/b* 12:00 (C)
LDH + 419 UI/L (less than 250) on 08/06/b* 12:13 (C)
Herpes 6 IgM (IF) greater than 20 titre Positive is greater than or equal to 20 on 13/06/b* 15:32 (C)
Herpes 6 IgG (IF) greater than 20 titre Positive is greater than or equal to 20 . on 13/06/b* 15:32 (C)

No similar episodes in the past, no other infection signs. No anaemia in our lab results.

Finally, we consider this not to be a HIV related condition but probably an hepatitis due to a reactivation of the Virus HHV6.

Diagnostic test results:
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Investigator text:

since 01/jun/b*, the patient present headache, fever, muscular pain, diarrhoea and vomiting -

Protocol Id: ING114467
Investigator Number: 084698
Subject Number: 006455
Treatment Number: 2347, 2347
Case Id: Z0016517A, Z0016517B
Suspect Drugs: Atripla
Serious Events: Lower limb fracture, Spinal fracture

This 30-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 18 April . The subject was randomized to receive Atripla once daily.

On 27 July, 466 days after the start of investigational product, the subject fell off his horse and developed grade 2 or moderate vertebral fracture. The subject was hospitalised. X-ray showed fracture. Treatment with blinded trial medication-viiv was continued. The fracture was stable therefore no intervention was required and the subject was discharged the next day. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the vertebral fracture may have been caused by investigational product.

Investigator text:

Subject fell off his horse and fractured a vertebrae. Was admitted over night for investigation. Fracture stable so no intervention required and patient was discharged.

On 30 July, 469 days after the start of investigational product, the subject developed grade 3 or severe lower leg fracture. The subject had suffered a fall and developed a compound tibia/fibula fracture. The subject was hospitalised. The fractures were confirmed by an X-ray. The subject underwent operative reduction and internal fixation. The subject was treated with paracetamol and ibuprofen. Treatment with blinded medication-viiv was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the lower leg fracture may have been caused by investigational product.

Investigator text:

Subject fell off his horse and fractured a vertebrae. Was admitted over night for investigation. Fracture stable so no intervention required and patient was discharged.

b*: Following year
Module 2.7.4 Summary of Clinical Safety

Investigator text:

Patient suffered fall with traumatic injury to leg. Admitted to hospital. Compound tibia/fibula fracture requiring operative reduction and internal fixation. -

Protocol Id: ING114467
Investigator Number: 083535
Subject Number: 006618
Treatment Number: 4024
Case Id: Z0016537A
Suspect Drugs: Atripla, Hydromorphone hydrochloride
Serious Events: Anaphylactic reaction, Cellulitis pharyngeal

This 42-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 07 March 1994.

The subject was randomized to receive Atripla once daily.

Concomitant medications included hydromorphone hydrochloride.

On 30 July 1995, 511 days after the start of investigational product, the subject developed grade 2 or moderate peritonsillar parapharyngeal phlegmon/cellulitis. The subject was hospitalised. On 02 August 1995, post-admission day 3, the subject developed grade 3 or severe anaphylactic reaction. The subject was treated with amoxicillin trihydrate, Clavulin and Tylenol #3. The anaphylaxis responded well to Benadryl. Treatment with blinded trial medication-viiv was continued. The anaphylactic reaction resolved on 02 August 1995. The subject was discharged on 03 August 1995. The peritonsillar parapharyngeal phlegmon/cellulitis resolved on 14 August 1995. The investigator considered that there was no reasonable possibility that the peritonsillar parapharyngeal phlegmon/cellulitis and anaphylactic reaction may have been caused by investigational product and that the anaphylactic reaction was possibly due to the concomitant medication, hydromorphone hydrochloride.

Diagnostics:

X-ray of the neck's soft tissues done on July 31st showed significant prevertebral soft tissue swelling. No subcutaneous emphysema is seen. CT scan of neck on July 31st suggested a right tonsillar abscess with surrounding inflammatory change and fluid extending down into the retropharyngeal space. Chest x-ray done on August 3rd is normal.

Investigator text:

b*: Following year

* 新薬承認情報提供時に置き換え
Subject presented to the Emergency room on July 31st with a 2-day history of right-sided sore throat. He saw his family physician who prescribed amoxicillin. He had significant right-sided odynophagia and some trismus. An incision and drainage of the right peritonsillar space was done at the time to allow for possible aeration and drainage of the tissues. He was placed on intravenous piperacillin/tazobactam and vancomycin and placed in the High Acuity Unit. His first day he did have some desaturation to 85%. He received dexamethasone the following night and did not desaturate. He was transferred to the ward on post-admission day 2. He did have a reaction to Dilaudid on post-admission day 3 which responded well to Benadryl. Subject discharged from hospital on August 3rd and given a prescription for Clavulin and Tylenol #3s. Awaiting copies of hospital chart to obtain correct dosage of medicines given during hospitalization. Will update page once obtained. Seen in the out-patient department on August 14th. Subject's infection has resolved.

Protocol Id: ING114467
Investigator Number: 086977
Subject Number: 006703
Treatment Number: 2250
Case Id: Z0015834A
Suspect Drugs: Atripla
Serious Events: Humerus fracture

This 49-year-old female subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 04 April.

On 24 May b*, 416 days after the start of investigational product, the subject developed grade 3 or severe humerus fracture. The subject was hospitalised on 04 June b* and underwent surgical treatment on 05 June b*. The subject was treated with ketoprofen, paracetamol and omeprazole. Treatment with blinded trial medication-viiv was continued. The event resolved on 08 June b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the humerus fracture may have been caused by investigational product and that the event was due to a fall.

Follow-up information received on 18 June b* via answered query report:

The subject did not undergo investigations during his hospitalisation.

Investigator text:

By telephone contact with the patient tells me that due to a fall on the beach the patient broke his right humerus on 24/MAY/b*. The patient went to emergency room but wasn't admitted. The 4/JUN/b* the patient was hospitalized and the 5/JUN/b* was operated to reduce the fracture. The patient was discharged on 8/JUN/b* at good condition.
This 34-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 11 April.

The subject was randomized to receive GSK1349572+Epzicom/Kivexa once daily. On 01 April, 356 days after the start of investigational product, the subject developed grade 2 or moderate pleomorphic adenoma. The subject was hospitalised and underwent surgical treatment on 20 June. Chemotherapy was not required due to benign pathology of the tumour. Treatment with blinded trial medication-viiv was continued. The event resolved on 21 June and the subject was discharged. The investigator considered that there was no reasonable possibility that the pleomorphic adenoma may have been caused by investigational product.

Diagnostics:

A biopsy was performed on May. And the result of pathological anatomy (on July) is a benign pleomorphic adenoma (parotid tumour).

Investigator text:

This is a patient with parotid tumour (pleomorphic adenoma). He was diagnosed on 25 April of this year; and biopsy was performed on 22 May. He had a surgery for this pathology on 20 June. He was hospitalized during one day, until 21 June. This patient will not require any chemotherapy, because it’s a benign pathology.
This 38-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 14 April 2018.

The subject was randomized to receive Atripla once daily.

Concomitant medications included clonazepam, tizanidine hydrochloride and amitriptyline hydrochloride.

On 10 July b*, 453 days after the start of investigational product, the subject developed grade 3 or severe syncope. The subject was hospitalised. Treatment with blinded trial medication-viiiv was continued. The event resolved on 12 July b*. The investigator considered that there was no reasonable possibility that the syncope may have been caused by investigational product.

Diagnostics:

CT of head at admission showed normal. ECG at admission showed normal sinus rhythm, ventricular pre-excitation, WPW pattern type B. Abnormal ECG. Blood pressure at admission showed 136/78 and respiration rate of 20

Investigator text:

Per nurses station at hospital: patient is being discharged today because they cannot find anything wrong with him and feel that he is a drug seeker. There is no test that shows validates his problem and he is more interested in getting pain meds and going to smoke than trying to figure out what his problem might be. The patient also gave false information to the hospital at intake in order to get pain medication. PI concurs and has signed off on the SAE. -

Protocol Id: ING114467
Investigator Number: 088547
Subject Number: 006858
Treatment Number: 4172
Case Id: Z0016270A
Suspect Drugs: Atripla
Serious Events: Overdose

This 38-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 02 May.
The subject was randomized to receive Atripla once daily.

The subject's past medical history included attempted suicide. Medical conditions at the time of the event included depression. Concomitant medications included lamotrigine.

On 05 July b*, 430 days after the start of investigational product, the subject developed grade 3 or severe acute overdose. The subject was hospitalised. The subject was treated with ondansetron hydrochloride and lorazepam. Treatment with blinded trial medication-viiv was continued. The event resolved on 09 July b*. The investigator considered that there was no reasonable possibility that the acute overdose may have been caused by investigational product.

Diagnostics:

At intake in ER patient had an alcohol level of 22, and a positive drug screen for cannabinoid and amphetamine. Patient was admitted through ER where he was lethargic, covered in dirt and urine and admitted to taking half a bottle of Lamictal. He was assessed, administered sedatives, cleaned up and admitted for observation. He was released on 09JUL b* and told to follow up with his therapist.

Investigator text:

Doctor [deleted] was called 09JUL b* and asked about current medications patient was on and that he was in the hospital. Records have been requested and all other information will be added as necessary. -

Protocol Id: ING114467
Investigator Number: 086973
Subject Number: 007858
Treatment Number: 2237
Case Id: Z0017427A
Suspect Drugs: Atripla
Serious Events: Chest pain

This -year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects. The subject received oral investigational product at 1 tablet per day from 01 April .

The subject was randomized to receive Atripla once daily.

On 28 July b*, 484 days after the start of investigational product, the subject developed grade 2 or moderate chest pain. The subject was hospitalised. Blood analysis and chest X-ray results were within normal limits. ECG detected sinus bradycardia 49bpm. The
subject's bradycardia was asymptomatic and was not considered a serious adverse event as it was a pre-existing condition. The subject was treated with Cafinitrina, aspirin and dipyrrone. The pain disappeared and coronary disease was ruled out. Treatment with investigational product was continued. Chest pain resolved on 29 July b* and the subject was discharged in good condition. The investigator considered that there was no reasonable possibility that the chest pain may have been caused by investigational product.

Investigator text:

On 28 JULY b*, patient suffers chest pain and went to the hospital. Patient was admitted at emergency room and stayed during night. A blood analysis and chest XR were performed and all results were within normal limits. A EGC was also performed and was found a sinus bradycardia 49bpm. In the morning of 29 JULY b*, patient was discharged at good condition.

Protocol Id: ING114467
Investigator Number: 81284
Subject Number: 5473
Treatment Number: 2210
Case Id: B0819897A
Suspect Drugs: Atripla
Pregnancy

This 34-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection.

The subject received oral investigational product at 1 tablet per day from 29 March a* to 13 July a*.

The subject was randomized to receive Atripla (once daily)

Concomitant medications included TriNessa.

Approximately 16 months after the start of investigational product, the subject became pregnant (last menstrual period 04 June b*). On 13 July b*, her pregnancy urine screen was positive and her quantitative HCG test was 6 mIU/mL (reference range less than 3). Investigation product was stopped on 13 July b*. On 19 July b*, the subject underwent an uncomplicated elective termination of the pregnancy.

On 25 July b*, the subject was seen for follow up in the clinic and there were no reports of sequelae from the procedure.

Protocol Id: ING114467
Investigator Number: 86919

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
This 36-year-old female subject was enrolled in a ViiV-sponsored blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 21 March.

The subject was randomised to receive oral dolutegravir 50 mg once daily and oral Kivexa one tablet daily.

The subject had had one previous pregnancy, which resulted in a normal birth. The subject's partner had a medical history of necrosis of the femoral head.

On an unspecified date after the start of investigational product, the subject was found to be pregnant (urine and pregnancy test). Her last menstrual period occurred on 08 September b*. Treatment with the investigational product was stopped on 25 October b*. The subject was exposed to the investigational product before conception and during the first trimester etc. At the time of reporting the outcome of the pregnancy was ongoing. The estimated date of delivery was 15 June c*.

9.6.4. ING111762 SAE and Pregnancy Case Narratives

9.6.4.1. Cases Reported up to 04 September

The narratives included in this section correspond to the SAEs and Pregnancy cases included in both the ING111762 Week 24 CSR (with a data lock point of 04 September for safety data), which is included in m5.3.5.1, and the ISO outputs. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.

Protocol Id: ING111762
Investigator Number: 081321
Subject Number: 000806
Treatment Number: 5009
Case Id: Z0009259A
Suspect Drugs: Raltegravir
Serious Events: Cytomegalovirus oesophagitis

b*: Following year
c*: 2 years later
Confidential

Module 2.7.4 Summary of Clinical Safety

This 48-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 25 APR.

This subject was randomised to receive oral RAL 400 mg twice daily.

Concomitant medications included sodium chloride.

On 30 APR a*, five days after the start of investigational product, the subject developed grade 3 or severe cytomegalovirus esophagitis. The subject was hospitalised on 30 APR a* due to dehydration and esophagitis. The subject was treated with magnesium hydroxide, Aluminium hydroxide + magnesium hydroxide + simethicone, docusate sodium, bisacodyl, zolpidem, ondansetron hydrochloride, sodium chloride, potassium chloride, paracetamol, Hydrocodone APAP, morphine, oral ulcer medication, pantoprazole, sucralfate, enoxaparin, levofloxacin, fluconazole, ganciclovir, propofol, lignocaine hydrochloride and magnesium sulphate. Treatment with blinded trial medication was continued. Follow-up information received on 10 MAY b* via answered query report stated that the subject had colon surgery in i* which was not considered relevant to the SAE by the investigator. The event resolved with sequelae on 17 MAY a*. The investigator considered that there was no reasonable possibility that the cytomegalovirus esophagitis may have been caused by investigational product.

Diagnostics:

CT of Chest on 30 APR a*. Findings: No discrete filling defects are seen within the pulmonary arterial system to suggest pulmonary embolic disease. There are calcified right hilar nodes. Calcified granulomata are present within the right lower lobe. Mild paraseptal emphysema is present. There is bronchial wall thickening with adjacent inflammatory change in the left lung base which is stable. There is distension of the oesophagus with a thickening of the mucosa. This may be due to esophagitis and/or dysmotility. Impression: 1) No pulmonary embolic disease or acute cardiopulmonary process. The patient also had recent CT angiograms of the chest 01 APR a* and 08 FEB a*, which were also negative for pulmonary embolic disease. 2) Old granulomatous disease. 3) Distension of the oesophagus with mucosal thickening which may represent esophagitis and/or dysmotility. Given the patient's HIV status, the aetiology the chest pain is likely related to infectious esophagitis.

Chest X-Ray on 30 APR a*. Findings: Single view demonstrates a normal heart size. The lungs are clear. No focal infiltrate or mass. Stable calcified granuloma the right lower lobe with calcified right hilar lymph node. Osseous structures February are intact. Impression: No acute process in the chest or significant change from a*.

Investigator text:

a*: The year
b*: Following year
i*: 5 years ago

* 新薬承認情報提供時に置き換え
Patient was admitted to hospital 30 APR a* for dehydration and esophagitis. Medical records requested. New information will be submitted once received.

Protocol Id: ING111762
Investigator Number: 081168
Subject Number: 000651
Treatment Number: 7003
Case Id: Z0009707A
Suspect Drugs: Dolutegravir
Serious Events: Pancreatitis

This 36-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 08 FEB a*.

This subject was randomised to receive oral DTG 50 mg once daily.

Concomitant medications included atazanavir and maraviroc.

The subject started atazanavir/ritonavir 300/100 once daily, maraviroc 150 mg twice daily and blinded trial medication on 08 FEB a*: Baseline HIV-1 RNA and CD4 cell count were 5.63 log10 copies/mL and 188 (18%) cells/mm3. Other concomitant medications included: vitamin C, Mucinex (28 DEC e* to 14 FEB a*), MVI, Tylenol cold/Flu (28 DEC e* to 14 FEB a*), lisinopril and ibuprofen. Current medical history included hypertension, hypercholesterolemia, hypertriglyceridemia, metabolic disorder NOS. Past medical history included anxiety, depression and suicidal ideation. The subject denied ever using illicit drugs. On screening and day 1, lipase was 61 and 50 U/L (NR: 7-60). The subject had grade 2 lipase elevation noted at week 4 (98 U/L), which persisted through week 8 (96 U/L) and week 12 (87 U/L grade 1). Triglycerides were persistently elevated (Day 1- 310 mg/dL; week 12 - 349 mg/dL). There was no other evidence of common bile duct obstruction was apparent in the study labs (alkaline phosphatase and total bilirubin). Concomitant medications included: sodium chloride 0.9% solution, pantoprazole, hydromorphone, ondansetron hydrochloride, barium sulphate, iopamidol, and ketoralac.

The subject presented with mid-epigastric abdominal pain on 24 MAY a*, 105 days after the start of investigational product. Chemistries were obtained, and the lipase value was noted to be below approximately 900. Amylase was significantly elevated. The subject was hospitalized with grade 3 or severe pancreatitis, abdominal pain resolved after a couple of hours. An ultrasound obtained on 25 MAY a*, showed biliary sludge but no gallstone. Lipase level resolved quickly with a decline to approximately 500. Treatment with blinded trial medication was interrupted 24 MAY a* and was re-started on 27 MAY a* due to the subject being NPO. The subject returned to oral intake on...
26 May a* without recurrent pain. The event resolved on 26 MAY a*. ALT was also elevated with a peak at approximately 200 on 25 MAY a*. The subject never developed a fever, rash or shortness of breath - but did have nausea and one episode of vomiting. The subject had no history of biliary colic or gallstones. Relevant laboratory results during hospitalization included: On 24 MAY a*, ALT 96 (NR: 7-55), 25 MAY a* 358 and 26 MAY a* 244. AST 87 (NR: 10-40) on 24 MAY a*, 247 on 25 MAY a* and 89 on 26 MAY a*. Total bilirubin on 25 MAY a* 1.3 and 0.9 on 26 MAY a*. On 24 MAY a* amylase 417 units/L (NR:25.0-115.0) and lipase 9425 U/L (NR: 72.0-393.0). The investigator considered that there was no reasonable possibility that the pancreatitis may have been caused by investigational product.

Investigator text:

Patient called the office today to inform us that he is admitted at the hospital for pancreatitis. He is currently on NPO status, hence, all HIV drugs including his study drugs were temporarily stopped on the evening of 24 MAY a*. Patient does not drink alcohol, denies illicit drug use and states that he never had pancreatitis in the past. Patient was discharged on 26 MAY a*. All HIV meds including blinded IP were resumed on 27 MAY a*. 

Protocol Id: ING111762
Investigator Number: 084118
Subject Number: 002312
Treatment Number: 7018
Case Id: Z0010216A
Suspect Drugs: Raltegravir
Serious Events: Anal ulcer

This 47-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 19 MAY.

This subject was randomised to receive oral RAL 400 mg twice daily.

Concomitant medications included azithromycin, sodium rabeprazole and dextropropoxyphene hydrochloride.

On 03 JUN a*, 15 days after the start of investigational product, the subject developed grade 2 or moderate perianal ulcer. The subject was hospitalised due to complaints of painful perianal ulcers that had been deteriorating. The subject also developed fever of unknown origin and diarrhoea. Per the investigator, due to initiation of fever antibiotic treatment with metronidazole, gentamicin sulphate, tigecycline, and aztreonam commenced while serologic tests came back negative. Herpes simplex virus was
suspected (but never confirmed) and the subject was also treated with acyclovir, followed by phenoxymethylpenicillin potassium and moxifloxacin hydrochloride. Biopsy performed on 20 JUN a* did not confirm HSV in samples or IgM serology, but fungi presence on perianal ulcers. The fever aetiology remained unknown, and thought possibly due to ulcer contamination, or infection of GI or respiratory origin. Treatment with blinded trial medication was continued. The event resolved on 21 JUL a* and the subject was discharged in good clinical condition. The investigator considered that there was no reasonable possibility that the perianal ulcer may have been caused by investigational product.

Investigator text:

the subject came in during w4 visit complaining of painful periannal ulcers ongoing since the 3rd of June that had been deteriorating, without any other complains. He was admitted in order to be investigated, received painkillers and initially zovirax. lesions were biopsied and penicillin was given for prophylaxis due to initiation of fever.

Protocol Id: ING111762
Investigator Number: 084734
Subject Number: 002359
Treatment Number: 3093
Case Id: Z0016857A
Suspect Drugs: Raltegravir
Serious Events: Lipase increased

This □-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 16 August b* to 17 July b*, followed by an open-label oral raltegravir at 800 mg per day from 17 July b*.

The subject was randomized to receive raltegravir 400 mg twice daily.

On 17 August b*, 367 days after the start of investigational product and 31 days after the start of open-label raltegravir, the subject developed grade 2 or moderate increased lipase level (154 U/L; normal range 7.0 - 60.0). The subject was hospitalised on 31 August b*. Laboratory test results dated 31 August b* included lipase 599 U/L (normal range 23-300) and amylase 232 U/L (normal range 30-110). Re-test performed on 01 September b* showed amylase result of 223 U/L and lipase result of 645 U/L.

The investigator considered the increased amylase not to be a separate serious adverse event but an incidental finding while the subject was hospitalised. Treatment with open label raltegravir was stopped on 17 August b*. The subject then received hospital supplied raltegravir until 01 September b* when treatment was stopped. The subject was treated with ertapenem sodium, dextrose and sodium chloride. The event resolved on 02 September b*. The investigator considered that there was a reasonable
Module 2.7.4 Summary of Clinical Safety

possibility that the increased lipase level may have been caused by investigational product.

Investigator Text:

We saw results from Quest in August 29, b*, I telephoned patient who left Bucharest at 450 km distance. He said that before August 17 was at the gym and now not accuse any pain.

The patient came to the hospital in 31Aug for lab retest in Quest and local lab analysis. After PI saw local results, amylase and lipase increased 2 times decided hospitalized patient with medical supervision. The patient stay in hospital from 31aug-02 sep. In 02 sep results for amylase and lipase are in normal range. Also, the patient stopped Raltegravir since 01 sep b* after we received email (Dr [deleted]). The Follow up visit was on 18th of September with normal lipase.

Protocol Id: ING111762
Investigator Number: 081798
Subject Number: 000862
Treatment Number: 1022, 1022
Case Id: Z0010004A, Z0010004B
Suspect Drugs: Dolutegravir
Serious Events: Alcohol abuse, Suicidal ideation

This 39-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 04 MAY.

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included agoraphobia, anxiety, borderline personality disorder, depression, polysubstance abuse and post-traumatic stress disorder. The subject denied any use of cocaine, heroin or methamphetamines in the past. The subject's past medical history also included mental illness with prior suicidal ideation and cutting. Concomitant medications included maraviroc, darunavir/ritonavir, prazosin, mirtazapine and clonazepam. The subject consumed a 6 pack of beer per week (however there could be more). The subject also took marijuana 2-3 times per week. The subject has 3 children and often cares for her grandchildren, which is stressful for her. There have been past and current family issues which could have attributed to her recent suicidal thoughts.

On 04 JUN a*, 31 days after the start of investigational product, the subject developed grade 3 or severe suicidal ideation with a plan. The event was life-threatening.

a*: The year
b*: Following year
Treatment with blinded trial medication was continued. The subject also received tetanus vaccine, aspirin and bacitracin at the time of the event. The subject was placed on suicide precaution and observed for 7.5 hours and then discharged. The event resolved on 08 JUN a*. The investigator considered that there was no reasonable possibility that the suicidal ideation with a plan may have been caused by investigational product.

Investigator text:

Received information today that patient's therapist referred her to [deleted] Hospital ER for evaluation/observation for suicidal ideation (with a plan) and cutting of self. ethanol consumption was also noted. Patient has past medical history of mental illness with prior suicidal ideation and cutting. Patient was placed on suicide precaution and observed for 7.5 hours and then discharged home. Study meds were not discontinued as PI does not believe that there is a relationship between event and meds.

On 01 AUG a*, 89 days after the start of investigational product, the subject developed grade 3 or severe alcohol abuse. The subject was hospitalised. Treatment with blinded trial medication was continued. The event improved on an unspecified date. The subject was no longer hospitalised. The investigator considered that there was no reasonable possibility that the alcohol abuse may have been caused by investigational product. The subject's past medical history included alcohol abuse.

Investigator text:

Patient has long standing psych history with Alcohol abuse. Her ALT was elevated at her 25 AUG a* visit and she was asked to come in for a follow up visit. Patient admitted that she was consuming large amounts of ethanol for the month of August secondary to stressors. She was willing to seek treatment and ethanol detox was arranged. She was admitted on 31 AUG a* and is still presently at the facility.

Patient is no longer hospitalized.

Protocol Id: ING111762
Investigator Number: 081036
Subject Number: 000492
Treatment Number: 5010
Case Id: Z0010343A
Suspect Drugs: Raltegravir
Serious Events: Pneumonia

This 492-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 26 APR .
This subject was randomised to receive oral RAL 400 mg twice daily.

On 16 JUN a*, 51 days after the start of investigational product, the subject developed grade 3 or severe pneumonia. The subject experienced fever. The subject was hospitalised on 16 JUN a*. Treatment course is unknown. HIV viral load done result >10,000,000 but no high/low reference ranges given, blood cultures were negative, chest x-ray was nonspecific, mild splenomegaly. Treatment with blinded trial medication was continued. The event resolved on 19 JUN a*. The subject left hospital on 18 JUN a* against medical advice. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by investigational product.

Investigator text:

Patient states she had fever, went to hospital and admitted, pneumonia, patient was unsure of diagnosis. Hospital records are being requested. Dr [deleted] believes this may have been an immune reconstitution response. Patient records received, patient was admitted 16 JUN a* to 18 JUN a*. Patient left hospital against medical advice so tx course is unknown.

Protocol Id: ING111762
Investigator Number: 081175
Subject Number: 000674
Treatment Number: 1002
Case Id: Z0010545A
Suspect Drugs: Dolutegravir
Serious Events: Joint abscess

This 20-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 17 DEC .

This subject was randomised to receive oral DTG 50 mg once daily.

The subject has no relevant medical history.

On 10 JUL b*, 205 days after the start of investigational product, the subject developed grade 1 or mild abscess of elbow. The subject was hospitalised on 12 JUL b* and treated with intravenous antibiotics. Wound culture was positive for staphylococcus aureus. Treatment with investigational product was continued. The event resolved on 16 JUL b*. The subject was discharged on 18 JUL b*. The investigator considered that there was no reasonable possibility that the abscess of elbow may have been caused by investigational product.

a*: The year
b*: Following year

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Module 2.7.4 Summary of Clinical Safety

Investigator text:

Received call from patient today. She was admitted to the hospital 12 JUL b* to receive intravenous antibiotics for abscess right elbow. Doing well. Will update medications when available. 18 JUL b* discharged from hospital to home. Doing well. Awaiting records to record intravenous and oral medications.

Protocol Id: ING111762
Investigator Number: 081176
Subject Number: 000706
Treatment Number: 1060
Case Id: Z0016759A
Suspect Drugs: Dolutegravir
Serious Events: Pancreatitis

This -year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 11 October.

This subject was randomised to receive oral dolutegravir 50 mg once daily.

The subject's past medical history included pancreatitis. Medical conditions at the time of the event included marijuana use. Concomitant medications included zidovudine, ritonavir and darunavir.

On 20 August b*, 314 days after the start of investigational product, the subject developed grade 3 or severe pancreatitis. He had complained of a one week history of upper abdominal pain. The subject was hospitalised. Laboratory test dated 20 August b* revealed lipase result of 190 units/HI (normal range 7 - 60). Treatment with blinded trial medication was continued. The event resolved on 23 August b*. The investigator considered that there was no reasonable possibility that the pancreatitis may have been caused by investigational product.

Initial SAE report and hospital discharge summary received on 21 August b*:

Mr. is a -year-old African American man with history of HIV, pancreatitis, and tobacco abuse who presents with a several-day history of abdominal pain. It is last Friday, while he was in state XXXX. He attended a local ER there, was told he had pancreatitis/elevated lipase, kept for the night and given analgesia and discharged the next day as he said he wanted to follow-up with his doctors here. Today he continued to have abdominal pain, he felt it was worse with eating, although he did not actually vomit anything back up. He did not have diarrhoea, fever, chills. He told his study nurse and was told that he should attend the emergency department for further evaluation. He denies any trauma, new medication, alcohol use or illicit substance use. He feels the symptoms are very compatible with previous episodes of pancreatitis.

b*: Following year

* 新薬承認情報提供時に置き換え
Review of Systems

Negative other than that mentioned in history of present illness

Current medications:

Azithromycin 600 mg oral tablet: 1,200 mg, 2 tab(s), Oral, Every 1 wk (int), 4 tab(s)
Atripla oral tablet: Daily (std)
Bactrim oral tablet: 1 tab(s), Oral, Daily (std)
Isentress equivalent: 2 tab(s), Oral, Daily (std)
Norvir 100 mg oral tablet: 200 mg, 2 tab(s), Oral, Daily w bkfast (std)
Prezista 600 mg oral tablet: 1,200 mg, 2 tab(s), Oral, Daily (std)
HIV study drug: 1 tab, Oral, Daily (std), white, round pill
Zidovudine 300 mg oral tablet: 600 mg, 2 tab(s), Oral, Daily (std)

Concurrent Problems:

Diarrhoea, Sinusitis, Tobacco abuse, Pancreatitis, Oral candidiasis, HIV (Human Immunodeficiency Virus Infection).

Past Medical History:

Resolved

Insomnia : Onset in a* at □ years. Resolved in b* at □ years.
GORD - Gastro-esophageal reflux disease: Onset in a* at □ years. Resolved in b* at □ years.
Clostridium difficile colitis: Onset in e* at □ years. Resolved in e* at □ years.
Gonorrhea : Onset in h* at □ years. Resolved in g* at □ years.
HIV (Human Immunodeficiency Virus Infection) Resolved.
Pancreatitis: Resolved.

Procedure history: No active procedure history items have been selected or recorded.

Social History

a*: The year
b*: Following year
e*: Last year
g*: 3 years ago
h*: 4 years ago
Module 2.7.4 Summary of Clinical Safety

Social & Psychosocial Habits

Alcohol
08/20/b Use: Within the past year

Substance Abuse 09/19/a Type: Marijuana
Use: Current

Tobacco 09/19/a Smoking status: Never smoker

Physical Examination

Vital Signs (midnight yesterday to current)

<table>
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<th>PARAMETER LAST CHARTED</th>
<th>MINIMUM</th>
<th>MAXIMUM</th>
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<tbody>
<tr>
<td>Temperature C</td>
<td>36.5 (08/21 00:37)</td>
<td>36.8 (08/20 14:23)</td>
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<tr>
<td>Heart Rate</td>
<td>64 (08/21 00:37)</td>
<td>110 (08/20 14:23)</td>
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<tr>
<td>Resp Rate</td>
<td>16 (08/21 00:37)</td>
<td>18 (08/20 14:23)</td>
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<td>Sp02</td>
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<tr>
<td>Pain Score</td>
<td>0 (08/21 00:18)</td>
<td>0 (08/21 00:18)</td>
</tr>
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</table>

General: Alert and oriented, No acute distress.

HENT: Normocephalic.

Neck: Supple, Non-tender, No jugular venous distention.

Respiratory: Lungs are clear to auscultation, Respirations are non-laboured.

Cardiovascular: Normal rate, Regular rhythm, No murmur, No oedema.

Gastrointestinal: Non-distended, Normal bowel sounds, tender to palpation in epigastic area, moderate palpation.

Genitourinary: No costovertebral angle tenderness.

Musculoskeletal: Normal range of motion.

Neurologic: Alert, Oriented, Normal sensory, Normal motor function.
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Module 2.7.4 Summary of Clinical Safety

Cognition and Speech: Oriented, Speech clear and coherent.

Psychiatric: Cooperative, Appropriate mood & affect.

Review 1 Management

Results review: Lab results.

08/20/b* 16:40 Sodium 137 mEq/L
Potassium 3.3 mEq/L
Chloride 99 mEq/L
Bicarbonate 26 mEq/L
AGAP 12.0 mEq/L
Glucose Level 86 mg/dL
BUN 12 mg/dL
Creatinine 1.0 mg/dL
GFR Calc >60 mL/min/1.73 m2 NA
calcium 9.6 mg/dL
Bili Total 0.4 mg/dL
Alk phos 78 Units/L
AST 25 Units/L
GGT 14 Units/L
Lipase Level 190 Units/L HI
WBC 6.10 10^A3/cmm
RBC 3.79 10^A6/cmm LOW
Hgb 14.3 g/dL
Hct 41 %
MCV 108 fL HI

b*: Following year
Module 2.7.4 Summary of Clinical Safety

MCH 38 pg HI
MCHC 35 g/dL
Platelet 230 10A3/cmm
RDW 14.6 %
MPV 8 fL NA
Neutrophils 61 %
Abs.Neutrophils 3.73 10A3/cmm NA
Lymphocytes 29 %

Follow-up information received from medical monitor on 23 August b*:

This subject's lipase was G3 at study Day 1 (292 U/L), but decreased to G1 at week 8 and was normal for the last two visits (week 32 on 22-May-b* and week 40 on 19-Jul-b*). We had followed this subject lipase abnormality in the past (see attached message) and the PI opinion was that it was associated to Atripla use, which led to Atripla discontinuation on 11-Oct-a*.

The subject's medical history registers at the CRF a past GI disorder NOS.

Follow-up information received on 28 August b* via query response:

The subject did not receive any other non HIV ART corrective therapy for reported SAE.

Investigator text:

Patient complaining of upper, abdominal pain for one week. He went to ER while out of state. He was diagnosed with pancreatitis/elevated lipase. He dose have a history of daily marijuana use. Patient feels symptoms are compatible with previous episodes of pancreatitis. -

<table>
<thead>
<tr>
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<tr>
<td>Investigator Number:</td>
<td>085169</td>
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<tr>
<td>Subject Number:</td>
<td>002919</td>
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<td>Treatment Number:</td>
<td>1030</td>
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<tr>
<td>Case Id:</td>
<td>Z0014355A</td>
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<tr>
<td>Suspect Drugs:</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Serious Events:</td>
<td>Anal abscess</td>
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</table>
This 67-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 08 JUN.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject had no relevant medical history. Concomitant medications included darunavir and tenofovir.

On 16 JUL, 38 days after the start of investigational product, the subject developed grade 2 or moderate perianal abscess. The subject was hospitalised on 16 JUL due to perianal abscess with pain. The subject was treated with dipyrone, omeprazole and Augmentin (oral). All blood test results were normal. Treatment with blinded trial medication was continued. The subject was discharged on 17 JUL. The event resolved on 23 JUL.

Investigator text:

The patient had a perianal abscess with pain and he had to be admitted in the night in a hospital with one day of admission (16-July till 17-July). Today I have got the file.

Protocol Id: ING111762
Investigator Number: 081669
Subject Number: 000942
Treatment Number: 8002
Case Id: Z0010676B
Suspect Drugs: Dolutegravir, Entecavir
Serious Events: Pyrexia

This 67-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 23 MAY.

This subject was randomised to receive oral DTG 50 mg once daily.

Concomitant medications included entecavir, ceftriaxone and paracetamol.

On 26 JUL, 64 days after the start of investigational product, the subject developed grade 3 or severe fever. The subject was hospitalised. The event resolved on 26 JUL. The investigator considered that there was no reasonable possibility that the fever...
may have been caused by investigational product and that the event was possibly due to
the concomitant medication, entecavir.

Investigator Text:

Subject went to ER c/o fever of 105.0. No verification of same in ER, but he was
admitted for fever w/u. Workup was negative, and he was discharge 2 days later.
Discharge diagnosis was "reaction to antiviral medication, specifically Entecavir.
During the hospitalization he was noted to have elevated LFTs, but they were actually
improved from the prior week.

Protocol Id: ING111762
Investigator Number: 081798
Subject Number: 000865
Treatment Number: 1029, 1029
Case Id: Z0011028A, Z0011028B
Suspect Drugs: Raltegravir
Serious Events: Pneumonia, Substance abuse

This 50-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of
the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice
daily, both administered with an investigator selected background regimen over 48 weeks
in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults.
The subject received oral investigational product from 07 JUN a.

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included polysubstance abuse.

On 09 AUG a*, 63 days after the start of investigational product, the subject developed
grade 3 or severe hospitalization for substance abuse. The subject was hospitalised in a
detox facility due to heroin abuse. The subject was treated with trazodone and
methadone hydrochloride. Treatment with blinded trial medication was continued. The
event resolved on 12 AUG a*. The investigator considered that there was no
reasonable possibility that the hospitalization for substance abuse may have been caused
by investigational product.

Investigator text:

Received telephone call from a detox facility stating that subject requesting
hospitalization for Heroin Detox. Patient has longstanding issues with polysubstance
abuse since w*. No relevant diagnostic tests or Con Meds noted at this time.

The subject received investigational product until 18 JAN b*.
On 06 FEB b*, 244 days after the start of investigational product and 19 days after the last dose, the subject developed grade 2 or moderate community acquired pneumonia. The subject presented at the ER on 09 FEB b* with complaints of cough with green sputum and subjective fever and chills at home x 4 days. The subject was hospitalised. Chest x-ray obtained showed either atelectasis or early pneumonia. The subject was treated with ceftriaxone sodium and azithromycin. The event resolved on 16 FEB b*.

The investigator considered that there was no reasonable possibility that the community acquired pneumonia may have been caused by investigational product.

Investigator text:

Patient went to [deleted] ER on 09 FEB e* w. c/o productive cough w. green sputum and subjective fever and chills at home x 4 days. Presumed diagnosis of Community Acquired Pneumonia. Patient missed his wk 32 visit which was due on 18 JAN b* & numerous attempts to contact patient failed. His last PVL on 01 DEC a* was <50 and CD4 6% and 57. RN is estimating stop date of study agents as 18 JAN b*. ER visit is 09 FEB b* not e*.

Protocol Id: ING111762
Investigator Number: 084218
Subject Number: 002054
Treatment Number: 7032
Case Id: Z0011439B
Suspect Drugs: Raltegravir
Serious Events: Progressive multifocal leukoencephalopathy

This 51-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 30 JUN b*

This subject was randomised to receive oral RAL 400 mg twice daily.

Concomitant medications included hydroxyzine hydrochloride and tramadol hydrochloride.

CD4 lymphocytes measured on 31 MAY a* showed result of 79 per cmm (normal range 490-1740).

On 24 AUG a*, 55 days after the start of investigational product, the subject developed grade 4 progressive multifocal leukoencephalopathy. The subject experienced memory problems with anterograde amnesia, prosopagnosia, and episodes of temporospatial disorientation. The subject was hospitalised. Treatment with blinded trial medication was discontinued on 21 SEP a* and the subject was withdrawn from the study. The event

a*: The year
b*: Following year
e*: Last year
was and will remain unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the progressive multifocal leukoencephalopathy may have been caused by investigational product.

Diagnostics:

The patient with memory disorders had an MRI on 07 SEP a* showing a diffuse infiltration in the frontal area. This could be a lymphoma or a pmle. This will be confirmed in coming days other investigations are planned. This event is probably not related to study drug. Progressive multifocal leukoencephalopathy was proved by JC virus detection in the cerebrospinal fluid; A neurocognitive assessment was made on 12 SEP a* showing impairment of cognitive functions, with a frontal profile (impaired executive functioning with deficits in working memory, mental flexibility, inhibition and attention divided; preserved memory function). Oversights observed explained by disorders of executive functions. An EEG done on 09 SEP a* shows a plot right frontal slow non-paroxysmal. An MRI performed on control 20.9 objectifying a marked increase in the FLAIR hyperintense lesion in the right frontal lesion, with extension through the corpus callosum to the left frontal lobe, extending into the right thalamus and right basal ganglia. There is also an increase in size of the lesion right parietal.

Investigator text:

Hospital for assessment of memory disorders (brain MRI and lumbar puncture). Troubles memory for 2 weeks were noted with anterograde amnesia, prosopagnosia, and episodes of desorientatio temporo-spatial minima.

Protocol Id: ING111762
Investigator Number: 083527
Subject Number: 002430
Treatment Number: 7053
Case Id: Z0011698A
Suspect Drugs: Raltegravir

This 51-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received blinded oral investigational product from 17 AUG 2013.

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included human immunodeficiency virus. Concomitant medications included abacavir sulphate and stavudine.

a*: The year
Subject had several episodes of bleeding during August, they were reported as dysfunctional uterine bleeding by gynaecologist. On 27 AUG a*, 10 days after the start of investigational product, the subject developed grade 3 or severe uterine haemorrhage. On 31 AUG a*, the subject developed grade 3 or severe cervical carcinoma. The events were clinically significant (or requiring intervention). Cervical biopsy performed on 31 AUG a* showed moderately differentiated squamous cell cancer. The subject was treated with ethamsylate, paracetamol and Augmentin and gamma-ray teletherapy (total dose 14 Gy) was initiated on 16 SEP a*. Treatment with blinded trial medication was discontinued on 21 SEP a* and the subject was withdrawn from the study. The uterine bleeding resolved on 30 AUG a*. The cervical carcinoma was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the cervical carcinoma and uterine haemorrhage may have been caused by investigational product.

Investigator text:

The subject had several episodes of dysfunctional uterine bleeding (including one before Baseline that started on 10 AUG a*) since June a*. As the subject didn't have bleeding by the time of Baseline she was randomized and received study medication. She had two more bleeding episodes after Baseline and was finally referred to oncologist by her gynaecologist. Oncologist performed cervical biopsy on 31 AUG a*. Results became available on 08 SEP a* and confirmed invasive carcinoma however the subject didn't report this to investigator until Week 4 visit that took place on 13 SEP a*. Radiotherapy is indicated for this subject immediately. Subject was withdrawn from the study on 22 SEP a* because gamma-ray teletherapy (total dose 14 Gy) was initiated on 16 SEP a*.

Protocol Id: ING111762
Investigator Number: 085168
Subject Number: 002209
Treatment Number: 1005
Case Id: Z0011575A
Suspect Drugs: Raltegravir, Zidovudine
Serious Events: Hepatotoxicity, Lactic acidosis

This 35-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product twice per day from 26 JAN a*.

The subject was randomised to receive RAL 400 mg twice daily.

Medical conditions at the time of the event included chronic hepatitis c infection and methadone treatment. Concomitant medications included zidovudine.
On 29 AUG a*, 215 days after the start of investigational product the subject developed grade 4 liver toxicity. On 05 SEP a*, the subject developed grade 2 or moderate lactic acidosis. The subject was hospitalised. The subject was treated with metoclopramide. Treatment with investigational product was discontinued on 05 SEP a* and the subject was withdrawn from the study. The events resolved on 27 NOV a*. The investigator considered that there was no reasonable possibility that the liver toxicity and lactic acidosis may have been caused by investigational product and that the lactic acidosis was possibly due to the concomitant medication, zidovudine.

Investigator text from initial SAE notification received on paper on 30 AUG a*:

The patient began IP on 26 JAN a* and his optimized background therapy (OBT) is Prezista and Retrovir. Patient has been suffering from epigastric pain, nausea and occasional vomiting approximately since 4 weeks ago. He has been attending to GP several times. Due to his symptoms the patient has reduced the alimentary intake (not medication). During the initial assessment of the patient (and considering lab reports), diet, antacids and metoclopramide (for vomiting) was given. With this treatment that patient symptoms improved and nausea disappeared but a weight loss was seen. A gastroscopy was considered but patient refused to complete the procedure. The patient had a relapse of symptoms and examined again on 26 AUG a*. Investigator decides to hospitalize the patient on 29 AUG a* to complete additional assessments and initiate a new treatment for this event. Today the patient feels better only with symptomatic treatment. Patient has been compliant with study IP except for one day (yesterday). Subject is continuing in the study.

Follow up received on 05 SEP a* from the Medical Monitor:

The subject was a 40 year old man with a long standing history of HIV and prior treatment who was randomised on 26 JAN a*. The back ground regimen was comprised of zidovudine 250 mg and darunavir/ritonavir 600/100 twice daily. Prior ART included zidovudine (NOV w* - JAN v*), stavudine (NOV l* - AUG k*), lamivudine (NOV l* - SEP j*), Kaletra (NOV l* to FEB k*, JAN e* to MAR e*), efavirenz (MAR e* to JAN a*), and etravirine (MAR e* to JAN a*). The subject was noted to have a co-infection with hepatitis C (positive hepatitis C antibody at Day 1) and is noted to have hepatitis C since v*.

The subject was admitted to the hospital on 29 AUG a* due to 10 days of vomiting and weight loss. Liver transaminases were noted to be elevated, and venous lactate was noted to be 49 mg/dL. All study medications study drug and background regimen were discontinued on 05 SEP a*. The subject was improving with metaclopramide and diet.

Pertinent evaluations from hospitalization were noted. Gastroscopy was unremarkable. On 02 SEP a* labs were as follows: AST-430 (ULN-37 U/L), ALT 173 (ULN 41 U/L) total bilirubin 2.3 mg/dL (ULN 1.1 mg/dL), direct bilirubin 2.1 mg/dL (ULN: 0.3 mg/dL), INR in normal range (97%), haemoglobin 8.8 g/dL, WBC 1.46x 10^3,
neutrophils 0.78 x 10^3, platelets 100 x 10^3, lactate (venous) 49 mg/dL. Hepatic elastography 11.1 UPc.

Concomitant medications included: zidovudine, Septra, metaclopramide, Darunavir/ritonavire, Zidovudine, Cipralex, Zyprexa, Rohipnol, Etumina, Septrim, Methadone, Benerva, Benadon and Almax.

Past medical history included: ear and labyrinth disorders, eye disorders, hepatobiliary disorders (current), respiratory, thoracic, mediastinal disorders, skin subcutaneous tissue disorders, infections/infestations, injury/poisoning procedural complications, past GI disorder NOS, anxiety (current), depression (current) and nervous system NOS (current).

Follow up information received on 08 SEP a* from the site via email:

The subject had a history of an encephalic trauma after a causal fall. The subject had no history of any poisoning and he did not have any mood alterations at the time of the event or the weeks before. The subject does not drink alcohol. The subject was on stable therapy with methadone, clorazepate 50 mg a day and flunitracepam 2 mg at night.

The subject had not received therapy for the hepatitis C infection in the past due to his immunodeficiency and adherence. In this admission an ecography had been performed and the biliary tree did not show dilatation. A CT scan of the thorax, abdomen and pelvis showed a moderate mucosal in the distal oesophagus growing with two endoscopies with a normal result. There was also one adenopathy near the oesophagus. The lactic acidosis was possibly due to zidovudine.

Follow-up information received on 19 SEP a* via query response:

After episode we saw that vomiting was probably a consequence of the SAE, not a cause.

Follow up received from the Medical Monitor on 19 SEP a*:

The subject continued to have significant liver chemistry elevations. Laboratory data on 12 SEP a*, ALT 183 u/L, 518 u/L, 42 umol/L and alkaline phosphate 108. On 14 SEP a*, ALT 185 u/L, AST 535 u/L, 39 umol/L and alkaline phosphate 119. Liver event laboratory data included: HCV RNA 1,030, 000 IU/mL, EBV VCA IgM negative, Hep B sag non-reactive, Hep B core IgM negative, CMV IgM ab 1.4, AnA positive (1:80), AnA none detected and Actin IgG <20 and LKM-1 IgG <20.

Follow-up information received on 20 SEP a* from Clinical:

Report (discharge summary) date: 08 SEP a*

Reason for being hospitalized: Vomiting

At discharge: Improvement

a*: The year
Previous history: No drug allergy, Tuberculosis at t*, zoster Herpes at l*, oral candidiasis, depression and anxiety. Currently AZT 250 mg BID, Darunavir/rtv and sailing protocol treatment. Tranxilium 50 at lunch. Rohipnonol 1 mg two tablets at night. Takes Metadona.

Current illness: The patient is involved in a clinical trial presenting nauseas and vomiting with 10 days of evolution, that did not improved with diet and pharmacology treatment with Primperan. In the previous week the patient respond positively to a similar symptoms.


Additional exams: Cranial MRI (normal), abdominal echography (echogenicity hepatic Unclear increased related with the hepatic impairment diffuse, steatosis. Cholelithiasis.

CT of thorax, abdomen and pelvis he distal oesophagus with an unspecific adenopathy near the oesophagus. Thyroid left nodule. Suprarenal right nodule. Small quantity of Free pelvic liquid. panacinar emphysema, with predomination in upper lobules.

Endoscopy: Normal

Follow-up information received on 21 SEP a* from Clinical:

The investigator has requested abdominal MRI and 24h urine (renal tubular acidosis). For the moment he has ruled out a liver biopsy because the performance of this procedure in his site is not optimal. The patient will come tomorrow to the hospital and the idea is to request new tests: CMV, RPR, Parvovirus.

Follow up received on 29 SEP a* from investigator:

On 28 SEP a*, the subject called the investigator complaining of vomiting and weakness. He did not have fever, dysphagia, neither abdominal pain. The subject was admitted to hospital on 29 SEP a*. On 30 SEP a*, a liver biopsy was done. In blood tests, the pH was normal at the moment and lactic acid was 40 (with a normal range until 22). An esophagoscopy and a MNR was planned.

Follow up received from medical monitor on 10 OCT a*:

The last lab results were received. ALT and AST values have improved slightly (220 and 482 respectively). The platelets were trending down (to 82000) and haemoglobin was slightly low again (91 g/L).

Diagnostic Results:

Lactate (5/9/a*) 49.0 mg/dL (5.7 - 22)
Lactate (6/9/a*) 64.0 mg/dL (5.7 - 22)

PH (6/9/a*) 7.3

Bicarbonate (6/9/a*) 23.3

Echography (30/8/a*): liver echogenicity increased, absence of focal lesions  Hepatic elastography 11.1 uPc

Gastroscopy (1/9/a*): normal

TAC (6/9/a*): it shows in the distal part of the oesophagus a moderate thickness with an inespecific adnopathy.

Follow-up information received on 19 DEC a*:

The investigator confirmed the event epigastric pain was not a serious adverse event as previously reported, it was considered to be an associated symptom of the final diagnoses liver toxicity and lactic acidosis.

Follow-up subsequently retrieved from the liver CRFs included:

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the previous week. The subject did not consume alcohol.

Medical conditions included current Chronic hepatitis C and current drug related liver disease, past Chronic hepatitis B, past Cytomegalovirus hepatitis,

There were diagnostic imaging tests performed on 30 AUG a*. The liver imaging method was ultrasound- transabdominal. The images were optimal for technical adequacy. The liver was size was not applicable, texture was heterogenous, and diffuse and/or geographic fatty infiltrate grade was not described steatosis possible. Ascites was not present, no hepatic lesions, no gallstones or gallbladder lesions, no biliary ductal lesions and no portal/hepatic vein abnormalities.

There were diagnostic imaging tests performed on 06 SEP a*. The liver imaging method was computerized tomography. The images were optimal for technical adequacy. The liver was normal for size, texture was normal and diffuse and/or geographic fatty infiltrate grade was not available . Ascites was present, no hepatic lesions, no gallstones or gallbladder lesions, no biliary ductal lesions and no portal/hepatic vein abnormalities.

There were no liver biopsies performed.

Investigator Text:

a*: The year
Admitted to the hospital on 29 AUG a* due to epigastric pain, vomiting and weight loss during last two-three weeks. Transaminases have been increasing since the last control. We have repeated blood analysis to confirm values (for lactate levels too), then we have stopped all the medication (on September 5th) in accordance with the protocol. Vomiting was resolved with metoclopramide and diet.

Patient loose 4 kgs. altogether. Today the 14 SEP a*, the patient continues with anorexia, without vomiting. The transaminases are already elevated in the same range. And lactic acid is 70 mg/dL, with a pH of 7.29 and bicarbonate of 21.7 mmmol/L.

Protocol Id: ING111762
Investigator Number: 081162
Subject Number: 000396
Treatment Number: 3078
Case Id: Z0011729A
Suspect Drugs: Raltegravir
Serious Events: Pneumonia

This 34-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 01 AUG 2018.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included pneumocystis carinii pneumonia. Concomitant medications included Truvada.

On 07 SEP a*, 37 days after the start of investigational product, the subject developed grade 3 or severe community acquired pneumonia. The subject started with a dry cough on 07 SEP a*. The symptoms worsened and the subject presented to ER on 11 SEP a* and was hospitalised. Chest X-ray showed bilateral basilar segmental atelectasis. Laboratory test results dated 11 SEP a* included hematocrit 36.6% (normal range 41-50), haemoglobin 12.2 g/dl (normal range 13.8-17.2), potassium 5.13 MEQ/L (normal range 3.5-5.3), sodium 139 meq/l (normal range 135-146) and WBC count 6.3 thou/mcl (normal range 3.8-10.8). Ultrasound performed on 13 SEP a* due to right upper quadrant pain showed normal result. The subject was treated with moxifloxacin hydrochloride, salbutamol sulphate, azithromycin, paracetamol, enoxaparin, old tuberculin, ondansetron hydrochloride, lorazepam, sodium chloride, mirtazapine, pantoprazole, morphine and Bactrim. Treatment with blinded trial medication was continued. The subject was discharged on 13 SEP a*. The event resolved on 25 OCT a*. The investigator considered that there was no reasonable possibility that the community acquired pneumonia may have been caused by investigational product.

a*: The year
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Module 2.7.4 Summary of Clinical Safety

Investigator text:

Patient developed dry cough on 07 SEP a*. Symptoms worsened and went to ER 11 SEP a* and was admitted for pneumonia. Discharge date was 13 SEP a*. Chest x-rays show bilateral basilar segmental atelectasis. Conmeds will be updated with medications given to patient at discharge. Right quad pain Ultra sound done 13 SEP a* with normal results and a diagnosis of Hyperkalemia.

Protocol Id: ING111762
Investigator Number: 081150
Subject Number: 000586
Treatment Number: 7041, 7041
Case Id: Z0012121A, Z0012121B
Suspect Drugs: Ciprofloxacin hydrochloride, Metronidazole, Raltegravir
Serious Events: Dehydration, Malignant hypertension

This 42-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 28 JUL.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included essential hypertension, hypertension, lacunar infarction and rectal carcinoma. Concomitant medications included aspirin, atorvastatin calcium, paracetamol, clonidine, enalapril maleate, etravirine and darunavir.

On 14 SEP a*, 48 days after the start of investigational product, the subject developed grade 3 or severe malignant hypertension. The subject presented to the ER on 14 SEP a* with chief complaint of shortness of breath, dizziness and unable to walk for one block. The subject was hospitalised with working diagnosis of malignant hypertension (blood pressure 180/110 mmHg; normal systolic 90-139, normal diastolic 60-89) with non-serious rectal bleed. The subject was started on treatment with Lotrel. An ECHO was performed to rule out pulmonary embolism. Most laboratory test results were unremarkable apart from B-type natriuretic peptide of 54 on 15 SEP a*. On 16 SEP a*, the blood pressure remained unstable at 159/100 mmHg and the subject continued to manifest rectal bleeding. The subject denied any chest pain. Colonoscopy result was normal. It was considered that the rectal bleeding was probably secondary to external haemorrhoids and not clinically significant. The event resolved on 16 SEP a* and the subject was discharged on Anusol cream and Lotrel. The investigator considered that there was no reasonable possibility that the malignant hypertension may have been caused by investigational product.

Investigator text:

a*: The year

* 新薬承認情報提供時に置き換え
Was admitted with working dx of Malignant HTN (180/110) with rectal bleed. On 14 SEP a* presented to ER with chief c/o SOB and dizziness unable to walk for 1 block. Patient has chronic HIV infection and hx rectal carcinoma. Patient was closely monitored in DOU for unstable hemodynamics; Arterial B/P at 180/110. Cardiology consult was obtained and was started on Lotrel. An ECHO was performed to rule out Pulm Embolism. 16 SEP a*, Blood pressure remained unstable, 159/100, and continue to manifest rectal bleeding. Admitted to telemetry. Denied chest pain. GI bleed evident, mainly rectal, most labs unremarkable with the exception of BNP. GI was consulted and colonoscopy was done, which was normal. It was considered that the rectal bleeding was probably secondary to external hemorrhoids. On 16 SEP a*, the subject was discharged on Anusol cream and instructed to take Lotrel since instructed by Cardiology.

On 08 DEC a*, 133 days after the start of investigational product, the subject developed grade 3 or severe dehydration. The subject was hospitalised. The subject's past medical history included diarrhea. Concomitant medications included ciprofloxacin hydrochloride, metronidazole, etravirine and darunavir. The subject was treated with sodium chloride and vancomycin. Stool was tested for Clostridium difficile toxin B PCR, Escherichia coli toxin, stool culture, Campylobacter direct antigen, Wright stain; all results were negative. Treatment with blinded trial medication was continued. The subject was discharged home in stable condition on 09 DEC a*. The event resolved on 14 JAN b*. The investigator considered that there was no reasonable possibility that the dehydration may have been caused by investigational product and that the event was possibly due to the concomitant medication, ciprofloxacin hydrochloride and metronidazole.

Subject presented to the Clinical site Asymptomatic and afebrile for study visit IP resupply for Wk16. While conducting the IP dispensation subject shared that he was discharged from the local hospital on 10 DEC a*. Stated he presented to the hospital with diarrhoea, after evaluation by ER Doctor, he was informed that he was going to be admitted for dehydration and r/o C-difficile. No hospital admission record available at this time. Additional information will follow once medical records are received. On 08 DEC a* years old Caucasian male subject presented to the local ER hospital for Dehydration secondary of ongoing diarrheal secondary of Shigella flexneri. He was recently treated for Shigella Flexner with empiric Cipro and Flagyl. This subject has Medical History of AIDS, hypertension, anal cancer, stroke and ongoing Diarrhoea; during his hospitalization the following procedures were performed: B/P140/87, Temp. 98. F, Heart Rate 78, Respiration 18, Stool for Clostridium difficile toxin B PCR, Escherichia coli toxin, stool culture, Campylobacter direct antigen, Wright stain; all negative. It was considered that his symptoms were antibiotic associated (Cipro and Flagyl) diarrhoea and abdominal pain, subject was stable upon discharged home on 09 DEC a*.

Protocol Id: ING111762
Investigator Number: 085520

*a*: The year
*b*: Following year

* 新薬承認情報提供時に置き換え
This 41-year-old male subject was enrolled in a Viiv-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 15 AUG.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included incarcerated incisional hernia. Concomitant medications included Kaletra, zidovudine, clarithromycin, trimethoprim, sulphamethoxazole, nystatin, metoclopramide, omeprazole and Truvada.

On 15 SEP a*, 31 days after the start of investigational product, the subject developed grade 2 or moderate extra pulmonary tuberculosis. The subject was asymptomatic. The subject was hospitalised. Laboratory test results dated 20 SEP a* included ALT 64 U/L (NR 5-41), alkaline phosphatase 972 U/L (NR 40-129), AST 141 U/L (NR 5-38), bilirubin 0.50 mg/dl (NR 0.2-1.1), CRP 18 mg/l (upper normal 10), GGT 563 U/L (NR 15-73), INR 1.32 and prothrombin time 14.7 seconds (lower normal 11.9). Ultrasound of liver and bile ducts performed on 22 SEP a* showed 2 images compatible with abscesses, one in left lobe and one in right lobe. Mycobacterium Tuberculosis PCR (polymerase chain reaction) assay of samples obtained from liver cyst on 27 SEP a* was negative. Also an anatomo-pathologic study was performed on 28 SEP a* which showed no relevant results. Percutaneous liver biopsy was performed on 05 OCT a*. Histological evaluation on 05 OCT a* showed granulomatous inflammation and the presence of acid fast bacilli on ZN stain. The subject was treated with pyrazinamide + ethambutol hydrochloride + rifampicin + isoniazid (Dotbal) and Vitamin B Complex. Treatment with blinded trial medication was discontinued on 10 OCT a* and the subject was withdrawn from the study. The event was unresolved at time of reporting. The subject was discharged with only some pain in the puncture site. The investigator considered that there was no reasonable possibility that the extra pulmonary tuberculosis may have been caused by investigational product.

Investigator text:

We received a lab alert from Quest about a Grade 3 alkaline phosphatase elevation (870 U/L) performed on week4 visit. This abnormality was present at Day 1 but the patient was asymptomatic and during physical examination no relevant signs were found. Therefore we decided to keep monitoring this lab result and the patient's clinical conditions. By 15 SEP a* we received the complete laboratory results where we found
as relevant: AST 176 U/L, ALT 79U/L, bilirubin 8umol/L, CPK normal. After reviewing these and the remaining laboratory results, we concluded that these don't appear to be related to the liver rather than boney disease, so patient came back for a re-evaluation of liver chemistries and ultrasound of liver and bile ducts. The us was performed on 22 SEP a*, and it showed 2 images compatible with abscesses, one in left lobe and one in right lobe. Because of this, subject was hospitalized to figured out the cause of the abscesses and set a treatment. This is SAE follow up of the previous already reported. A sample of the liver cyst/abscess was obtained on 27 SEP a* by percutaneous puncture of the cyst/abscess. It was a clear and serosanguineous sample, and a PCR assay and a anathomopathologic study were made to the sample, with no relevant results. Subject was discharged on 27 SEP a* with only some pain in the puncture site. After no relevant results obtained and considering the extremely low level of CD4+ cell count and the evidence of an infiltrative process, a percutaneous liver biopsy was performed on 05 OCT a*. Histological evaluation showed granulomatous inflammation and the presence of acid fast bacilli on ZN stain. Therefore the patient needs to start on anti-TB drugs and he will be removed from the study because rifampin is not allowed as concomitant medication. Patient will come to a withdrawal visit on 10 OCT a*; clarifying the diagnosis: it means hepatic abscess secondary to tuberculosis.

Protocol Id: ING111762
Investigator Number: 084854
Subject Number: 009016
Treatment Number: 8017
Case Id: Z0012245A
Suspect Drugs: Dolutegravir
Serious Events: Parvovirus infection

This 7-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 05 SEP .

This subject was randomised to receive oral DTG 50 mg once daily.

The subject's past medical history included anaemia. Medical conditions at the time of the event included red cell aplasia consistent with parvovirus infection. Concomitant medications included Aluvia, lamivudine-HIV, stavudine and tenofovir.

On 19 SEP a*, 14 days after the start of investigational product, the subject developed grade 3 or severe parvovirus infection. The subject had been hospitalized twice prior to enrolling in the study. During the first admission of 06 JUN a* bone marrow biopsy and PCR confirmed the Parvovirus infection. The subject was hospitalised on 19 SEP a* due to recurrent anaemia with haemoglobin level of 71 g/l (normal range 120-156). The subject was treated with normal immunoglobulin and 3 units of whole blood. Repeat a*: The year
blood tests performed on 16 NOV a*, 17 NOV a* and 31 JAN b* respectively showed haemoglobin of 9 g/dl, 11.1 g/dl (normal range 12.1-16.3) and 42 g/l (normal range 120-156). Treatment with blinded trial medication was continued. The event was unresolved at time of reporting and the investigator considered it unlikely to completely resolve. The investigator considered that there was no reasonable possibility that the parvovirus infection may have been caused by investigational product.

Investigator text:

First admission: Participant was admitted to hospital with clinical symptoms of anaemia on 06 JUN a* (Hb 6.1g/dl). Bone marrow biopsy and FBC were done on 08 JUN a*. Hb was 9.8 g/dl. Parvovirus PCR was positive and TB culture negative. The diagnosis of the bone marrow biopsy was consistent with pure red cell aplasia secondary to parvovirus infection. Second admission: Was admitted to hospital for recurrent Anaemia (due to Parvovirus Infection). Received 3 units of whole blood. Was referred back to the clinic for conmeds. 3rd admission: Patient with recurrent anaemia (due to Parvo virus infection).

This -year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 04 AUG a* to 01 DEC a*.

The subject was randomised to DTG 50 mg once daily.

The subject's past medical history included high fat diet. There was no other medical history of hepatobiliary disease. Subject was noted to be hepatitis B (surface antigen) and C (antibody) negative at study Day 1. Concomitant medications included Robitussin DM. Subject was not taking acetaminophen.

On 23 SEP a*, 50 days after the start of investigational product, the subject developed grade 3 or severe liver event (increased bilirubin and ALT). The event was clinically significant (or requiring intervention). The subject called the clinic on 28 NOV a* reporting dark coloured urine and pain described as "gas bubble" on the left side of abdomen. On 29 NOV a* a history was obtained and physical exam was performed: temperature 98.3; pulse 72; BP 130/88; Resp 20. 200 poundsHeart: WNL, subject denied
chest pain; Lungs: clear x 5 A and P, Participant stated that he has had congestion and cough since 25 NOV a*, taking Robitussin DM Abdomen: Soft, non-distended, no pain or tenderness upon palpation (patient was actually laughing), no tenderness when liver and spleen palpated. Participant states that BM’s have been normal for him. Describes intermittent abdominal pain usually when lying down. "It feels like a gas bubble that starts here (points to lower left quadrant of abdomen) and moves to here (points to under left ribs). Then, usually when I poop, it goes away." Denied nausea and vomiting.

Skin: Acne and blackheads scattered throughout body. Eczema noted on base of neck. Rash on chest appears to be consistent with the outline of a necklace, +pruritis, slight erythema and no discharge. Participant states, "This man sold me a fake necklace." Rash considered to be an allergic reaction to the jewelry.

Mild to moderate conjunctival icterus

Urogenital: Negative CVA, urine tea colored and cloudy, denies pain or burning with urination.

Musculoskeletal: WNL

Discussion: Participant states that he has a rotten tooth and it needs to be pulled because he can taste it rotting in his mouth.

Education: Discussed risks of infected teeth. Recommended that participant see his care coordinator asap to get a referral to the dentist. Discussed increasing fluid intake to "good" fluids like water, flavoured water and juices. Decrease the pop. Discussed decreasing fast food intake and foods that are high in fat, salt and fried. Participant verbalizes understanding and says he is motivated to make changes.

Ongoing AEs included mild rash on neck since 06 AUG a*; flatus since 04 AUG a*; bloating of abdomen since 09 SEP a*. Subject had eaten lot of grilled chicken, salad and fruit since last visit.

Diarrhoea since 01 DEC a*.

No treatment was given for the SAE. Treatment with investigational product was discontinued on 01 DEC a* and the subject was withdrawn from the study. The investigator saw the subject on 08 DEC a* as part of his routine care. He was doing well and had no abnormal physical examination findings (no hepatomegaly, no abdominal tenderness, no jaundice) and his vital signs were normal. It was noted that there was no plan to obtain liver imagery or a liver biopsy as the subject was clinically stable and his LFTs were normalising rapidly. The event resolved on 12 JAN b*. The investigator considered that there was no reasonable possibility that the liver event (increased bilirubin and ALT) may have been caused by investigational product. Additional follow-up noted that the subject had a Day 1 HCV RNA that was
undetectable, so the data was consistent with an acute HCV infection causing or contributing to the aetiology of the liver chemistry elevation.

Laboratory test results:

23 SEP a*: ALT 71U/L; grade 1 (reference range 0-48U/L); total bilirubin 2.6 (grade 2; reference range 0-1.3 mg/dL); alkaline phosphatase 146 (reference range 20-125U/L); AST 40U/L (reference range 0-42)

18 NOV a*: ASAT 76 (reference 0-42U/L); ALAT 102 (grade 1; reference range 0-48U/L), ALK PHOS 129, Total Bili 3.0 (grade 2; reference range 0-1.3 mg/dl), Direct Bili 0.6 (reference range 0-0.4 mg/dL)

28 NOV a*: Called clinic with report of dark collared urine, pain described feeling like "gas bubble"  on Left side abdomen. Scheduled for Clinic Visit 11/29/a*

29 NOV a*: ASAT 370, ALAT 470, ALK PHOS 140, Total Bili 5.0, Direct Bili 2.0


Additional Diagnostic Results:

Laboratory results from 01 DEC a* disclosed an HCV RNA 54,300 IU/mL with an HCV RAN LOG of 4.73. ALT was 456 (9.5 x ULN), AST was 323 (7.7 x ULN), Alk Phosp was 137 U/L (1.1 x ULN), and Total Bilirubin was 8.1 mg/dL (6.2 x ULN; 43% due to direct bilirubin). As previously noted, Hepatitis C antibodies were Non-Reactive at study Day 1 (02 AUG a*), when medical history was captured as negative for both hepatobiliary disorders and infections and infestations other than HIV-1.

Lab results from 06 DEC a* showed improvement: ALT of 122 (2.5 x ULN), AST of 45 (1.1 x ULN), with Alk Phosp and Bilirubin within normal ranges.

Additional information received via email from clinical team on 15 DEC a*:

The subject's elevated liver chemistries had been trending down since the beginning of December. However, on 13 DEC a* the SGOT and SPGT both elevated again.

Follow-up subsequently retrieved from the liver CRFs included:

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the previous week. The subject did not consume alcohol.

Medical conditions included current chronic hepatitis C. The subject had no drug related liver disease conditions and no other relevant medical conditions.
There were no diagnostic imaging tests performed. There were no liver biopsies performed.

Investigator text:

see Above description. Investigational drug and Background regimen discontinued on 01 DEC a*. Last dose taken at 0600 on 01 DEC a*.

This 3-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 01 JUL a.

This subject was randomised to receive oral DTG 50 mg once daily.

The subject had an upper respiratory tract infection since 30 SEP a* (reported as an AE). Concomitant medications included trazodone, doxepin, lovastatin, citalopram, multivitamins, fish oil, Glucosamine/chondroitin, B vitamins, pseudoephedrine hydrochloride, Ester C, ibuprofen, paracetamol, cyclobenzAPRine hydrochloride, salbutamol sulphate, maraviroc, darunavir, fluticasone propionate and ritonavir.

On 09 OCT a*, 100 days after the start of investigational product, the subject developed grade 2 or moderate pneumonia. It was unknown if the upper respiratory infection was a symptom of the pneumonia. His symptoms worsened and the subject was hospitalised. Chest x-ray at admission showed densities in the right middle lobe consistent with pneumonia. At the time of admission, WBC was 28,200; blood cultures were negative; BUN was 20 mg/dL (7.0-18.0); creatinine 1.4 mg/dL (0.6-1.3); sodium 130 mmol/L (136-145). The subject was treated with ceftriaxone sodium, azithromycin, Septra-DS and cephalexin. Treatment with blinded trial medication was continued. The event resolved on 21 OCT a*. At the time of discharge, WBC 14.6 K/mm3 (4.6-10.2); BUN 11 mg/dL (7.0-18.0); creatinine 0.9 mg/dL (0.6-1.3); sodium 134 mmol/L (136-145). The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by investigational product.

Investigator text:

a*: The year
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Module 2.7.4 Summary of Clinical Safety

Patient had an upper respiratory infection. On 07 OCT a*, he called and asked for a work excuse as he thought he was improving. Over the weekend, his symptoms worsened and he presented to the hospital and was admitted with pneumonia.

no relevant medical history.

Protocol Id: ING111762
Investigator Number: 084854
Subject Number: 009052
Treatment Number: 8022
CaseId: Z0012363A
Suspect Drugs: Dolutegravir
Serious Events: Lower respiratory tract infection

This 23-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 21 SEP.

This subject was randomised to receive oral DTG 50 mg once daily.

No relevant medical conditions were known. Concomitant medications included Aluvia.

On 12 OCT a*, 21 days after the start of investigational product, the subject developed grade 2 or moderate lower respiratory tract infection. The subject developed shortness of breath and was hospitalised. The subject was treated with ampicillin trihydrate, Purbac and ibuprofen. Treatment with blinded trial medication was continued. The event resolved on 17 OCT a*. The investigator considered that there was no reasonable possibility that the lower respiratory tract infection may have been caused by investigational product.

Investigator text:

Participant experienced shortness of breath and was admitted to hospital No relevant medical conditions known. Final diagnosis: LRTI. No further investigations done.

Protocol Id: ING111762
Investigator Number: 081345
Subject Number: 000894
Treatment Number: 4018
CaseId: Z0012272A
Suspect Drugs: Raltegravir
Serious Events: Cerebrovascular accident

a*: The year
This 47-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product per day from 06 JUN 2019.

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included ataxic gait, chronic pulmonary coccidioidomycosis, essential tremor, pneumocystis carinii pneumonia and presyncope. Concomitant medications included fluconazole, enoxaparin, pravastatin and aspirin.

On 13 OCT a*, 129 days after the start of investigational product, the subject developed grade 4 posterior cerebral artery stroke. The subject presented to the emergency room with sudden onset of right sided sensory loss and weakness. CT scan and angiogram showed occlusion of the left P2. CT perfusion showed decreased blood flow with increased transient time and no change CBV in left parietal occipital lobe. The subject was hospitalised and the event was life-threatening. The subject was treated with Lortab, alteplase (tPA, tissue plasminogen activator), aspirin and nicardipine hydrochloride. The treatment with the tPA was successful with reperfusion of the involved artery. Treatment with investigational product was continued. The subject was discharged on 19 OCT a*. The event resolved on 26 JAN b*. The investigator considered that there was no reasonable possibility that the posterior cerebral artery stroke may have been caused by investigational product.

Investigator text:

Per Dr. [deleted], the subject was admitted to the hospital on 13 OCT a* after he presented to the emergency room with sudden onset of right sided sensory loss and weakness. CT scan and angiogram showed occlusion of the left P2. The final diagnosis was thrombotic stroke of the left posterior cerebral artery. Subject was treated with tPA(tissue plasminogen activator) successfully. He was also given 325 mg of aspirin. He was transferred to ICU and subsequently rehabilitation unit. He was given lovenox 40 mg subcutaneous daily while in rehab. He was started on prevastatin 20 mg once daily, Lisinopril 10 mg daily as needed for blood pressure and aspirin 325 daily. He was started on physical and occupational therapy. Study medications were continued during hospitalization. the study was seen for a follow-up on 2 NOV a*. He was doing well without any residual deficits.

Protocol Id: ING111762
Investigator Number: 083829
Subject Number: 002476
Treatment Number: 3087
Case Id: Z0012317A
Suspect Drugs: Dolutegravir
Serious Events: Cerebrovascular disorder

*a*: The year
*b*: Following year
This 51-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 08 AUG 2018.

This subject was randomised to receive oral DTG 50 mg once daily. The subject's past medical history included alcohol abuse. Medical conditions at the time of the event included arterial hypertension. Concomitant medications included enalapril, Tenoric and Kivexa. On 13 OCT 2018, 66 days after the start of investigational product, the subject developed grade 2 or moderate aggravated cerebrovascular disease. A vertebral x-ray obtained on 13 OCT 2018 showed signs of cervical osteochondrosis of C5-C7. The subject was hospitalised on 17 OCT 2018. An ECG obtained that day showed disturbances in intraventricular and intraatrial conduction as a consequence of hypertension. HR was 80 per minute. EchoEG and EEG (date unknown) showed signs of intracranical hypertension, changes in brain electrical activity of desorganized type. The subject was treated with thioctic acid, oxpentifylline, ipidacrine and Milgamma. Treatment with investigational product was continued. The event resolved on 31 OCT 2018 and the subject was discharged. The investigator considered that there was no reasonable possibility that the aggravated cerebrovascular disease may have been caused by investigational product.

Investigator text:

On 18 OCT 2018 the investigator received updated information from subject and his physician that is not compliant with previous report. On 13 OCT 2018 the subject went country-side and took alcohol (beer). In the evening he felt bad and fainted for several minutes. He went back home and called ambulance that registered high blood pressure (with SBP up to 200 mmHg). Subject was advised to refer to his family physician. He did so on 14 OCT 2018 and was referred to hospital (department of neurology) for further assessment and treatment. He was hospitalized on 17 OCT 2018 and reported this to investigator on the same day. Subject was in the hospital until 31 OCT 2018 and received metabolic and vasoactive treatment noted above as well as intravenous cavinton 10% N 10, trental 2% N 10, pyracetam 20% N 14, intramuscular vitamins B2, B12, B6 (no start and stop dates are known from the discharge summary). The subject was discharged with significant improvement and no change of antihypertensive treatment because his hypertension is now well controlled by current therapy.

Protocol Id: ING111762
Investigator Number: 081060
Subject Number: 000181

a*: The year

* 新薬承認情報提供時に置き換え
This 50-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product per day from 29 JUN.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included soft tissue infection. Medical conditions at the time of the event included chronic hepatitis c and recurrent perianal herpes simplex virus.

On 15 OCT, 108 days after the start of investigational product, the subject developed grade 2 or moderate perianal herpes simplex virus. The subject was hospitalised. The subject was treated with acyclovir, magnesium oxide, lignocaine hydrochloride, morphine and oxycodone. Laboratory assessments showed no toxicities as defined by DAIDS criteria. Treatment with investigational product was continued. The event resolved on 05 NOV. The investigator considered that there was no reasonable possibility that the perianal herpes simplex virus may have been caused by investigational product.

Investigator Text:

17 OCT: ER visit for rectal bleeding and pain. Sent home with ongoing Valtrex Rx.
24 OCT: 2nd ER visit, worsening rectal pain and bleeding. Admitted to hospital for IV acyclovir and pain control. Abscess was drained. Patient was discharged from hospital 28 OCT. All symptoms resolved by 5 NOV. SAE due to perianal HSV 2.
This 52-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 28 SEP.

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included previous infection of histoplasma. Concomitant medications included heparin, chlorpheniramine maleate, paracetamol, meropenem, moxifloxacín hydrochloride, sodium chloride, potassium chloride, Potassium chloride + Potassium bicarbonate, metoclopramide, omeprazole, platelet concentrate, plasma, blood products, blood, amphotericin, tenofovir and Lopinavir + ritonavir.

On 19 OCT a*, 21 days after the start of investigational product, the subject developed grade 3 or severe immune reconstitution inflammatory syndrome and grade 3 or severe histoplasmosis disseminate. On 20 OCT a*, the subject developed grade 1 or mild disseminated intravascular coagulation. The subject was hospitalised and the events were life-threatening. Laboratory test results dated 19 OCT a* included haemoglobin 8.63 g/dl (NR 12-17). Laboratory test results dated 20 OCT a* included CD4 lymphocytes 81 cel/ml (NR not specified), haemoglobin 7.08 g/dl, lymphocytes 300 cel/ul, platelet count 76.01 mil/ul (NR 142-424), prothrombin time 14.5 (NR 10-13). Laboratory test results dated 21 OCT a* included haemoglobin 8.53 g/dl. A bronchoscopy with bronchoalveolar lavage performed on 21 OCT a* showed negative stainings, with culture results pending and immunofluorescence test results negative D-dimer 326 ug/l (to 250). Laboratory test results dated 23 OCT a* included platelet count 58.6 k/ul, potassium 3.04 mmol/l (NR 3.6-5). Laboratory test results dated 24 OCT a* included platelet count 61.51 mil/ul, potassium 3.00 mmol/l, prothrombin time 13.2. On 25 OCT a*, platelet count was 53.01 mil/ul. The subject was treated with Trimethoprim + sulfamethoxazole, prednisone, amphotericin, paracetamol and Potassium chloride + Potassium bicarbonate. Treatment with blinded trial medication was continued. The subject was discharged on 26 OCT a*. D-dimer <40 ug/l (to 250) on 04 Nov a*.

The immune reconstitution inflammatory syndrome and histoplasmosis disseminate resolved on 01 NOV a*. The disseminated intravascular coagulation resolved on 04 NOV a*. The investigator considered that there was no reasonable possibility that the immune reconstitution inflammatory syndrome, histoplasmosis disseminate and disseminated intravascular coagulation may have been caused by investigational product.

Investigator text:

In previous visit, reported cough with sputum, fever is not quantified, and chest pain, chest X-ray with mild interstitial micronodular infiltrates, thought of a community-acquired pneumonia and start treatment with levofloxacín 500 mg PO once daily, one and three days later had a telephone conversation with him and referred improvement of general condition and cough. 19 OCT a*, referring to a visit comes one day reappear.
before chest pain, dyspnoea appears not fever. The lung scan abnormalities were not found significant, but respiratory rate 30 per minute and heart rate 120 per minute, chest X-ray shows increased interstitial and micronodular infiltrates on the previous chest X-ray.

IRIS suspect a possibly associated with P. jiroveci pneumonia, deciding hospitalization and empirical treatment with bactrim with prednisone, and microbiological diagnosis approach be performed to establish definitive diagnosis. At the second day: The patient began with disseminated intravascular coagulation with fever + thrombocytopenia + clotting times prolonged and D-dimer increased; a cervical node biopsy was made with positive staining for yeasts consistent with Histoplasmosis capsulatum and Amphotericin B treatment was started. A bronchoscopy with bronchoalveolar lavage showed negative stainings, with culture results pending and immunofluorescence test results was negative to P. Jiroveci. However, we will maintain the P. jiroveci treatment because we can not to discard this pathogen. Currently, the patient is stable without fever and dyspnoea, only persists clotting times prolongation and thrombocytopenia as part of disseminated intravascular coagulation secondary by Histoplasmosis infection. The patient was discharged from the hospital on 26 OCT a* and continue with outpatient therapy to complete the Amphotericin B and trimethoprim + sulfamethoxazole treatment.

This 18-year-old male subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 16 AUG.

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included hypertension. Concomitant medications included lisinopril, etravirine, darunavir and ritonavir.

On 24 OCT a*, 69 days after the start of investigational product, the subject developed grade 2 or moderate non cardiac chest pain. The subject was hospitalised on 24 OCT a* due to chest pain and shortness of breath. The subject was treated with nitroglycerine, metoprolol, valsartan, frusemide, aspirin, metoprolol tartrate and clopidogrel bisulphate. Results of diagnostic tests were as follows:

Protocol Id: ING111762
Investigator Number: 081143
Subject Number: 000612
Treatment Number: 3095, 3095
Case Id: Z0012728A, Z0012728B
Suspect Drugs: Raltegravir
Serious Events: Cardiomyopathy, Non-cardiac chest pain

* 新薬承認情報提供時に置き換え
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CK, Total 260 Normal range (39-308 U/L)

CK-MB 2.8  0.0 - 5.0 ng/ml

CK-MB Index 1.1  0.0 - 4.0

Troponin-T <0.01  <0.03

D-Dimer, ELISA  883 0 - 500

ECG Normal sinus rhythm with left ventricular hypertrophy.

Chest X-Ray - No radiographic evidence of acute cardiopulmonary disease.

NM Lung scan - Normal perfusion

Treatment with blinded trial medication was continued. The event resolved on 25 OCT a* and the subject was discharged in a stable condition. The investigator considered that there was no reasonable possibility that the non cardiac chest pain may have been caused by investigational product and that the event was possibly due to the subject's uncontrolled hypertension.

Investigator text:

08 NOV a*-Patient came in for Week 12 visit and reported he went to [deleted] Hospital 24 OCT a* due to Chest Pain and Shortness of breath. He was treated and discharged home 25 OCT a* in stable condition. Data will be updated as soon as records is available from hospital.

On 14 JUN b*, 303 days after the start of investigational product, the subject developed grade 3 or severe decompensated cardiomyopathy. The subject presented to the ER on 16 JUN b* with shortness of breath. The subject was hospitalised. Medical conditions at the time of the event included cardiomyopathy. Concomitant medications included salbutamol sulphate, darunavir, etravirine and ritonavir. Three sets of cardiac enzymes were all negative for acute myocardial infarction. (16 JUN b* 1420 CKMB 3.7, 6/16/b* 2205 CKMB 2.8 troponin <0.01, 17 JUN b* 0755 CKMB 2.3 troponin <0.01. Normal CKMB range is 1-3, normal troponin range is <0.01). 2D echo was obtained which demonstrated ejection fraction of 15-20% (normal EF above 65%). The subject was treated with aspirin, enoxaparin, famotidine, lisinopril and nitroglycerine. Treatment with blinded trial medication was continued. The event resolved on 18 JUN b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the decompensated cardiomyopathy may have been caused by investigational product.

Investigator text:

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
Subject presented to ER on 16 JUN b* with shortness of breath. He has a history of cardiomyopathy, he had 3 sets of cardiac enzymes which were all negative as above for acute myocardial infarction. 2D echo was obtained which demonstrated ejection fraction of 15-20%. Subject was seen in consultation by cardiologist and treated with lasix, lisinopril, nitroglycerin. He was discharged home on 18 JUN b*.

Protocol Id: ING111762
Investigator Number: 081143
Subject Number: 000611
Treatment Number: 4016
Case Id: Z0012653A
Suspect Drugs: Raltegravir
Serious Events: Dyspnoea, Hyperglycaemia

This -year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 02 JUN .

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included diabetes mellitus type 2. Concomitant medications included sodium chloride.

On 28 OCT a*, 148 days after the start of investigational product, the subject developed grade 3 or severe dyspnoea and grade 3 or severe hyperglycaemia. The subject was hospitalised on 28 OCT a* with complaints of shortness of breath and fatigue. Serum glucose on admission on was 652 mg/dl (normal range 70-110), CO2 29.9 and urine analysis was negative for ketones. CT angio of chest performed on 28 OCT a* was negative for pulmonary embolism; D-dimer was 0.44 (unremarkable). The subject was treated with glipizide, insulin aspart and short-acting insulin. Treatment with blinded trial medication was continued. Re-test on 30 OCT a* showed serum glucose of 226 mg/dl. The events resolved on 31 OCT a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the dyspnoea and hyperglycaemia may have been caused by investigational product.

Investigator text:

PI received call from patient's Primary Care Physician who reported patient was admitted to [deleted] hospital recently for dyspnoea and increased blood sugar. Work up negative. Primary Care Physician did more work up - result negative. Records to be obtained from the hospital and patient scheduled for follow up visit. 09 NOV a*

Patient followed up in office and reported she was admitted to [deleted] Hospital on 28 OCT a* with complaints of shortness of breath and fatigue. She was discharged.

a*: The year
b*: Following year
This 35-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 01 SEP.

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included hypertension. Hypertension was documented on Day 01, 01 SEP a*. Worsening of Hypertension since 31 OCT a*.

On 31 OCT a*, 60 days after the start of investigational product, the subject developed grade 3 or severe hypertension aggravated with blood pressure of 255/156 mmHg (normal range 80-120). The subject was hospitalised on 01 MAY b*. The subject was treated with enalapril maleate, amlodipine-S and hydrochlorothiazide. Treatment with blinded trial medication was continued. The event resolved on 03 MAY b* and the subject was discharged with blood pressure of 142/92 mmHg and heart rate 75 bpm.

The investigator considered that there was no reasonable possibility that the hypertension aggravated may have been caused by investigational product.

Blood pressure measurements:

23 NOV a*: 129/93 mmHg, 28 NOV a*: 168/112 mmHg, 19 DEC a*: 159/101 mmHg, 16 FEB b*: 113/82 mmHg, 12 APR b*: 246/144 mmHg, 26 APR b*: 146/102 mmHg

Investigator text:

Protocol Id: ING111762
Investigator Number: 084854
Subject Number: 002905
Treatment Number: 4042
Case Id: Z0015368A
Suspect Drugs: Raltegravir
Serious Events: Hypertension
Patient was admitted to hospital on 01 MAY b* due to Hypertension. No blood tests or other procedures were done. He received new Hypertension medication and was discharged on 03 MAY b*. Participant informed the site immediately about incident. BP on site was 142/92, Pulse 75 (03 MAY b*).

Protocol Id: ING111762
Investigator Number: 084775
Subject Number: 009113
Treatment Number: 3105
Case Id: Z0012975A
Suspect Drugs: Dolutegravir
Serious Events: Fibula fracture

This 38-year-old male subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 31 AUG a*

This subject was randomised to receive oral DTG 50 mg once daily.

Concomitant medications included omeprazole for peptic ulcer prophylaxis.

On 04 NOV a*, 65 days after the start of investigational product, the subject had a sprained ankle and developed grade 2 or moderate fibula fracture. Fractured fibula was diagnosed by X-ray. The subject was given ibuprofen and scheduled for surgery. The subject was hospitalised on 22 NOV a* and underwent placement of osteosynthesis material on the same day. The subject was treated with cephalaxin. Treatment with blinded trial medication was continued. The subject was discharged on 23 NOV a* without complications. The event resolved on 21 DEC a*. Per the investigator, there were no predisposing conditions. The investigator considered that there was no reasonable possibility that the fibula fracture may have been caused by investigational product.

Investigator text:

Patient had a sprained ankle on 04 NOV a*. He consulted the hospital the same day and a fractured fibula was diagnosed by X-ray. It was indicated analgesics and a surgery was scheduled for placement of osteosynthesis material. Meanwhile, the patient remained at home and on 22 NOV a* he was admitted at the hospital for the surgery and was discharged the following day without complications.

a*: The year
b*: Following year
This 43-year-old male subject was enrolled in a ViiV-sponsored, Phase III randomized, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 Weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 25 OCT.

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included neutropenia. Concomitant medications included stavudine and Aluvia.

On 12 NOV a*, 18 days after the start of investigational product, the subject developed grade 2 or moderate tuberculosis of liver. Symptoms included generalised headaches, fever and night sweats. The subject was hospitalised for investigations and to exclude meningitis. No specific findings on examination. The subject was treated with Piperacillin/tazobactam, itraconazole, tramadol hydrochloride, filgrastim, pethidine hydrochloride, Rifafour and pyridoxine. Treatment with blinded trial medication was discontinued on 16 NOV a* and the subject was withdrawn from the study. Other anti-retroviral medication was stopped on 16 NOV a*. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the tuberculosis of liver may have been caused by investigational product.

Diagnostics:

CD4, Viral load, Hb, WCC, Neutro, Platelets, Total Bili, Alk Phos, GTT, ALT, AST, Potassium, Serum Bicarb, Urea, Creat, EGFR, Lumbar Puncture, Chest Xray, Ultrasound abdomen, MRI brain, Toxoplasma IgG, RPR, CMB IgM, urine + blood cultures, liver biopsy CD4, Viral load, WCC, Neutrophils, Alkaline phosphatase, GTT, ALT, AST, Urea, Creatinine, eGFR, Liver biopsy, Hb (these were abnormal and not clinically significant)

Investigator text:

Generalised headaches + fever + night sweats since 12 NOV a*. No specific findings on examination. Patient admitted for investigations and to exclude meningitis. All anti-retroviral therapy stopped 16 NOV a*.

* 新薬承認情報提供時に置き換え
This 31-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 03 OCT 2020.

This subject was randomised to receive oral DTG 50 mg once daily.

The subject's past medical history included pneumocystis carinii pneumonia. Concomitant medications included dapsone, tenofovir disoproxil fumarate and maraviroc.

On 12 NOV a*, 40 days after the start of investigational product, the subject developed grade 3 or severe methemoglobinemia and grade 3 or severe viral pneumonia. The subject presented to the ER complaining of shortness of breath and productive cough and was hospitalised. Oxygen saturation at admission on 12 NOV a* was 88%. Treatment with investigational product was interrupted on 12 NOV a*. On 16 NOV a*, the subject developed grade 2 or moderate hyperkalemia of 5.4 mmol/l (normal range 3.3-4.9). Methemoglobin level on 16 NOV a* resulted at 18% (upper limit of normal at 1.9%). The subject was treated with clindamycin, primaquine, methylene blue, azithromycin, calcium gluconate, dextrose, insulin and sodium polystyrene sulfonate. Treatment with investigational product was restarted on 20 NOV a*. The events resolved on 20 NOV a*. The investigator considered that there was no reasonable possibility that the methemoglobinemia, viral pneumonia and hyperkalemia may have been caused by investigational product and that the methemoglobinemia was possibly due to the concomitant medication, dapsone.

Investigator text:

Patient reported to Emergency Room with complaint of shortness of breath and productive cough, O2 saturation at admission was 88%. Methemoglobinemia possibly related to Dapsone medication for treatment of PCP which is an ongoing medical history condition.

Methemoglobin level found to be at 18% on 16 NOV a*. Potassium levels on 16 NOV a* were at 5.4 mmol/L.

a*: The year
On 29 MAR b*, 178 days after the start of investigational product, the subject developed grade 3 or severe pneumonia and grade 3 or severe respiratory distress. Chest X-ray on 29 MAR b* showed diffuse interstitial infiltrates. Sputum tests for TB and PCP were both negative for growth. Additional laboratory test results from 29 MAR b*: Chloride 96 mmol/l (NR 97-110); creatinine 1.42 mg/dl (NR 0.7-1.3); neutrophils 14 K/cumm (NR 1.8-6.6); potassium 5.1 mmol/l (NR 3.3-4.9); WBC count 16 K/cumm (NR 3.8-9.8); pCO2 72 mmHg (NR 35-45); pH 7.29 (NR 7.35-7.45); pO2 72 mmHg (NR 80-105).

On 11 APR b*, 191 days after the start of investigational product the subject developed grade 3 or severe rhabdomyolysis. The subject presented with complaints of pain in his lower extremities and stiffness and pain in his neck. He was hospitalized with concerns of worsening of his pneumonia and pain. Concomitant medications at the time of admission included heparin sodium, paracetamol, prochlorperazine, Percocet and azithromycin. Medical conditions at the time of the event included asthma and chronic obstructive pulmonary disease. The subject was treated with salbutamol sulphate, azithromycin, naloxone, clindamycin, primaquine, prednisone, vancomycin, cefepime, ipratropium bromide, moxifloxacin hydrochloride and sodium chloride. CT Scan of the chest on 11 APR b* showed pneumonia but this was determined to be stable and improving, so all antibiotics were discontinued after 12 hours. Lumbar puncture performed on 11 APR b*, contained no white cells. Multiple cultures were done on 11 APR b*, none showed growth after 48 hours.

Treatment with investigational product was continued. The respiratory distress resolved on 02 APR b*, rhabdomyolysis resolved on 13 APR b*, and the pneumonia resolved on 18 APR b*. Final diagnosis was Rhabdomyolysis. Infectious Disease was consulted and they suggested a possible interaction between Avelox and Tenofovir as a potential cause for this. Subject was aggressively hydrated and the symptoms resolved. The investigator considered that there was no reasonable possibility that the pneumonia, respiratory distress and rhabdomyolysis may have been caused by investigational product, and that the rhabdomyolysis was caused by pneumonia and dehydration. The investigator did not agree with a possible interaction being the cause for the subjects symptoms, but more likely due to the pneumonia and dehydration considering the symptoms were resolved with hydration and the short duration of the symptoms. Subject has previously taken Avelox while on Tenofovir and had no issues at that time.

Additional follow-up information was received 07 JUN b*: CPK follow up was done on May 14th with a value of 1082 u/l. No influenza testing was completed. Several Creatinine levels were obtained as follows: 11 APR b* at 00:22, 0.82 mg/dl; 11 APR b* at 23:55, 0.80 mg/dl; 12 APR b* at 23:05, 0.99 mg/dl and on 14 MAY b* 1.00 mg/dl, with eGFR Creatinine Clearance value of 92 mL/min/1.73

Investigator text:

Subject admitted to hospital for pneumonia after presenting due to shortness of breath, cough, and fever. Subject has a history of COPD and Asthma. Subject discharged from
hospital on 02 APR b*. Returned to the hospital on 11 APR b* due to pain in lower extremities and possible worsening of pneumonia. Started on IV antibiotics however pneumonia was deemed stable and improving, antibiotics discontinued. Subject was diagnosed with rhabdomylosis. Subject was aggressively hydrated and symptoms improved. Discharged on 13 APR b* after symptoms resolved. PI believes rhabdomylosis was caused by combination of pneumonia and dehydration.

Protocol Id: ING111762
Investigator Number: 084735
Subject Number: 002371
Treatment Number: 7069, 7069
Case Id: Z0013025A, Z0013025B
Suspect Drugs: Raltegravir
Serious Events: Anaemia, Immunoblastic lymphoma

This 41-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 27 SEP .

The subject was randomized to receive RAL 400 mg twice daily.

The subject presented with grade 3 anaemia at enrolment.

On 22 NOV a*, 56 days after the start of investigational product, the subject developed grade 4 anaemia aggravated. Haemoglobin was measured at 63 G/L (normal range 120 to 156). The subject experienced pallor and weakness. The subject was hospitalised. The subject was treated with Tot'hema and red blood cells. Treatment with blinded trial medication-viiv was interrupted on 28 NOV a*. The event resolved on 13 DEC a* with haemoglobin of 94 G/L. Treatment with investigational product was restarted on 16 DEC a*. The investigator considered that there was no reasonable possibility that the anaemia aggravated may have been caused by investigational product.

Investigator text:

The SAILING Subject 002371 was in immunological and virologic failure at the time of enrolment, with anaemia caused by some action on HIV, but also low-iron diet (iron deficiency anaemia). At the time of enrolment, patient presented G3 anaemia, but G3 was maintained at future visits (Day 1, W4) without clinical manifestations. In 22 NOV a*, despite the Hb value (G4), patients had only pallor and weakness.

The patients was treated with TOT'HEMA 20 ml/12h(start in 28 NOV a*, ongoing) and Red cell transfusions in 28 and 29 NOV a*, 1 UNIT/day. After UNSCH of 13 DEC a*, the HB was 94 g/l and patient re-started taking therapy on 16 DEC a*.
On 01 MAR b*, 156 days after the start of investigational product, the subject developed grade 4 immunoblastic lymphoma. The subject was hospitalised on 01 MAR a*. No relevant medical history was reported. Concomitant medications at the time of admission included tenofovir disoproxil fumarate and emtricitabine. Jaundice was noted at the time of admission. Blood test performed on 02 MAR b* showed haemoglobin 5.2 g/dl (normal range 11-15) and platelet count 33x10^3/µl (normal range 150-350). The subject was treated with red blood cells. Following treatment with red blood cells, haemoglobin increased to 86 g/l on 06 MAR b*, but platelets decreased to 15 G/l on 06 MAR b*. The value of bilirubin on 02 MAR b* was 5.35 mg/dl (normal range 0.2-1.1) and worsened to 13.29 mg/dl on 09 MAR b*. The subject was diagnosed with lymphoma on 06 MAR b* and transferred to the haematology section of the hospital. The subject was further treated with platelet concentrate and ursodeoxycholic acid. No additional treatment was given. It was unconfirmed whether the subject was scheduled to receive chemotherapy. A biopsy was scheduled to be performed after the subject's thrombocytopenia resolved (to date not resolved and biopsy not performed). Both anaemia and thrombocytopenia were considered related to the lymphoma. Treatment with investigational product was discontinued on 02 MAR b* and the subject was withdrawn from the study. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the immunoblastic lymphoma may have been caused by investigational product.

Investigator text:

The patient was admitted to hospital for social reasons (she became homeless) on 01 MAR b*. She was showing only jaundice because of Reyataz but we decided to test the blood. Her HB dropped at 5 g/dl and today we have stopped her medication. After red cells transfusion, Hb increased = 86g/l in 06 MAR b*, but platelets decreased = 15 G/l in 06 MAR b*. The value of Billirubin in 02 MAR b* was 5.35 mg/dl and worsened in 09 MAR b* = 13.29 mg/dl. She was diagnosed with lymphoma in 06 MAR b* and transferred to the haematology section of the hospital. All the events mentioned at the beginning we think are related with the lymphoma. There was no additional treatment for lymphoma. The patient is still unconfirmed.
daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 30 AUG 

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included bipolar disorder. Concomitant medications included mirtazapine, aripiprazole, darunavir, ritonavir and etravirine.

On 02 DEC a*, 94 days after the start of investigational product, the subject developed grade 3 or severe suicidal ideation. The subject was hospitalised on 02 DEC a* for evaluation of suicidal ideations. The subject has not refilled concomitant mirtazapine. No diagnostic tests were performed. Treatment with blinded trial medication was continued. The subject was found stable and was discharged on 06 DEC a*. The event resolved on 09 DEC a*. The investigator considered that there was no reasonable possibility that the suicidal ideation may have been caused by investigational product.

Investigator text:

subject was hospitalized 02 DEC a* through 06 DEC a* for evaluation of Suicidal Ideations. Had not refilled conmed (mitazapine). No diagnostic tests were done, instead subject was hospitalized for observational purposes. subject was found stable and released on 06 DEC a*. Subject is following up with psych counsellor. Subject was followed up in office with PI on 09 DEC a*, dose for mirtazapine and Abilify has not changed.

Protocol Id: ING111762
Investigator Number: 084854
Subject Number: 009095
Treatment Number: 4077
Case Id: Z0013617A
Suspect Drugs: Raltegravir
Serious Events: Anaemia

This 47-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 14 NOV .

This subject was randomised to receive oral RAL 400 mg twice daily.

Concomitant medications included lamivudine-hiv and tenofovir.
On 06 DEC a*, 22 days after the start of investigational product, the subject developed grade 4 anaemia with haemoglobin of 45 g/l (normal range 120-156). The subject developed palpitations, malaise and frontal headache on 06 DEC a*. The subject was hospitalised on 15 DEC a* by a non-study physician and received 2 units of blood. Stools were MCS and clostridium neg. SPEP: no monoclonal bands Treatment with blinded trial medication was interrupted on 06 DEC a*. Haemoglobin on 21 DEC a* measured 8.2 g/dl (normal range 12.1-16.3). The subject was withdrawn from the study on 11 JAN b* because of receiving different ART during her stay in the hospital. The event resolved on 11 JAN b*, with haemoglobin result of 97 g/l.

The investigator considered that there was no reasonable possibility that the anaemia may have been caused by investigational product.

Investigator text:

Participant was admitted to hospital on 15 DEC a* and only reported it to the site on 09 JAN b*. She need to go back to the hospital for follow-up on 10 JAN b* and will ask the doctor to contact the site. Entries will be updated once more information available. She is still off-product.

Received 2 units of blood. Hospital record indicates: Presented with history of palpitations, malaise and frontal headache.

Protocol Id: ING111762
Investigator Number: 081669
Subject Number: 000947
Treatment Number: 8014
Case Id: Z0013254A
Suspect Drugs: Raltegravir
Serious Events: Depression suicidal

This 37-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 29 AUG .

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included depression. Concomitant medications included darunavir, etravirine and ritonavir.

On 08 DEC a*, 101 days after the start of investigational product, the subject developed grade 3 or severe exacerbation depression with suicidal ideation. The subject presented at the clinic on 08 DEC a* tearful, depressed and expressing suicidal
ideation. The subject was hospitalised. The subject was treated with lexapro, lisinopril and zolpidem. Treatment with blinded trial medication was continued. The event resolved on 16 DEC a*. The investigator considered that there was no reasonable possibility that the exacerbation depression with suicidal ideation may have been caused by investigational product.

Investigator text:

Patient presented to clinic on 8 DEC a* tearful, depressed and expressing suicidal ideation. She has a history of depression for which she was under treatment at study entry. She was observed in the Psychiatric Emergency Room overnight and admitted to an inpatient psychiatric unit the next day. As this is a young woman, perinatally infected with HIV, currently failing treatment, and has a history of depression currently under treatment, worsening of depression is not a surprising complication. Subjects in studies are closely monitored by both the study team and primary care provider, and interventions are often timely when appropriate. It is unlikely that we can prevent such problems in the future, but we can intervene as was done in this case.

Protocol Id: ING111762
Investigator Number: 081164
Subject Number: 001015
Treatment Number: 8010, 8010, 8010
Case Id: Z0013536A, Z0013536B, Z0013536C
Suspect Drugs: Hydrocodone, Raltegravir
Serious Events: Intestinal obstruction, Mental status changes, Small intestinal obstruction

This 22-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 16 AUG a*. This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included chronic diarrhoea. Medical conditions at the time of the event included chronic pain. Concomitant medications included darunavir, ritonavir, tenofovir disoproxil fumarate, Combivent, alprazolam, ammonium lactate, aspirin, Symbicort, rosuvastatin calcium, cetirizine hydrochloride, ciprofloxacin, diltiazem hydrochloride, diphenhydramine, docusate, enoxaparin, ethacrynic acid, fluconazole, gabapentin, hydralazine, hydromorphone hydrochloride, ketorolac tromethamol, magnesium sulfate, metoclopramide, miconazole, treacle, morphine, nalbuphine, ondansetron hydrochloride, pantoprazole, phenol, potassium chloride, valaciclovir hydrochloride, zolpidem, mupirocin and Potassium phosphate.

* 新薬承認情報提供時に置き換え
On 12 DEC a*, 118 days after the start of investigational product, the subject developed grade 4 intestinal obstruction. The subject presented at the ED on 25 DEC a* complaining of acute abdominal pain. The subject was hospitalised on 26 DEC a* and the event was life-threatening. Abdominal CT showed high grade partial small bowel obstruction. The subject underwent laparoscopic lysis of adhesions with relief of her obstruction on 26 DEC a*. During the operation an enterotomy was repaired primarily. Postoperatively she did well however she did have an ileus which responded well to an aggressive bowel regimen. The subject was treated with albumin and cefoxitin sodium. Treatment with blinded trial medication was interrupted on 25 DEC a*. The event resolved on 02 JAN b* and the subject was discharged. The subject also had a UTI which was treated with ciprofloxacin, but which was not considered to be serious. Treatment with investigational product was re-started on 03 JAN b*. The investigator considered that there was no reasonable possibility that the intestinal obstruction may have been caused by investigational product.

Investigator text:

- years old female went to ED on night of 25 DEC a* complaining of acute abdominal pain and was admitted to general surgery service on 26 DEC a* after abdominal CT confirmation consistent with small bowel obstruction. In retrospect she believes she was having some minor abdominal pain leading up to this acute event for 2 weeks prior but ignored it. On 26 DEC a* she underwent laparoscopic lysis of adhesions with relief of her obstruction. During the operation an enterotomy was repaired primarily. Postoperatively she did well however she did have an ileus which responded well to an aggressive bowel regimen. During her hospital stay she was also found to have a UTI which she received 3 days of IV Cipro & discharged home with a 10 day course of po Cipro. She was discharged home on 02 JAN b* recovered. Her study medications were held from her 25 DEC a* pm dose and resumed 03 JAN b* in full. The cause of her obstruction is unclear yet it is not thought to be related to any study medications or study related procedures. She will follow up as scheduled 30 JAN b*.

On 30 MAR b*, 227 days after the start of investigational product, the subject developed grade 4 small intestine obstruction. The subject developed stomach pain on 30 MAR b*. The subject was hospitalised on 01 APR b* and the event was life-threatening. The subject underwent exploratory laparotomy with lysis of adhesions as corrective treatment. Treatment with blinded trial medication was interrupted on 01 APR b* and re-started on 12 APR b*. The event resolved on 12 APR b*. The investigator considered that there was no reasonable possibility that the small intestine obstruction may have been caused by investigational product and that the event was possibly due to the concomitant medication, hydrocodone.

Medical conditions at the time of the event included chronic knee and back pain, and substance abuse. Concomitant medications included hydrocodone, darunavir, ritonavir, tenofovir disoproxil fumarate, Vicodin, ammonium lactate, cetirizine hydrochloride, calcium carbonate, clopidogrel, aspirin, diltiazem hydrochloride, diphenhydramine, gastrointestinal drug(s), haloperidol, heparin, hydralazine, hydromorphone hydrochloride,
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labetalol hydrochloride, lisinopril, loperamide hydrochloride, lorazepam, magnesium oxide, magnesium sulfate, metoprolol, morphine, multivitamins, nitroglycerine, pantoprazole, promethazine, rosuvastatin calcium, thiamine, valaciclovir hydrochloride, zolpidem, cefoxitin sodium and ondansetron hydrochloride.

Investigator text:

Subject was admitted to hospital on 01 APR b* for stomach pain starting on 30 MAR b* and underwent exploratory laparotomy with lysis of adhesions while in hospital. This event has likely been caused by her use of hydrocodone which she uses for chronic back and knee pain.

On 03 JUN b*, 292 days after the start of investigational product, the subject developed grade 1 or mild mental status changes due to benzodiazepines and opioids. Her potassium result on 03 JUN b* was 2.9 mEq/L (normal 3.5 - 5.0 mEq/L). She had been found unresponsive in a smoke filled house and taken to the emergency department. Urine drug screen (UDS) came back positive for cocaine and 'benzos' (benzodiazepines). The subject was hospitalised. CT scan of head was normal, carboxyhemaglobin was normal. Urine analysis (UA) was positive for UTI and she was treated with ciprofloxacin. The events resolved on 04 JUN b*, repeat potassium result was 4.4 mEq/L (3.5 - 5.0 mEq/L).

The subject's past medical history included polysubstance abuse - cocaine. Concomitant medications included paracetamol, ciprofloxacin, heparin, potassium chloride, darunavir and tenofovir.

The investigator considered that there was no reasonable possibility that the mental status changes may have been caused by investigational product and that the event altered mental status was related to cocaine and 'benzo' abuse.

Investigator text:

subject was found unresponsive in smoke filled house & taken to ED. UDS came back positive for cocaine & benzos. UA positive for UTI- treated with cipro. She was kept in observation- CT head normal, carboxyhemaglovin normal. Impression is that altered mental status is related to cocaine and benzo abuse. She was discharged at 24 hours awake and alert. She was informed to b/u with her study team on Thursday.

Protocol Id: ING111762
Investigator Number: 081138
Subject Number: 001152
Treatment Number: 30584
Case Id: Z0013466A
Suspect Drugs: Raltegravir
Serious Events: Cellulitis, Gangrene, Peripheral arterial occlusive disease

b*: Following year
This 53-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 13 DEC.

This subject was randomised to receive oral RAL 400 mg twice daily. Concomitant medications included darunavir, ritonavir, maraviroc, amitriptyline hydrochloride, famotidine, quetiapine, amlodipine, Prempro, fluoxetine hydrochloride, docusate sodium, hypromellose, magnesium hydroxide, diphenhydramine hydrochloride, bisacodyl, esomeprazole, Duoneb and zolpidem tartrate.

On 13 DEC a*, same day after the start of investigational product, the subject developed grade 3 or severe arterial occlusion of lower leg and grade 3 or severe cellulitis. The subject had symptoms - warm and tender right foot - at day 1 visit. The subject was hospitalised on 22 DEC a* and the events were disabling and life threatening. Treatment with investigational product was interrupted on 22 DEC a* and restarted on 26 DEC a*. Lower Extremity Sonogram 22 DEC a* revealed acute arterial occlusion. Abdominal aortogram 22 DEC a* revealed occlusion of the common iliac arteries bilaterally. CXR 22 DEC a* revealed COPD without acute abnormality.

The subject underwent femoral/popliteal bypass. The bypass and subsequent bypass were unsuccessful. Abdominal Aortogram on 28 DEC b* revealed 2 new occlusions in the right leg. On 28 DEC a* the subject underwent a revision of the graft and removal of clots. On 10 JAN b*, 28 days after the start of investigational product, the subject developed grade 4 gangrene. The subject had toes 3 to 5 amputated on 11 JAN b*. The subject was discharged on 16 JAN b*. The subject was re-admitted on 04 FEB b* with pain in the right leg. Attempts at bypass were again unsuccessful. Attempts at revascularization were undertaken on the 05, 06 and 07 FEB b*. Aortogram 06 FEB b* revealed complete occlusion of the right common iliac artery and occlusion of the right femoral-popliteal bypass. The subject underwent a below the knee amputation on 10 FEB b*. The subject was treated with hydromorphone hydrochloride, cephalexin, heparin, cephalizin sodium, Percocet, morphine, diphenhydramine hydrochloride, midazolam hydrochloride, fentanyl, zolpidem, Lortab, alprazolam, hydralazine hydrochloride, ampicillin trihydrate, promethazine, ondansetron hydrochloride, ketorolac trometamol, pethidine hydrochloride, clopidogrel bisulphate, enoxaparin, paracetamol, esmolol hydrochloride, labetalol hydrochloride, piperacillin sodium, vancomycin, albumin, frusemide and potassium chloride. Investigational product was interrupted from 04 to 15 FEB b*. The gangrene resolved on 10 FEB b*. The arterial occlusion of lower leg resolved with sequelae on 28 FEB b* and the subject was discharged on the day. The cellulitis was resolved with sequelae on 29 FEB b*. The investigator considered that there was no reasonable possibility that the arterial occlusion of lower leg, cellulitis and gangrene may have been caused by investigational product.
Investigator text:

Subject had symptoms at day one visit. Right foot was warm and tender. Tx with antibiotics. Subject went for U/S and was admitted to hospital on 22 DEC a*. Had femoral/popliteal bypass. Hospital staff was unresponsive to patient assertion that she was on clinical trial. Staff was not contacted here until 26 DEC a*. Hospital pharmacy contacted and patient allowed to restart her study drugs and OBT at that time. The bypass and subsequent bypass were unsuccessful. On 28 DEC a* she has a revision of the graft and removal of clots. On 11 JAN b* She had toes 3-5 amputated. She was discharged home on 16 JAN b*. She was admitted to a second hospital on 04 FEB b* with pain in the right leg. Attempts at bypass were again unsuccessful. Attempts at revascularization were undertaken on the fifth, sixth and seventh of February. She underwent a below the knee amputation on 10 FEB b*. She was off her study medications from 04 - 15 FEB b*. She was discharged home on 28 FEB b*.

Protocol Id: ING111762
Investigator Number: 084854
Subject Number: 009012
Treatment Number: 8018
Case Id: Z0013537A
Suspect Drugs: Raltegravir
Serious Events: Acute hepatic failure, Coagulation factor deficiency, Epistaxis, Infection, Renal failure acute

This *year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 06 SEP .

The subject was randomised to receive oral RAL 400 mg twice daily.

The subject had no known risk factors. Concomitant medications included Aluvia.

On 19 DEC a*, 104 days after the start of investigational product, the subject developed grade 2 or moderate infection unknown origin. On 31 DEC a*, the subject developed grade 4 acute hepatic failure, grade 2 or moderate acute renal failure, grade 2 or moderate epistaxis and grade 2 or moderate coagulation factor deficiency. The subject was hospitalised. The subject was treated with red blood cells, lactulose, vitamin k and plasma. Treatment with investigational product was discontinued in December a* (exact date unknown) and the subject was withdrawn from the study. The epistaxis and coagulation factor deficiency were resolved on 01 JAN b*. The subject died on 01 JAN b* due to acute hepatic failure and acute renal failure. The infection unknown origin was unresolved at the time of the subject's death. The investigator considered that there was no reasonable possibility that the acute hepatic failure, infection unknown origin...
origin, acute renal failure, epistaxis and coagulation factor deficiency may have been caused by investigational product.

Diagnostic Results (31 Dec a*)

Bilirubin, 164 mol/L (0.0 - 21.0)
Aspartate Amino Transferase, 2950 uL (5.0 - 40.0)
Alanine Amino Transferase, 749 UL (5.0 - 40.0)
Alkaline phosphatase, 271 UL (40.0 - 120.0)
Gamma-glutamyltransferase, 196 UL (0.0 - 60.0)
Lactic dehydrogenase, 1995 UL (100.0 - 190.0)
Creatine, 678 mo/L (60.0 - 120.0)
Phosphate, 2.71 mmol/L (0.8 - 1.4)
C-reactive protein, 129.1 mg/L (0.0 - 10.0)
Prothrombin time, 33 secs (9.0 - 11.0)
Prothrombin time, greater than 120 secs (26.0 - 34.0)

Additional information received 06 JAN b* via medical monitor:

This was a 27 year-old African heritage male. He was screened to SAILING on 2 AUG a* and performed Day 1 visit on 6 SEP a*. Medical history was negative for both hepatobiliary disorders and infections and infestations other than HIV-1. AEs listed at the CRF prior to liver enzymes elevation included recent myalgia (11 NOV a* to 20 NOV a*), Flu (12 NOV a* to 20 NOV a*), and Malaise (20 NOV a* to ongoing). It was also documented that the subject has taken paracetamol/codeine (11 NOV a* to ?), Brufen (ibuprofen; 11 NOV a* to ?), Allergex (chlorpheniramine; 14 NOV a* to ?), paracetamol (14 NOV a* to 20 NOV a*) and Voltaren (diclofenac; 14 NOV a* to 20 NOV a*). Con ART listed was Aluvia (since 6 SEP a*).

When we started following this subject's liver enzymes the available results were the following:

02 AUG a*: AST 25 U/l (0-42), ALT 14 U/l (0-48), Alkaline phosphatase 95 U/l (20-125), total bilirubin 7 umol/l (0-22)

06 SEP a*: AST 34 U/l, ALT 19 U/l, Alkaline phosphatase 96 U/l, total bilirubin 6 umol/l, Hep B surf AG non-reactive, Hep C Ab non-reactive

*a*: The year
b*: Following year
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20 SEP a*: AST H@47 U/l, ALT 40 U/l, Alkaline phosphatase 79 U/l, total bilirubin 12 umol/l

04 OCT a*: AST H@43 U/l, ALT 46 U/l, Alkaline phosphatase 89 U/l, total bilirubin 13 umol/l

01 NOV a*: AST 20 U/l, ALT 15 U/l, Alkaline phosphatase 92 U/l, total bilirubin 8 umol/l

29 NOV a*: AST G3 H@298U/l, ALT G3 H@308 U/l, Alkaline phosphatase 91 U/l, total bilirubin 15 umol/l

The subject was contacted by the site on 02 DEC a*

He informed that he had been on and off Disprin for recurrent headaches, stopped drinking alcohol 5 months ago, had no change in diet and did not ingest mushrooms for a very long time, since they were not part of his daily diet. The subject also confirmed no use of herbal medications, and no study IP overdose. The subject was a gardener, but denied contact with chemicals. He had one sex partner, his girlfriend and are staying together.

The patient informed a history of diarrhoea from 28 NOV a* to 01 DEC a* which resolved without medication. As he was feeling tired on the 30 NOV a*, he sought attention with a Chemist (as stated telephonically on Friday) and bought the Disprin extra strength 500 mg to take prn p.o., Panamol tablets (Paracetamol) to take prn p.o., Multivitamins 1 daily p.o., Vit. BCO 1 daily p.o. (bought after the 29 NOV a*, a day after his follow up visit). He also informed that he felt a mild left sited chest pain on 02 DEC a* while running and had stopped. No cough, no abdominal pains. His physical at that date was unremarkable.

Follow up lab tests were performed on 14 DEC a* (AST = 134 U/L, ALT = 95 U/L, Alk Phosp = 61 U/L, and total bilirubin = 8 umol/L) and on 19 DEC a* (AST= 506 U/L, ALT= 365 U/L, Alk Phosp= 239 U/L, total bilirubin= 34 umol/L, and direct bilirubin of 17 umol/L). The last labs were still not compatible with liver stop criteria but were close to the stopping criteria for ALT elevation alone.

The site was contacted on 29 DEC a* regarding the liver enzyme elevations.

Dr [deleted] was following up on this when he got the information that the subject passed away.

Other pertinent lab information:

Screening: HIV RNA RT PCR 263559, Absolute CD4 cell count 107.0, %CD4 12.0, creatinine 41.1 (69.8-117.6 umol/l), glucose 5.2 (3.9-5.5 mmol/l), sodium 138, potassium 3.4, lipase 12, WBC 3.9, Hgb @12.3, platelets 377000, absolute neutrophils 2.95, absolute lymphocytes 0.63.

a*: The year
D1: HIV RNA RT PCR 323469, Absolute CD4 cell count 109.0, %CD4 14.0, creatinine 48.4, glucose 5.8, sodium 134, potassium 3.8, lipase 12, WBC @2.9, Hgb @13.4, platelets 293000, absolute neutrophils 1.89, absolute lymphocytes @0.73.

WK2: creatinine 66.4, glucose 5.9, sodium 133, potassium 4.0, lipase 16, WBC 4.4, Hgb @12.2, platelets 340000, absolute neutrophils 3.50, absolute lymphocytes @0.75.

WK4: HIV RNA RT PCR 109, Absolute CD4 cell count 106.0, %CD4 10.0, creatinine 54.3, glucose 4.9, sodium 138, potassium 4.5, lipase 25, WBC @2.8, Hgb @10.9, platelets 276000, absolute neutrophils 1.92, absolute lymphocytes @0.68.

WK8: HIV RNA RT PCR less than 50, Absolute CD4 cell count 135.0, %CD4 11.0, creatinine 47.5, glucose 5.4, sodium 134, potassium 4.1, lipase 26, WBC @2.7, Hgb @12.5, platelets 343000, absolute neutrophils @1.58, absolute lymphocytes 0.92.

WK12: HIV RNA RT PCR less than 50, Absolute CD4 cell count 125.0, %CD4 19.0, creatinine 80.8, glucose 5.7, sodium 127, potassium 4.0, lipase 34 (retest 92), WBC @3.1, Hgb @9.8, platelets 274000, absolute neutrophils 2.32, absolute lymphocytes @0.47.

WK16 (19 DEC a*): HIV RNA RT PCR less than 50, Absolute CD4 cell count 27.0, %CD4 15.0, creatinine 101.5, glucose 6.9, sodium 128, potassium 4.5, lipase 69, WBC @1.8, Hgb @9.0, platelets 256000, absolute neutrophils @1.56, absolute lymphocytes @0.19.

On 19 DEC a*, the subject presented for his Week 16 visit and was noted to have an acute illness with a fever, rigors, arthralgias, and fatigue. On examination, the subject was noted to have an elevated temperature at 39.5 C. No other focal findings were noted on examination. CXR showed no infiltrates or evidence for other pathology. Dr. [deleted] was concerned that the subject may have pneumonia, so he administered ceftriaxone 2 grams IV daily for 5 days (19-24 DEC a*). Over the course of this treatment, the subject reported feeling subjectively better, including resolution of the fever. No documentation of vital signs was available. As the subject appeared significantly improved, Dr. [deleted] asked the subject to return in 1 week. The subject did not return for that visit on 29 DEC a*. Dr. [deleted] contacted Dr. [deleted] on 29 Dec to follow up on the Week 16 lab abnormalities.

On 31 Dec, the subject was admitted to the hospital with the following summary:

The subject was admitted on 31 DEC a* presenting with confusion, jaundice and renal impairment. His physical exam was significant for a BP of 107/60 mmHg, pulse of 100 bpm, apparent fever (temperature not documented), tachypnea, tachycardia 9:11 AM EST and possible terminal neck stiffness.

Diagnostic tests performed showed total bilirubin of 164 mol/L (7.8 x ULN; 83% due to conjugated bilirubin), AST of 2950 U/L (73.8 x ULN), ALT of 749 U/L (18.7 x ULN),
ALP of 271 U/L (2.3 x ULN), GGT of 196 U/L (3.3 x ULN), Ammonia of 128 mol/L (21-71), Lactate Dehydrogenase of 1995 U/L (10.5 x ULN), PTT > 120.0 sec, and INR of 2.68.

Increased serum creatinine (678 mol/L; 5.7 x ULN), increased serum urea (36.0 mmol/L; 5.1 x ULN), hyponatremia (121 mmol/L), hyperkalemia (5.8 mmol/L), decreased carbon dioxide (6 mmol/L), decreased corrected calcium (1.77 mmol/L), decreased albumin (13 g/L), increased phosphorus (2.71 mmol/L), and increased CRP (129.1 mg/L) were also documented.

Hepatitis A, B, and C antibodies were reported as negative.

The subject was prescribed with a pRBC transfusion.

Deterioration of consciousness and epistaxis were noted and the subject was started on lactulose, Vit K and FFP.

The subject passed away 48 h after admission. The final diagnosis was not documented at the Discharge Summary.

In discussion with Dr. [deleted], he has no documentation of tuberculosis in his records or from the records he received from the government clinic that has been following this subject. He is not sure that the subject's report of TB in the hospital records is reliable due to the noted mental status changes for this subject. He discussed an autopsy with the family this week, and they refused.

Follow-up information received on 10 FEB b* via query response:

No treatment was given.

Follow-up subsequently retrieved from the liver CRFs included:

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the previous week. The subject consumed alcohol. The average number of units consumed per week was 6 units. The subject had no liver disease medical conditions, no drug related liver disease conditions and no other relevant medical conditions.

There were no diagnostic imaging tests. There were no liver biopsies performed.

Investigator Text:

Participant was called to return to the clinic for follow-up as discussed via E-mail. Relatives informed us that he passed away on 01 JAN b*. Participant presented with pyrexia to touch, and seemed acute chronically ill. Jaundice and renal impairment queried. Complaints of painful feet. Participant was admitted to hospital on 30 DEC a*.
and passed away on 01 JAN b*. The reason for death is Acute Liver and Kidney failure.

Protocol Id: ING111762
Investigator Number: 084854
Subject Number: 009079
Treatment Number: 4069
Case Id: Z0014577A
Suspect Drugs: Raltegravir
Serious Events: Aortic arteriosclerosis, Arteriosclerosis, Gas gangrene, Infective myositis, Postoperative wound infection

This 56-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 01 NOV .

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included stroke. Concomitant medications included Aluvia, fluconazole, amitriptyline hydrochloride, tramadol hydrochloride, ascorbic acid, folic acid, paracetamol and carbamazepine.

On 23 DEC a*, 52 days after the start of investigational product, the subject developed grade 3 or severe accelerated aortic atherosclerosis and grade 3 or severe accelerated distal artery atherosclerosis. Doppler test was performed on 21 FEB b* with results confirming Vasculitis (Neg art flow both lower legs). CTA: Complete occlusion of aorta infra renal. Large IMA present. Left reform at left CIA Bifurcation. Right reform at distal Profunda. Isolated TA + Peroneal. Not reconstructable.

The subject was hospitalised on 24 FEB b* and the events were disabling. Laboratory test results dated 24 FEB b* included albumin 33 g/l (NR 35-52), ESR >90 mm/h (NR 0-15), LDH 217 U/L (NR 100-190). On 05 MAR b* her right leg was amputated under the knee. On 07 MAR b*, the subject developed grade 3 or severe gas gangrene and grade 3 or severe polymicrobial myositis. On 08 MAR b* a further amputation was done under the right groin (5-10 cm below the groin). On 10 MAR b*, the subject developed grade 3 or severe sepsis of stump. The subject was treated with morphine, vinegar, dressing, cefuroxime sodium, cloxacillin sodium, metronidazole, Dolorol forte, Bactrim, ibuprofen, benzylpenicillin and blood. Treatment with blinded trial medication was interrupted on 02 APR b* and re-started on 17 APR b*. The accelerated aortic atherosclerosis and accelerated distal artery atherosclerosis resolved on 08 MAR b*.

The gas gangrene, polymicrobial myositis and sepsis of stump resolved on 18 APR b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the accelerated aortic atherosclerosis, accelerated distal artery
atherosclerosis, gas gangrene, polymicrobial myositis and sepsis of stump may have been caused by investigational product.

Investigator text:

Patient had a stroke 7-9 years ago. Affected right side arm and leg. HIV diagnoses in 1994 and treatment started. Doppler test performed on 21 FEB * indicated one month less blood flow in right foot, 2nd and 3rd toe + anterior lower leg slightly black. Her husband called the site on 07 MAR * and informed us that the Patient was admitted to hospital on 24 FEB *. On 5 MAR * her right leg was amputated under the knee. Still on hospital. Will bring hospital records to site once available. Patient developed Gas Gangrene and Polimicrobal Miositis and on 08 MAR * a further amputation was done under the right groin (5 - 10cm below the groin). She also had sever sepsis. Updated information on 14 MAR * is that patient is better but the wound still has necrotic tissue. Sepsis is better. Pseudomonas still in wound and treated with Vinegar Acid and will later add vacuum dressings. Patient is mobilized into a wheelchair. Report will be forwarded to the site. Patient reported back to the clinic on 12 JUN *. Confirmed that she was discharged from hospital on 18 APR *. All above mentioned conditions also resolved on 18 APR *. Patient is doing well and well mobilized into the wheelchair.

Protocol Id: ING111762
Investigator Number: 081061
Subject Number: 001081
Treatment Number: 1069, 1069, 1069
Case Id: Z0013647B, Z0013647C, Z0013647D
Suspect Drugs: Dolutegravir
Serious Events: Alcohol poisoning, Alcohol withdrawal syndrome, Depression

This 38-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 07 NOV .

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included recurrent alcohol intoxication (multiple episodes of alcohol withdrawal since HIV diagnosis in h*) and depression. Concomitant medications included darunavir, ritonavir and tenofovir.

On 10 JAN *, 64 days after the start of investigational product, the subject developed grade 3 or severe alcohol withdrawal. The subject had been binge-drinking primarily vodka for at least three days and became suicidal (suicidal feeling confirmed non-serious), developed non-serious tachycardia with tremors and physical signs of withdrawal. The subject was hospitalised and received intravenous fluids but was
persistent tachycardic; not delirious but experienced worsening tremors. Laboratory test results dated 10 and 11 JAN b* included heart rate of 114, ethanol level 10 JAN b* < 10 (ref range 0-10), and AST 125 u/l (normal range 17-59). The subject was treated with diazepam, duloxetine and Duoneb. Treatment with investigational product was continued. The subject was discharged on diazepam taper over six days. The event resolved on 27 FEB b*. The investigator considered that there was no reasonable possibility that the alcohol withdrawal may have been caused by investigational product.

Investigator text:

Patient with a history of HIV, also recurrent alcoholism and multip episodes of ETHANOL withdrawal since HIV dx in h*. Binge drinking for at least 3 days, primarily vodka; became suicidal at home. Tachycardic w/tremors, physical signs of withdrawal. In ED, received intravenous fluids but was persistently tachycardic; not delirious but worsening tremors. Will be re-evaluated by psych after he is out of withdrawal.

1. Alcohol withdrawal. The patient responded well to oral Valium. Discharged on Valium taper over six days. Was seen by psychiatry: Abilify reduced from 10 to 5, Cymbalta increased from 60 to 90.

On 09 JAN b*, 63 days after the start of investigational product, the subject developed grade 3 or severe depression. The subject presented at the community hospital stating he will overdose on psychiatric meds if not admitted. Recent argument with a friend precipitated the event. The subject was hospitalised. The subject was cooperative, anxious and depressed but not psychotic. Urine drug screen was positive for benzodiazepines, THC; otherwise unremarkable. The subject was treated with duloxetine, clonazepam, lamotrigine and perphenazine. Treatment with blinded trial medication was continued. The subject was discharged on 23 JAN b*. The event resolved on 01 FEB b*. The investigator considered that there was no reasonable possibility that the depression may have been caused by investigational product.

The subject's past medical history included suicidal ideation. Medical conditions at the time of the event included alcohol abuse and depression. Concomitant medications included darunavir, ritonavir and tenofovir.

Investigator text:

Patient presented at community hospital ED stating he will overdose on psych meds if not admitted. Recent argument w/friend precipitated event. Admission H&P notes patient was cooperative, anxious and depressed but not psychotic. Psych meds were adjusted; patient discharged on 23 JAN b*.

On 12 APR b*, 157 days after the start of investigational product, the subject developed grade 3 or severe acute alcohol intoxication. The subject presented to the ER on 13 APR b* after excessive alcohol consumption. The subject was hospitalised for observation. The subject was treated with Librium. Treatment with investigational
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A 54-year-old male subject was enrolled in a ViiV-sponsored blinded study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 16 NOV.

The subject was randomised to receive DTG 50 mg once daily.

Medical conditions at the time of the event included positive HBsAg (hepatitis). Concomitant medications included amoxicillin trihydrate, Alcophyllex, Caffeine + codeine phosphate + meprobamate + paracetamol (Salterpyn) and Aluvia (lopinavir/ritonavir).

On 11 JAN, 56 days after the start of investigational product, the subject developed hepatic toxicity grade 4. The event was clinically significant (or requiring intervention). The subject was asymptomatic. Liver ultrasound was normal. No event treatment was given. Treatment with investigational product was discontinued on 16 JAN and the subject was withdrawn from the study. The event resolved with sequelae on 02 FEB.

The investigator considered that there was a reasonable possibility that the hepatic toxicity grade 4 may have been caused by investigational product.

Additional information received 20 JAN from medical monitor:

Presented to community hospital ED 13APR, excessive ethanol consumption. He was admitted for observation. Discharged on 15APR on Librium taper, instructed to avoid ethanol and follow up w/psychiatrist, referred to AA.
Baseline laboratory results from 16 November a* showed AST 21 U/L; ALT 15 U/L; Alkaline Phosphatase 124 U/L; Bilirubin, Total 5 umol/L; CPK, Total 238 U/L; Hep B Surf Ag Reactive; Hep C Ab Non-Reactive; Absolute CD4+ Cells 266 per cmm.

AEs registered within 30 days of transaminase elevation include URTI (08-Jan-b*-ongoing). Con Meds used within 30 days of transaminase elevation include Amoxil, Alcophyllex (combined Diphenhydramine hydrochloride, theophyline and Etofylline, to be confirmed) and Salterpyn (combined paracetamol, codeine and meprobamate, to be confirmed).

Subject presented on 11 January b* for the Week 8 visit and had no physical complaints. The labs showed AST of around 22 x ULN (909 U/L), ALT of around 21 x ULN (1101 U/L) and Total bilirubin of 1.5 x ULN (34 umol/L; 47% conjugated bilirubin). The absolute CD4 cell count for 11 January b* was 358 per cmm. As the chemistry results were reported on a Saturday, the subject returned to the clinic by Monday 16 January b* only. On 16 January b* the study drug and background therapy were stopped. The subject again had a normal examination and no complaints. The sub investigator performed a liver ultrasound in the patient, which was reported as "normal." Repeat labs on 16 January b* revealed that the ALT 1290 U/L), AST (1030 U/L), and Total Bilirubin (78 umol/L) corresponded, respectively, to 26.9 x ULN, 24.5 x ULN, and 3.5 x ULN (55% conjugated bilirubin).

Follow up information received on 26 JAN b* via medical monitor:

The subject did not take any herbal medication, denied alcohol abuse and did not take any other medication which could elevate the liver enzymes. However, the history regarding sexual partners and alcohol intake was not considered very reliable by the investigator. The subject has not been treated for hepatitis B in the past. Also, the subject denied new sexual partners, he has no systemic symptoms and was feeling very well.

Relevant assessments on 16 January b* included positive results for both hepatitis B-core IgM Ab and hepatitis B surface Ag. Relevant assessments on 19 January b* included ASAT which measured 680 U/L, ALAT measured 930 U/L, alkaline phosphatase measured 180 U/L, direct bilirubin measured 37 umol/L and total bilirubin measured 80 umol/L.

Follow-up received on 8 February b* via medical monitor: It was noted that the subject’s HBV DNA from 23 January b* (521,000 IU/mL) was 4 logs above the one documented for study Day 1 (43 IU/mL). The lab results from 06 February b* showed ALT of 51 U/L and AST of 29 U/L.

Follow-up received on 16 FEB b* (transferred from suffix B case):

The event term was changed to grade 4 hepatic toxicity (no ASAT specified) . The event resolved with sequelae on 02 FEB b*. Additional labs added on diagnostics screen.
Diagnostics:

Subject is Retrovirus reactive. Clinically stable with acute Hep B infection. Liver Ultrasound - Normal.

Investigator text (transferred from suffix B case):

Asymptomatic. No treatment was given. Apart from the Leuconychia, the Hepatologist did not find any clinical signs of acute liver failure or chronic liver disease. Patient was Withdrawn from study due to Active Hep B infection.

Case Z0013746A is a duplicate of Z0013746B. All future correspondence to be submitted to Z0013746A.

Protocol Id: ING111762
Investigator Number: 084204
Subject Number: 009457
Treatment Number: 30602
Case Id: Z0013854A
Suspect Drugs: Dolutegravir
Serious Events: Toxoplasmosis

This 50-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 12 JAN .

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included human immunodeficiency virus infection. Concomitant medications included oxcarbazepine.

On 13 JAN a*, one days after the start of investigational product, the subject developed grade 3 or severe neurotoxoplasmosis. The subject developed blurred vision and somnolence on 13 JAN a*. The symptoms worsened on 19 JAN a* and the subject was hospitalised on the same day. Clinical symptoms and magnetic resonance imaging of brain revealed many lesions suggestive of neurotoxoplasmosis. The subject was treated with pyrimethamine and dexamethasone. Treatment with blinded trial medication was continued. The event resolved with sequelae on 25 JAN a* and the subject was discharged. The nature of the sequelae was reported as diplopia and disorientation. The investigator considered that there was no reasonable possibility that the neurotoxoplasmosis may have been caused by investigational product.

Investigator text:

a*: The year

* 新薬承認情報提供時に置き換え
Patient had diagnosis of Neurotoxoplasmosis of severe intensity, grade 3, that required hospitalization in a semi-intensive care unit on 19 JAN a*. The event met criteria for an important/significant medical event. The symptoms started on 13 JAN a* and on 19 JAN a* it had worsened. The treatment was started and patient recovered with hospital discharged on 25 JAN a*. He persists with some symptoms, such diplopia, disorientation due to neurotoxoplasmosis diagnostic.

The symptoms started on 13 JAN a*, they were blurred vision and somnolence.

This 25-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 14 DEC a*

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included chronic sinusitis and sarcoidosis. Concomitant medications included etravirine, darunavir, ritonavir, fentanyl, potassium phosphate + sodium salt, potassium chloride and midazolam.

On 18 JAN b*, 35 days after the start of investigational product, the subject developed grade 3 or severe methicillin resistant Staphylococcus aureus pneumonia. On 20 JAN b*, the subject developed grade 3 or severe sinus disease. The subject was hospitalised with shortness of breath and cough which initially started on 18 JAN b* (mild severity) and worsened on 20 JAN b*. Chest X ray performed on 20 JAN b* showed findings consistent with exacerbation of the subject's known condition of sarcoidosis or possible infection. She was diagnosed with pneumonia after clinical examination. The pneumonia was considered to be possibly due to post-nasal drip caused by chronic sinusitis. The subject underwent bronchoscopy with bronchoalveolar lavage on 21 JAN b* and purulent secretions were found (caused by sinusitis). A CT scan of the sinuses showed sinus disease. The subject underwent bilateral maxillary anstrostomy on 27 JAN b*. The subject was treated with moxifloxacin hydrochloride, azithromycin, ceftaroline fosamcil, heparin, methylprednisolone sodium succinate, Albuterol/ipratropium, insulin aspart, intermediate/long-acting insulin, metronidazole, oxymetazoline hydrochloride, pantoprazole, piperacillin sodium, prednisone, vancomycin, pseudoephedrine
hydrochloride, Percocet, paracetamol, docusate, guaiphenesin, hydromorphone hydrochloride and morphine. Treatment with investigational product was interrupted on 20 JAN b* and re-started on 24 JAN b*. The subject was discharged on 01 FEB b* with symptoms of airway reactive disease still present, and given oral prednisone. The sinus disease resolved on 02 FEB b*. The methicillin resistant Staphylococcus aureus pneumonia resolved with sequelae (persistent shortness of breath) on 02 FEB b*. The investigator considered that there was no reasonable possibility that the methicillin resistant Staphylococcus aureus pneumonia and sinus disease may have been caused by investigational product.

Investigator text:

Subject was admitted with shortness of breath and cough which initially started on 18 JAN b* (mild severity) and worsened on 20 JAN b*. Was diagnosed as pneumonia after clinical examination. Pneumonia was possibly due to the post nasal drip caused by Chronic sinusitis. Chest X ray done on 20 JAN b* showed findings consistent with exacerbation of patient's known condition of sarcoidosis or possible infection. The presumptive diagnosis at the time of admission was pneumonia. Study medications and all other Concomitant ART were interrupted for four days and resumed without any events when it was decided that the SAE was not related to the study medications or other ARTs. The patient underwent bronchoscopy with BAL on 21 JAN b* and purulent secretions were found which was caused due to her sinusitis. Cultures of bronchoalveolar lavage specimens were negative. A CT scan of the sinuses showed sinus disease. Patient underwent bilateral maxillary antrostomy on 27 JAN b*. Patient was discharged on 01 FEB b*. She had persistent symptoms of shortness of breath and she was discharged with oral prednisone 10 mg.

Medical conditions at the time of the event included avascular necrosis status post bilateral hip arthroplasty. Concomitant medications included pantoprazole, etravirine, darunavir and ritonavir.

On 08 MAR b*, 85 days after the start of investigational product, the subject developed grade 3 or severe arthritis of hip joint. The subject presented to the ER on 09 MAR b* with complaints of one-day history of fever and severe sight sided hip joint pain. The subject was hospitalised. Arthroscopy was performed and the aspirated fluid was sent for culture and pathology. Culture results showed no infection and it was noted that the arthritis was due to degenerative disease. The subject was treated with prednisone, daptomycin, Duoneb, mupirocin and ciprofloxacin. Treatment with blinded trial medication was continued. The event resolved on 16 MAR b*. The subject complained of worsening shortness of breath of 15 MAR b* and prednisone was increased to 40 mg on 16 MAR b*. Just prior to discharge in hospital she was seen by ENT and had cultures taken in clinic (placed on ) which have subsequently grown Pseudomonas resistant to Ciprofloxacin and MRSA. (Earlier this year she had MRSA pneumonia source thought to be her sinuses). As she was relatively stable and ENT thought this represented more of a biofilm, the decision was made to treat topically again with close observation. Prednisone was tapered on 15 MAR b* to 30 mg PO daily.

b*: Following year
Plan to taper it to 20 mg PO daily on 30 MAR b*. The investigator considered that there was no reasonable possibility that the septic arthritis of hip joint may have been caused by investigational product.

Investigator text:

Subject went to the ER on 9 MAR b* late evening with complaints of fever and severe right sided hip joint pain for one day. Fluoroscopy guided left hip aspiration was done and the aspirated fluid was sent for culture and pathology. Culture results showed no infection and it was noted that the arthritis was due to degenerative disease. Subject complained of worsening shortness of breath of 15 MAR b* and prednisone was increased to 40 mg on 16 MAR b*. Just prior to discharge in hospital she was seen by ENT and had cultures taken in clinic (placed on [ ] ) which have subsequently grown Pseudomonas resistant to Ciprofloxacin and MRSA. (Earlier this year she had MRSA pneumonia source thought to be her sinuses). As she is relatively stable and ENT thought this represented more of a biofilm, the decision was made to treat topically again with close observation. Prednisone was tapered on 25 MAR b* to 30 mg PO daily. Plan to taper it to 20 mg PO daily on 30 MAR b*.

On 28 MAR b*, 105 days after the start of investigational product, the subject developed grade 3 or severe pulmonary alveolar proteinosis. The subject's past medical history included gastroesophageal reflux disease. Medical conditions at the time of the event included sarcoidosis. Concomitant medications included metoclopramide hydrochloride, etravirine, darunavir and ritonavir. The subject was hospitalised on 28 MAR b* with complaints of worsening breathlessness associated with orthopnea and reflux symptoms. The subject also complained of chest pain while lying flat. Vital signs were stable with oxygen saturation at 95% and no acute distress at admission. The subject was initially treated for candida esophagitis and subsequently stopped after EGD was performed which revealed extensive gastritis (non-serious) however no evidence suggesting candida esophagitis; biopsies were negative for H. pylori. Bronchoscopy did not reveal alternative diagnosis on TBNA. There was a moderate amount of lipid-laden macrophages. The subject was treated with Advair diskus, prednisone, Percocet and oxygen. The subject was found to have C. Diff positive diarrhea (non-serious) and was placed on 10-day course of oral metronidazole. She improved symptomatically and was ambulated around nursing station off oxygen and maintained oxygen saturations above 94%. Treatment with blinded trial medication was continued. The subject was discharged on 03 APR b*. The event resolved on 04 APR b*. The investigator considered that there was no reasonable possibility that the pulmonary alveolar proteinosis may have been caused by investigational product.

Investigator text:

Patient was admitted on 28 MAR b* to pulmonary service with complaints of worsening breathlessness associated with orthopnea and reflux symptoms. Complained of chest pain while lying flat. Vitals stable with oxygen saturation at 95 percent and no acute distress at admission. Initially treated for candida esophagitis and subsequently stopped
after EGD performed which did reveal extensive gastritis however no evidence suggesting candida esophagitis, biopsies were negative for H.pylori. Dyspnoea did improve with nebulizers and patient was continued on prednisone 30 mg daily as she had been taking on an outpatient basis. Had bronchoscopy performed which did not reveal alternative diagnosis on TBNA. There was a moderate amount of lipid-laden macrophages. Was not started on antibiotics for pneumonia however was found to have CDiff positive diarrhoea and was placed on treatment for that with oral metronidazole, ten day course. She improved symptomatically and was ambulated around nursing station off oxygen and maintained oxygen saturations above 94%. Subsequently discharged 3 APR b*.

On 04 JUN b*, 161 days after the start of investigational product, the subject developed grade 3 or severe sarcoidosis flare. The subject was hospitalised. The subject was afebrile. Medical conditions at the time of the event included sarcoidosis. Concomitant medications included azithromycin, insulin aspart, intermediate/long-acting insulin, piperacillin sodium, meprednisone, losartan potassium, hydralazine, benzonatate, Percocet, vancomycin, etravirine, darunavir, ritonavir and prednisone. A Chest X-Ray showed possible mild right upper lobe pneumonia. A CT scan of the chest was done in follow-up and was considered not significant. Blood and urine cultures were negative. The subject was treated with prednisone (tapered). The subject had hyperglycaemia which was known to be steroid induced though she has a past history of diabetes. Treatment with blinded trial medication was continued. The event resolved on 10 JUN b*. The investigator considered that there was no reasonable possibility that the sarcoidosis flare may have been caused by investigational product.

Investigator text:

Initial chest X-ray on admission showed subtle right upper lobe pneumonia and patient was started on broad spectrum antibiotics. She was also started on high dose intravenous steroids for possible sarcoidosis flare. CT scan of the chest did not show any significant changes. Given these findings antibiotics were stopped. Patient remained afebrile. Subject continued the HAART regimen including the investigational product. She was started on long acting insulin in addition to the sliding scale insulin until better glucose levels control till discharge. The dose of her regular antihypertensives were also increased.

Protocol Id: ING111762
Investigator Number: 081282
Subject Number: 000262
Treatment Number: 70597
Case Id: Z0013871A
Suspect Drugs: Dolutegravir
Serious Events: Suicidal ideation

b*: Following year
This 37-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 17 JAN.

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included anxiety and depression. Concomitant medications included maraviroc, tenofovir disoproxil fumarate, paroxetine hydrochloride, clonazepam and zolpidem tartrate.

On 23 JAN a*, six days after the start of investigational product, the subject developed grade 1 or mild suicidal ideation. The subject had his car broken into and had an altercation with the offender causing a small laceration of his right ankle. The subject then drank 4 glasses of wine and had his klonopin and ambien at the same time and was taken to the ER. The subject admitted to feeling suicidal. The subject was hospitalised for 24 hours in the psychiatric ward. The subject sobered up and denied suicidal ideation. Lab tests included normal CBC. Chem 12 normal except for chloride 110 Carbon dioxide 19, ALT 75, Protein 8.8, TSH 0.24, UA negative, Tox screen + only for Blood alcohol level of 161. No event treatment was given apart from the subject's regularly prescribed meds. Treatment with blinded trial medication was continued. The event resolved on 23 JAN a*. The investigator considered that there was no reasonable possibility that the suicidal ideation may have been caused by investigational product.

Investigator text:

Patient had his car broken into and he caught person and had an altercation and subsequent small laceration of his right ankle. He had drunk 4 glasses of wine, had his klonopin and ambien at that time and was taken to emergency room. When asked if he was ever suicidal, he said yes and so they committed him to the psychiatric ward. Now that he is sober and awake, he denies and will be released tomorrow after 24 hour hold.

Protocol Id: ING111762
Investigator Number: 081135
Subject Number: 000571
Treatment Number: 4021
Case Id: Z0015397A
Suspect Drugs: Raltegravir
Serious Events: Adenocarcinoma, Blood alkaline phosphatase increased

This 37-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks
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in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 22 JUN b* to 01 FEB b*.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject has no personal or family history of cancer. Concomitant medications included Truvada and maraviroc.

On 27 JAN b*, 219 days after the start of investigational product, the subject developed grade 4 metastatic adenocarcinoma of possible gastrointestinal origin and grade 4 increased alkaline phosphatase grade 4 of 942 U/L (normal range 20 to 125). The subject was hospitalised and the events were life-threatening. Laboratory test results showed alkaline phosphatase at 1760 U/L on 20 FEB b* (normal range 40 to 115); 2405 U/L on 09 MAR b* (normal range 20 to 125); 2855 U/L on 26 MAR b* (normal range (20 to 125), 2906 U/L on 26 MAR b* (normal range 45 to 129), 2390 U/L on 23 APR b* (normal range 45 to 129). The subject commenced chemotherapy with carboplatin and paclitaxel on 03 MAY b*. Repeat laboratory test showed results of 2004 U/L on 03 MAY b*, 1138 U/L on 08 MAY b*, 999 U/L on 24 MAY b* and 1012 U/L on 29 MAY b*. Treatment with blinded trial medication was discontinued on 01 FEB b* and the subject was withdrawn from the study. The subject made DNR on 18 JUL b* offered comfort measures only. The subject died on 31 JUL b* due to metastatic adenocarcinoma of possible gastrointestinal origin. The increased alkaline phosphatase grade 4 was unresolved at the time of death. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the metastatic adenocarcinoma of possible gastrointestinal origin and increased alkaline phosphatase grade 4 may have been caused by investigational product.

Additional information received on 27 APR b* via medical monitor:

This subject was found to have significant elevation of the alkaline phosphatase (AP) prompting initial discontinuation of the investigational drug and then discontinuation all ART; despite withdrawal of all drugs, the AP continued to rise.

He was initially entirely asymptomatic but in mid February he developed right sided rib pain; exam was unremarkable and chest x-ray with rib detail on 17 FEB b* revealed no abnormality save old granulomatous disease (calcified RUL granuloma) and normal cardiomedialstinal structures except calcification of the aorta.

About the time he was discontinued from the study, he complained of early satiety and dyspepsia as well as left shoulder discomfort, relieved by ibuprofen. He declined shoulder x-ray or orthopedic evaluation (due to concerns about payments <he has no health insurance>) but an abdominal ultrasound was done on 28 FEB b* revealed probable fatty liver and possible biliary sludge but no other pancreatic/biliary issues.

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Shortly thereafter the results of the initial evaluations of the elevated AP suggested primarily bone sources and he was referred to the Endocrine/Bone specialist. A Bone "SuperScan" on 16 MAR b* revealed diffusely increased bone tracer uptake throughout the axial, appendicular skeleton and skull suggestive of a boney metabolic abnormality. His PTH here was elevated at 115.6 although the one done by the study lab was normal earlier. Skull series on 26 MAR b* requested by the endocrine consultants revealed "diffuse heterogeneity of skull mineralization". He was referred for a bone biopsy.

About two weeks later he presented to the endocrine clinic complaining of severe constipation and continued early satiety; a KUB/upright CXR on 12 APR b* showed interval development of possible right perihilar airspace disease and patchy sclerosis throughout the osseous structures. His constipation apparently resolved with laxatives.

On 23 APR b* he presented to the endocrine clinic with shortness of breath (02 sat 83% post exercise) and was referred to the ER where spiral CT revealed no PE but "severe lymphadenopathy involving the mediastinum, perihilar, and upper abdomen (epigastric/perportal) nodes with focal oedema/inflammation of stomach suggestive of gastritis. He was admitted and bransbronchial biopsy on 24 APR b* revealed malignant cells consistent with adenocarcinoma. He also complains of continued early satiety, constipation and now has diffuse musculoskeletal pain and 11 kg weight loss. Other significant labs during the admission: WBC 9.9, Hgb 11.2 - 9.7 and platelets 60K-48k (of note, hemogram in February was essentially normal); D-dimer 4804; renal function normal; Ca 8.6, Alb 3.6; AP 2258. Bone Survey on 26 APR b* suggested multiple blastic lesions throughout the skeleton.

Follow up information receive on 24 JUL b* via answered query report:

The normal ranges for alkaline phosphatase were different as 20 -145 u/L was the Quest study lab reference range and 45 - 129 u/L were the local hospital lab reference range. The subject did not receive any corrective therapy for the increased alkaline phosphatase levels.

Follow up information received on 19 AUG b* via deletions report:

The concomitant medication RAL was deleted.

Diagnostics:

17 FEB b*: Chest x-ray: no abnormality except old calcified RUL granuloma.
Abdominal Ultrasound 28 FEB b*: probable fatty liver & biliary sludge. bone Superscan 16 MAR b*: suggestive of boney metabolic abnormality. KUB/Upright Chest x-ray, 12 APR b*: possible right perihilar airspace disease & patchy sclerosis throughout the osseous structures

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23 APR b*: Spiral CT: severe lymphadenopathy. 24 APR b*: bransbronchial biopsy: malignant cells consistent with adenocarcinoma. 26 APR b*: Bone survey: suggested multiple blastic lesions throughout the skeleton. 30 APR b* Bone marrow biopsy and 02 MAY b*: colon biopsy: both suggestive of gastrointestinal (mainly gastric or colonic) or pancreatobiliary primary. 09 MAY b*: PET, Skull to mid thigh: The most likely primary adenocarcinoma site is the rectum, with widespread metastatic disease diffusely throughout the bones, lungs, hila/mediastinum, lower right cervical level 4 lymph nodes, left ventricular anteroapical myocardium and/or pericardium, possibly spleen. 13MAY b*: CT head: skull base metastasis.

Death Summary: metastatic adenocarcinoma remains suspected GI primary; diagnosed: carcinomatosus meningitis May b*; had stroke and pneumonia in June, possible pulmonary embolis and acute kidney injury early July b*; made DNR 18 JUL b* offered comfort measures only, died 31 JUL b*.

Investigator text:

All the above was in work-up of elevated alkaline phosphatase, of 942, at the week 32 visit on 27 JAN b*, leading to the current diagnosis. Additional lab tests were done per Quest study lab, outside the usual. Please see Quest results, as they are not a choice in the dropdown box in this form. Work-up continues to find the origin, now thought to possibly be rectal. There is no documentation of previous personal or family history of cancer. Started chemo therapy on 03 MAY b*. Restarted HIV ART on 08 MAY b*.

Protocol Id: ING111762
Investigator Number: 081290
Subject Number: 000387
Treatment Number: 2005, 2005
Case Id: Z0014085A, Z0014085B
Suspect Drugs: Raltegravir
Serious Events: Oral mucosal blistering, Rash pruritic

This ☐-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 06 JAN .

The subject was randomised to receive RAL 400 mg twice daily.

The subject's past medical history included lupus. Concomitant medications included thyroxine sodium, darunavir, ritonavir, and etravirine.

On 30 JAN a*, 24 days after the start of investigational product, the subject developed grade 3 or severe diffuse pruritic maculopapular rash. The subject was hospitalised. The
subject was treated with diphenhydramine, prednisone, A + D ointment and petrolatum. Treatment with investigational product was discontinued on 05 FEB a* and the subject was withdrawn from the study. The event resolved on 07 MAR a*. The investigator considered that there was a reasonable possibility that the diffuse pruritic maculopapular rash may have been caused by investigational product.

Investigator text:

Patient started new ARV regimen on 06 JAN a*. Regimen includes etravirine, darunavir, ritonavir, raltegravir/p & dolutegravir/p. A pruritic diffuse maculopapular rash started on 30 JAN a*. Patient's rash was grade 2 when seen in clinic by study PI on 01 FEB a*. Patient treated with benadryl and 1% hydrocortisone ointment. Rash worsened on 02 FEB a* with oral mucosal involvement and patient went to area ED and admitted & treated. Patient discharged on 05 FEB a*. Patient seen in clinic today on 06 FEB a* and study withdrawal visit done. Patient's rash is improving and will be seen again on 15 FEB a*. Initially, patient was taking ritonavir boosted darunavir 600 mg bid, but then switch on 19 JAN a* to ritonavir boosted darunavir 800 mg daily.

On 03 FEB a*, 28 days after the start of investigational product, the subject developed grade 3 or severe oral mucosa blistering. The subject's past medical history included lupus. Concomitant medications included thyroxine sodium, etravirine, darunavir and ritonavir. The subject was hospitalised. The subject was treated with fluconazole, A + D ointment, petrolatum, prednisone and diphenhydramine. Treatment with investigational product was discontinued on 05 FEB a* and the subject was withdrawn from the study. The event resolved with sequelae on 15 FEB a*. The investigator considered that there was a reasonable possibility that the oral mucosa blistering may have been caused by investigational product.

Investigator Text:

Patient started new ARV regimen on 06 JAN a*. Regimen includes etravirine, darunavir, ritonavir, raltegravir/p & dolutegravir/p. A pruritic diffuse maculopapular rash started on 30 JAN a*. Patient's rash was grade 2 when seen in clinic by study PI on 01 FEB a*. Patient treated with benadryl and 1% hydrocortisone ointment. Rash worsened on 02 FEB a* with oral mucosal involvement and patient went to area ED and admitted & treated. Patient discharged on 05 FEB a*. Patient seen in clinic today on 06 FEB a* and study withdrawal visit done. Patient's rash is improving and will be seen again on 15 FEB a*. Initially, patient was taking ritonavir boosted darunavir 600 mg bid, but then switch on 19 JAN a* to ritonavir boosted darunavir 800 mg daily.

Protocol Id: ING111762
Investigator Number: 081042
Subject Number: 000091
Treatment Number: 1057
Case Id: Z0014165A
Suspect Drugs: Raltegravir

a*: The year
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Serious Events: Cerebrovascular accident

This 42-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 06 OCT.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject has no relevant medical history or pre-disposing risk factors. Concomitant medications included etravirine, darunavir and ritonavir.

On 06 FEB b*, 123 days after the start of investigational product, the subject developed grade 3 or severe stroke-right thalamic lacunar infarct. The subject presented to the ER on 06 FEB b* with LLE numbness and weakness present for the past 2-3 weeks. The subject was hospitalised for possible stroke. MR angiogram of head revealed right thalamic infarct. The rest of the stroke work-up was negative for large or medium vessel involvement or cardioembolic risk factors. The subject was treated with aspirin. Treatment with blinded trial medication was continued. The event resolved on 08 FEB b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the stroke-right thalamic lacunar infarct may have been caused by investigational product.

Investigator text:

Patient presented to emergency room on 06 FEB b* with LLE numbness and weakness for past 2-3 weeks. Patient was then admitted for possible stroke. He was discharged on Aspirin for a blood thinner. The rest of the stroke work-up was negative for large or medium vessel involvement or cardioembolic risk factors. Patient was discharged on 08 FEB b*. Thank You.

Protocol Id: ING111762
Investigator Number: 085245
Subject Number: 002809
Treatment Number: 7049
Case Id: Z0014263A
Suspect Drugs: Dolutegravir
Serious Events: Myositis, Renal failure acute

This 42-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks
in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 10 AUG.

The subject was randomised to receive DTG 50 mg once daily.

Concomitant medications included tenofovir and atazanavir.

Medical history was significant for current skin and subcutaneous tissue disorders and current anxiety only.

Laboratory test results dated 25 JAN b* showed CPK 4179 U/L (normal range 0-235). Treatment with investigational product was interrupted from 30 JAN b* to 12 FEB b*, and re-started on 13 FEB b*. Concomitant medication used within 90 days of the detection of elevated CPK included salbutamol (31 October a* to 31 October a*).

On 13 FEB b*, 187 days after the start of investigational product, the subject developed grade 3 or severe myositis and grade 3 or severe acute renal failure. The subject was hospitalised and the events were life-threatening. Laboratory test results dated 15 FEB b* showed creatinine clearance 58 ml/m/1.73 m2 (normal range 90-120). Treatment with investigational product was discontinued on 15 FEB b* and the subject was withdrawn from the study. The events resolved on 17 FEB b*. The investigator considered that there was a reasonable possibility that the myositis and acute renal failure may have been caused by investigational product.

Follow-up information received on 16 FEB b*:

IP was suspended from 30 JAN b* to 12 FEB b*, restarted on 13 FEB b* and interrupted again on 15 FEB b*.

Information on the case was received on 30 JAN b* when it was informed that the Principal Investigator was aware of the Grade 3 CPK elevation and was going to contact the subject and have the IP discontinued for a week after performing a repeat CPK. At the time the subject collected the CPK that resulted Grade 3, he was asymptomatic.

Follow-up information received on 22 FEB b* via clinical study team:

On an unspecified date after the Grade 3 CPK was detected, the patient reported myalgia for approximately 4 days, mild to moderate, attributed to the work related activity and exercise. The patient was not taking concomitant medications that may have altered the CPK. IP was interrupted and the subject was instructed to avoid exercising. Repeat testing was performed on 08 February. Results were received on February 13, confirming significant decrease in CPK (Grade 2), with improvement of renal function to levels similar to baseline ones. The IP was restarted on 13 February b*. The patient was asymptomatic. On 14 February b* the subject contacted the site by phone with complaints of lower limbs myalgia and weakness. The subject was later seen at the site. Blood pressure was 120/75 mmHg; the subject referred adequate diuresis with no change.

*a*: The year

b*: Following year
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in the urine colour. The study medication was stopped. On 15 February b* creatinine was 1.5 mg / dl, with glomerular filtration rate of 58. 11 ml / min and CPK of 441 U/L. The subject was admitted in the nephrology section of <name deleted> hospital with a diagnosis of rhabdomyolysis and acute renal failure. The patient remained hospitalized for 2 days with significant improvement of clinical symptoms and was discharged on 17 February b* with renal function tests within normal ranges. On 20 February b* the subject was contacted by phone and informed that he was in excellent condition, asymptomatic and working normally.

On 20 FEB b* the subject was contacted by phone and informed that he was in excellent condition, asymptomatic and working normally.

Follow-up information received on 23 February b* via medical monitor: The sub investigator informed that the subject was admitted to the diagnostic hypothesis Rhabdomyolysis and acute renal failure. These diagnoses were classified as SAE and recorded. During hospitalization, the nephrologists and the sub-investigator assigned a final diagnosis of myositis and acute renal failure.

Follow-up information received on 28 FEB b* via query response:

There was a permanent discontinuation of IP due to the CPK levels rechallenge.

Investigator text:

Lab results corresponding visit week 24 showed a grade 3 for CPK value, the sub investigator contacted to the patient in order to ask him for any symptoms. The patient said that just feel a mild pain in the legs. The investigator decide to stop the ART medication in order to evaluate with another lab sample, the retest results was evaluated by the investigator and the value was almost normal, the investigator decided to reinitiate the ART therapy. The patient took the night dose (13 FEB b*) and the morning dose (14 FEB b*), he felt very bad with a lot pain in the legs and mild oedema. The patient contacted to the investigator in order to alert the situation. The patient was evaluated by the investigator and performed a local exam. The investigator decided to hospitalize to the patient in order to follow the renal function. The patient was dispatched on 17 FEB b* with normal range in the local exams. The patient was discharged on 17 FEB b*, with the following diagnoses acute renal failure and miositosis. The patient has been in good health. Presented a mild headache between 20 and 23 FEB b*. On physical examination no significant findings.

Protocol Id: ING111762
Investigator Number: 084857
Subject Number: 002589
Treatment Number: 3115
Case Id: Z0014441A
Suspect Drugs: Raltegravir
Serious Events: Bronchopneumonia

b*: Following year

* 新薬承認情報提供時に置き換え
This 56-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 12 SEP.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject has no relevant medical history. Concomitant medications included tenofovir and Aluvia.

On 14 FEB, 155 days after the start of investigational product, the subject developed grade 2 or moderate left-sided bronchopneumonia. The subject was reported to be ill-looking but apyrexial, with normal colour and hydration. The subject was hospitalised. Her chest was clear, heart rate 103/min, blood pressure 115/69 mmHg, resting ECG was normal, and CVS/abdomen/CNS normal. Chest X-ray showed patchy consolidation in left lung. Results of other laboratory tests were Hb - 12.8g/dL, WBC - 14.22x10^9/L, platelets - 284x10^9/L, potassium - 3.9mmol/L, urea - 2.4mmol/L, creatinine - 65umol/L, LFT - non-contributory, sputum for acid fast bacilli and PCR - negative for mycobacterium tuberculosis. The subject was treated with ceftriaxone, Dilinct, Stilpane, Combivent nebulizer and cefpodoxime. Treatment with blinded trial medication was continued. The event resolved on 03 MAR. The investigator considered that there was no reasonable possibility that the left-sided bronchopneumonia may have been caused by investigational product.

Investigator text:

Ill-looking, apyrexial, colour and hydration - normal, chest clear, heart rate - 103/min, BP - 115/69mmHg and CVS/abdomen/CNS - normal.

Protocol Id: ING111762
Investigator Number: 084854
Subject Number: 009088
Treatment Number: 8028
Case Id: Z0015134A
Suspect Drugs: Raltegravir
Serious Events: Dehydration, Gastroenteritis

This 56-year-old male subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in hiv-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 02 NOV.

b*: Following year
The subject was randomised to receive RAL 400 mg twice daily.

No medical history was reported other than diarrhoea, which began on 23 NOV a*.. Concomitant medications included Aluvia and Bactrim.

On 18 FEB b*, 108 days after the start of investigational product, the subject developed grade 2 or moderate dehydration. On 05 MAR b*, the subject developed grade 2 or moderate chronic gastroenteritis. The subject was hospitalised from 13 to 23 MAR b* and from 19 to 23 APR b*. Abdominal sonar was negative for TB. Suppurative adenitis on Cloxacillin (confirmed to be a non serious AE). Pleural TAP culture did not detect any bacteria and no growth (aerobic as well as anaerobic). Laboratory test results dated 15 MAR b* included albumin 11 g/l, protein total 19 g/l and lactate dehydrogenase 67 U/l (normal ranges not available). The subject was treated with loperamide hydrochloride, cloxacillin sodium, paracetamol, Ringers lactate, cimetidine, hyoscine butylbromide, flucloxacillin sodium, potassium chloride, ciprofloxacin hydrochloride, sodium chloride, metoclopramide hydrochloride, metronidazole and Bactrim. Treatment with blinded trial medication was continued. Dehydration resolved on 23 APR b*. Chronic gastroenteritis resolved on 25 APR b*. The investigator considered that there was no reasonable possibility that the chronic gastroenteritis and dehydration may have been caused by investigational product.

Investigator text:

Patient was admitted to hospital on 13 MAR b* due to Chronic Gastro enteritis and dehydration. Abdominal sonar was done and TB negative in Abdomen. Pleural TAP culture was also done, no bacteria observed and no growth (Aerobic as well as anaerobic). The IP was not withdrawn during time of hospitalization. SAE was initially reported as IP related. After file revision from Hospital the investigator has decided to change the relationship to not IP related as this was diagnosed as Gastro Enteritis and not worsening of Diarrhoea. Patient was hospitalized twice for the same event. First event 13 MAR b* - 23 MAR b*. Second Event 19 APR b* - 23 APR b*.

Protocol Id: ING111762
Investigator Number: 085076
Subject Number: 002148
Treatment Number: 3013
Case Id: Z0014576A
Suspect Drugs: Dolutegravir
Serious Events: Alcohol withdrawal syndrome

This 18-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks.
in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 03 FEB

This subject was randomised to receive oral DTG 50 mg once daily.

The subject has no prior history of gait instability. Concomitant medications included darunavir.

On 20 FEB b*, 382 days after the start of investigational product, the subject developed grade 1 or mild gait instability due to alcohol withdrawal syndrome. The subject travelled from country X on 20 FEB b* with headaches, dizziness, nausea and constipation, and went for many hours without sleep. While in country X, the subject had too many alcoholic drinks. The subject was hospitalised. Brain CT, abdominal ECHO, EEG, MRI brain, blood count and biochemistry, urinalysis and ECG were performed with no clinically relevant findings. The subject was treated with ciprofloxacin, fluconazole, aspirin, pantoprazole, diazepam, enoxaparin, nystatin, hexetidine and Hidroxil. Treatment with blinded trial medication was continued. The event resolved on 24 FEB b*. The investigator considered that there was no reasonable possibility that the gait instability due to alcohol withdrawal syndrome may have been caused by investigational product.

Investigator text:

PATIENT COMES FROM (20 FEB b*) XXXX WITH HEADACHES DIZZINESS NAUSEA AND CONSTIPATION.

MANY HOURS WITHOUT SLEEP FOR travelling and transfer. While patient was in XXX took many alcoholic drinks. Brain CT, ABDOMINAL ECO, EEG, MRI Brain, blood count and biochemistry, urinalysis, ECG WHERE DONE. NO FINDINGS CLINICALLY RELEVANT in any test. PATIENT STABLE and asintomatic. not prior history of gaits.

Protocol Id: ING111762
Investigator Number: 081133
Subject Number: 000552
Treatment Number: 3024, 3024
Case Id: Z0014423A, Z0014423B
Suspect Drugs: Dolutegravir
Serious Events: Anaemia, Gastroenteritis viral, Oedema peripheral, Pneumonia, Pruritus, Renal failure

This ■-year-old male subject was enrolled in a ViiV-sponsored double-blind study of the safety and efficacy of dolutegravir 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks.

b*: Following year

* 新薬承認情報提供時に置き換え
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in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 24 MAR.

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included alcohol abuse, chronic diarrhoea, ibd and colitis/inflammatory bowel disease. Concomitant medications included omeprazole, mesalazine, Kaletra and maraviroc.

On 22 FEB, 335 days after starting blinded trial medication, the subject developed grade 3 or severe viral gastroenteritis. The subject was hospitalised. Signs and symptoms included nausea, vomiting, crampy lower abdominal pain, increased diarrhoea and increased creatinine. The subject was treated with sodium chloride, ondansetron hydrochloride, magnesium salt and potassium chloride. Treatment with blinded trial medication was continued. The event resolved on 26 FEB. The investigator considered that there was no reasonable possibility that the viral gastroenteritis may have been caused by investigational product and that the event was possibly due to other contributing factors.

Investigator text

subject presented to the emergency room with a 3 day history of nausea, vomiting, crampy lower abdominal pain and increased diarrhoea. He had been in contact with 2 young children with similar symptoms about 72 hours prior to the onset of his symptoms. Given this history, he was felt to have viral gastroenteritis. As subjects creatinine was markedly elevated from baseline, he was admitted for IV hydration with normal saline and anti-emetics. After 1 day, subject was able to eat and drink without vomiting, his diarrhoea had decreased, and his creatinine had returned to normal, so he was discharged.

On 01 MAY, 404 days after the start of investigational product, the subject developed grade 3 or severe upper lobe community acquired pneumonia of unknown origin. Concomitant medications included maraviroc and Kaletra. The subject presented with shortness of breath, pleuritic chest pain, nausea, cough with sputum production, fevers and chills. On 04 MAY, the subject developed grade 3 or severe renal failure and grade 3 or severe anaemia. A chest x-ray done on 04 MAY showed right upper lobe consolidation, blood cultures were negative x 2, sputum AFB was negative x 3. A repeat chest x-ray on 07 May showed improving right upper lobe pneumonia. A renal ultrasound was performed on 07 MAY renal ultrasound and was unremarkable. 9 MAY CT Scan of the thorax showed dense consolidation right upper lobe with bilateral ground glass opacities. On 11 MAY, the subject developed grade 1 or mild oedema of lower extremities. On 17 MAY, the subject developed grade 1 or mild itching. The subject was hospitalised. Laboratory test results dated 05, 13 and 29 MAY, respectively, showed creatinine 2.3 mg/dl, 7.4 mg/dl and 3.1 (normal range 0.8-1.5). Laboratory test results dated 18, 20 and 29 MAY, respectively, showed hematocrit 22%, 21% and 32% (normal range 40-54). The subject's haemoglobin level on 17 MAY, 20 MAY and 29 MAY were 7.8 g/dL.
7.2 g/dL and 10.8 g/dL (normal 13 - 18 g/dL) respectively. On the same dates as the haemoglobin results, the subject's red blood cell counts were 1.98 M/cmm, 1.89 M/cmm and 3.04 M/cmm (normal 4.3 - 5.6 M/cmm) respectively. The subject was treated with vancomycin, piperacillin sodium, heparin, ibuprofen, guaiphenesin, oxycodone, ceftriaxone, azithromycin, paracetamol, sodium bicarbonate, red blood cells, diphenhydramine hydrochloride, cetirizine hydrochloride, fexofenadine hydrochloride and petrolatum. Treatment with blinded trial medication was continued.

The upper lobe community acquired pneumonia of unknown origin resolved on 18 MAY b*. An ECHO was done on 21 MAY b* which was normal. Oedema of lower extremities resolved on 14 JUN b*. Itching resolved on 24 JUL b*. Renal failure and anaemia resolved on 07 AUG b*. The investigator considered that there was no reasonable possibility that the upper lobe community acquired pneumonia of unknown origin, renal failure, anaemia, oedema of lower extremities and itching may have been caused by investigational product. The lower extremity oedema and secondary pruritus were felt to be due to the renal failure as they peaked when BUN/creatinine were at their highest and resolved as the renal function returned to normal.

Investigator text:

1 MAY b*: patient first noted SOB, pleuritic chest pain, nausea, cough with sputum production, fevers and chills. He was admitted to the VA on 4 MAY b* after CXR revealed a RUL pneumonia. Sputum culture subsequently indicated that the pathogen was Klebsiella pneumonia. Patient was initially started on IV vancomycin and IV Zosyn; the vancomycin was discontinued after the aetiology determined. As a complication of his infectious process (SIRS), he developed acute tubular necrosis, which resulted in acute renal failure (FeNa 0.7%). He was treated with IVF and bicarbonate repletion. Creatinine peaked at 7.4 on 13 MAY b* and has continued to decline; was 3.1 at time of Nephrology f/u on 23 MAY b*; repeat pending. He was symptomatic in terms of his renal failure with LE oedema and pruritus. The LE oedema has resolved with a short course of Lasix and improvement in renal function. Patient continues to c/o some pruritus, but currently has xerosis on exam; prescribed topical agents and antihistamine. Lastly, patient had significant anaemia. He has baseline mild anaemia with HCT in the mid to upper 30s related to intermittent ethanol abuse, HIV and inflammatory bowel disease. HCT fell to a low of 21 on 21 MAY b* at which time he was given a transfusion of 2u PRBCs. HCT then increased to 28 the next day and was up to 32 at time of Nephrology f/u on 29 MAY b*; repeat HCT pending. The lower extremity oedema and secondary pruritus were felt to be due to the renal failure as they peaked when BUN/creatinine were at their highest and resolved as the renal function returned to normal. Of note, patient has had pruritus due to xerosis off and on for years and this is unchanged; the pruritus noted during his hospital admission was much worse than at baseline and has returned to baseline; is using Eucerin cream for pruritus due to xerosis with good response.

Protocol Id: ING111762
Investigator Number: 085092

b*: Following year
This -year-old male subject was enrolled in a ViIV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 02 DEC .

The subject was randomised to receive DTG 50 mg once daily.

Medical conditions at the time of the event included hepatitis B. Concomitant medications included darunavir, ritonavir, etravirine, trimethoprim, sulphamethoxazole and pargeverine.

On 29 FEB b*, 89 days after the start of investigational product, the subject developed grade 4 hepatitis. The event was clinically significant (or requiring intervention). The subject was treated with entecavir and hydroxyzine. Treatment with investigational product was interrupted on 28 FEB b*. The event resolved on 08 MAY b*. Treatment with investigational product was re-started on 05 JUL b*. The investigator considered that there was no reasonable possibility that the hepatitis may have been caused by investigational product.

Additional information received from medical monitor on 01 MAR b*:

Test results from 31 OCT a* included HIV-1 copies RT PCR 9787 copies/ml, CD4 helper cells 6% (normal range 30 - 61), and HLA-B*5701 negative. Test results from 02 DEC a* included HIV-1 copies RT PCR 10736 copies/ml, and CD4 helper cells 7%. Test results from 28 DEC a* included HIV-1 copies RT PCR less than 50 copies/ml, CD4 helper cells 8%, BUN 6.0 mmol/l (normal range 2.5 - 9.0), AST 25 u/l (normal range 0 - 42), ALT 20 u/l (normal range 0 - 48), alkaline phosphatase 65 u/l (normal range 20 - 125), total bilirubin 8 umol/l (normal range 0 - 22), and creatine phosphokinase 156 u/l (normal range 0 - 235). Test results from 26 JAN b* included HIV-1 copies RT PCR less than 50 copies/ml, CD4 helper cells 10%, BUN 7.0 mmol/l, AST 27 u/l, ALT 39 u/l, alkaline phosphatase 68 u/l, total bilirubin 6 umol/l, and creatine phosphokinase 71 u/l. Test results from 23 FEB b* included HIV-1 copies RT PCR less than 50 copies/ml, CD4 helper cells 11%, BUN 6.5 mmol/l, AST 567 u/l, ALT 681u/l, alkaline phosphatase 98 u/l, total bilirubin 24 umol/l, and creatine phosphokinase 60 u/l.

The subject was reported as feeling well in spite of the abnormalities. He was complaining of mild abdominal pain and choloria, but jaundice was not noted on physical
exam. There was no reference to the use of over-the-counter medications (e.g. acetaminophen).

Labs were collected yesterday and sent to the central lab and to a local lab in parallel. The results of the local lab analysis showed AST 1659, ALT 1990, total bilirubin of 5.0 (ULN of 1.4) with 2.8 of direct bilirubin, Alk Phosp 116 (ULN of 100), and GGT 126.

A 47-year-old White male from Argentina who was screened on 31-Oct-a* and performed Day 1 visit on 02 DEC a*. Medical History included past GI disorder NOS, past psychiatric condition NOS. The subject was HLA-B*5701 Negative and even though the med history did not document that, he was HBsAg Positive. Screening CD4 was 130 cells/cmm; screening INR 1.4; Day 1 labs showed ALT=29 U/L, AST=24 U/L, Alk Phosp= 64 U/L, Total Bilirubin = 6 umol/L.

Con ART includes Darunavir and Etravirine. Past ART included tenofovir (NOV k* to DEC a*), tipranavir (AUG i* to DEC a*), Maraviroc (OCT g* to DEC a*) and Zidovudine/Lamivudine (OCT g* to DEC a*).

Conc Med used within 90 days of the lab abnormality includes trimethoprim-sulfamethoxazole (since JUL p*). No AEs documented as of 28 FEB b*.

Additional information received via medical monitor on 12 MAR b*:

The investigator reported "As you know we are closely following our patient who fortunately is doing better clinically. After consultation with the Hepatology Section at our hospital our initial suspicion about the reason of this episode has changed somewhat. Although they cannot rule out yet a drug related toxicity, they believe this could be an Hepatitis B flare.

In retrospect he was actually stopped on lamivudine giving priority to his refractory HIV status, and probably this was not the best decision.

In this context, receiving the results of the Hep B viral load and DNA will be of great help. He already underwent a liver biopsy, and although final results are not yet available, the hepatologists told us that there was disseminated inflammation, which may be compatible with hep B flare, but as of today they cannot rule out completely an alternative diagnosis.

Patient was already started on entecavir which we have obtained from subject's primary provider and he reported to us that is feeling much better.

He will come to see Dr [deleted] tomorrow morning.

So, in summary, all the clinical steps had already been taken, subject is on activa anti Hep B medication, his transaminases have started to decrease and we are waiting for the definitive results of the biopsy and the Hep B specific test.
Our current working diagnosis is an Hep B flare which we will conform with pending results.

Test results from 29 FEB b* included HBV DNA Log greater than 8.23 iu/ml, HBV DNA PCR copies greater than 989000000, HBV DNA PCR greater than 170000000 iu/ml, Hep-B Core IgM AB and Hep-B Core IgM AB both reactive.

Additional information received from medical monitor on 19 MAR b*:

On 28 FEB b* it was reported that the subject's lab results from study week 12 visit (23 FEB b*) were significant for an ALT of 14.2 x ULN (681 U/L), AST of 13.5 x ULN (567 U/L), and total bilirubin of 1.1 x ULN (1.3 mg/dL).

On 29 FEB b* the subject was seen at the study site. He was feeling well but complaining of mild abdominal pain and choluria. Jaundice was not noted at the physical exam. There was no reference to the use of over-the-counter medications (e.g. acetaminophen). Biochemistry labs were collected and sent in parallel to the study central lab and to the local lab. the local lab results showed AST 1659, ALT 1990, total bilirubin of 5.0 (ULN of 1.4) with 2.8 of direct bilirubin, Alk Phosp 116 (ULN of 100), and GGT 126. It was agreed at that moment to have the event reported as an SAE. The central lab results were later released and were about the same range detected at the local lab, confirming the presence of an ALT of 39.3 x ULN and total bili of 3.7 x ULN (43.8% due to direct bilirubin).

On 02 MAR b* Dr [deleted] documented the possibility of the event being related to lamivudine discontinuation at the study start and not to the use of IP. It was also documented that the subject would be started on entecavir and may be submitted to a liver biopsy. It was also confirmed that the subject was diagnosed with Hep B back in p*.

The subject attended another visit at the site on 06 MAR b*. He was complaining of choluria and was presenting jaundice, but was better from an abdominal pain he previously experienced. He was started on entecavir and was scheduled to come back to the site to perform a liver biopsy, which was conducted on 08 MAR b*. The biopsy results are still pending.

On 14 MAR b* the study central lab released results of HBV DNA for 29 FEB b* showing a significant elevation from baseline, which defined, in the PI opinion, that the liver enzymes elevation corresponded to a HBV flare after discontinuation of lamivudine.

The subject is still under follow up and transaminases are still significantly high.

Investigator text:

We received a laboratory alert because ALT- AST results elevated on samples taken in week 12 visit. The patient came to the clinic and we repeated local and central lab.In
local lab, the new ALT / AST results has increased, and bilirubin was > 2 UNL. We reported hepatitis diagnosis as SAE event. IP was withdrawal. The patients returned on 02 and 06 MAR b*. We consulted to an hepatologist and decided to initiate entecavir, on 06 MAR b*. The liver biopsy was performed on 08 MAR b*. The preliminary inform of the biopsy indicates panlobulillar inflammation limpho-plasmocitary, without clear evidence of drug toxicity. The patient returned on 13 MAR b*, with improvement of the abdominal pain and persistence of jaundice. On 14 MAR b*, we received the HBV DNA of 29/2, which is consistence related to a HBV flare, and not with the investigational product. The patient returned on 16 MAR b*, without abdominal pain, but continues with jaundice, with mild abdominal distension. On 20 MAR b*, the patient said he had mild pruritus since 18 Mar b*, without abdominal distension. He was evaluated by the hepatologist. The pruritus seems related with the increased of bilirubin. On March 23 the pruritus was decreasing. The liver biopsy results with Hepatitis with intense inflammatory. He came to the clinic on 04 and 12 APR b*, stable, with less jaundice, and without another symptoms. (Pruritus resolved 04 APR b* without sequelae). He continued weekly follow up, improving laboratory results. On 08 MAY b*, we received normal transaminases, so the hepatitis event has resolved without sequelae.

Protocol Id: ING111762
Investigator Number: 084708
Subject Number: 002062
Treatment Number: 3098, 3098, 3098
Case Id: Z0014846A, Z0014846B, Z0014846C
Suspect Drugs: Raltegravir
Serious Events: Intervertebral disc protrusion, Intervertebral discitis, Postoperative wound infection, Subcutaneous abscess, Wound infection staphylococcal

This 40-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 22 AUG b*.

This subject was randomised to receive oral RAL 400 mg twice daily.

No relevant medical history.

On 15 MAR b*, 206 days after the start of investigational product, the subject developed grade 3 or severe intervertebral disc herniation. The subject developed acute lumbosciatalgia related to L4-L5 hernia of intervertebral disk. The subject was hospitalised and underwent microdiscectomy. Treatment with blinded trial medication was continued. The event resolved on 29 MAR b*. The investigator considered that...
there was no reasonable possibility that the intervertebral disc herniation may have been caused by investigational product.

Investigator text:

**ACUTE LOMBOSCIATALGIA RELATED TO L4-L5 HERNIA OF INTERVERTEBRAL DISK (TDM CONFIRMATION) PROGRAMMED HOSPITALISATION FOR SURGICAL TREATMENT (MICRODISCECTOMIE). CLEAR POST-OPERATIVE EVOLUTION**

On 20 APR b*, 242 days after the start of investigational product, the subject developed grade 3 or severe abscess of lumbar cicatrix. Concomitant medications included Bactrim, calcium folinate, tenofovir, darunavir and ritonavir. The subject was hospitalised and underwent surgical treatment on 01 JUN b*. No additional therapy was given. Treatment with blinded trial medication was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the abscess of lumbar cicatrix may have been caused by investigational product.

Investigator text:

**FLOW SINCE 20 APR b* ON LUMBAR SCAR. NO FEVER.SURGERY FOR ABSCESS OF LUMBAR CICATRIX.**

On 02 JUN b*, 285 days after the start of investigational product, the subject developed grade 3 or severe spondylodiscitis, grade 3 or severe post operative wound infection and grade 3 or severe staphylococcal wound infection. The subject's past medical history included postoperative super infection after surgical procedure (lumbar discal hernia) of 23 MAR b*. Concomitant medications included tenofovir, darunavir, ritonavir, Bactrim and calcium folinate. The subject was hospitalised. The subject underwent new surgical procedure for debridement and antisepsis on 3 and 6 JUN b*. Antibiotic therapy (unknown) has been adapted to bacterial isolation of Staphylococcus aureus during 45 days. Treatment with blinded trial medication was continued. The spondylodiscitis was unresolved at time of reporting. Outcome of post operative wound infection and staphylococcal wound infection was unknown at time of reporting. The investigator considered that there was no reasonable possibility that the spondylodiscitis, post operative wound infection and staphylococcal wound infection may have been caused by investigational product.

Investigator text:

post operative infectious complication, with staphylococcal L5-S1 spondylodiscitis and lumbar abscess, onset 50 days after first surgical intervention. Treatment with new surgical procedure for debridement and antisepsis on 3 JUN b* and 6 JUN b*; antibiotherapy adapted to bacterial isolation of Staphylococcus aureus during 45 days. End of treatment evaluation ongoing.
This 57-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 06 DEC.

This subject was randomised to receive oral RAL 400 mg twice daily. Concomitant medications included darunavir/ritonavir and maraviroc.

On 01 APR, 117 days after the start of investigational product, the subject developed grade 2 or moderate high grade squamous intraepithelial lesion (SIL) of uterus. The subject was hospitalised. Treatment with blinded trial medication was continued. The event resolved on 17 MAY. The investigator considered that there was no reasonable possibility that the high grade squamous intraepithelial lesion (SIL) of uterus may have been caused by investigational product.

Investigator text:

A diagnosis of cervix (uteri) leukoplakia was recently done. A biopsy was performed what required hospitalization of the Patient No complications or intercurrences relative to the surgery were observed. Result of the biopsy is pending.

This 57-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks
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in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 09 DEC. The subject was randomized to receive RAL 400 mg twice daily.

Medical conditions at the time of the event included Behcet’s Disease and insomnia. Concomitant medications included diazepam, dapsone, Trimethoprim/sulfamethoxazole, prednisone, tenofovir and atazanavir.

On 02 APR b* subject's lipase was at 424 U/L (normal range 13-60).

On 11 APR b*, 124 days after the start of investigational product, the subject developed grade 2 or moderate pancreatitis. The subject was hospitalised. Signs and symptoms included nausea and abdominal pain. An ultrasound result was normal. The subject was treated with ciprofloxacin and tramadol hydrochloride. Treatment with investigational product was discontinued on 12 APR b* and the subject was withdrawn from the study. On 17 APR b* subject's lipase level reduced to 118 U/L. The event resolved on 17 APR b*. The investigator considered that there was a reasonable possibility that the pancreatitis may have been caused by investigational product as the "event only began after the use of investigational product".

Investigator text:

Patient was hospitalised for clinic treatment due to pancreatitis diagnosed for other doctor. The medication of the study was suspended because of the possibility that the SAE may be related with the investigational product. During the time in the hospital it was made ultrasound and the result was normal. Without alterations and all the medication were suspended in 12 APR b*. the lipase get better and the result fell 118U/L in 17 APR b*.

Protocol Id: ING111762
Investigator Number: 081061
Subject Number: 001084
Treatment Number: 10590
Case Id: Z0015378A
Suspect Drugs: Raltegravir
Serious Events: Wound infection

This -year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product of RAL/placebo from 11 JAN and DTG/placebo from 12 JAN a*. (The start dates were confirmed as being different for the two drugs.)

a*: The year
b*: Following year
This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included (laparoscopic) cholecystectomy on 10 APR a* and gallstone. Concomitant medications included darunavir, ritonavir and tenofovir.

On 12 APR a*, 92 days after the start of investigational product, the subject developed grade 3 or severe wound infection. The subject returned to the ER on 12 APR a* with complaints of abdominal pain, fever, nausea and vomiting. The subject was hospitalised on 12 APR a* with wound infection which had a positive wound culture for proteus. The subject was treated with ciprofloxacin. The subject had a small infra-umbilical fluctuance which was incised and drained. Treatment with blinded trial medication was continued. The subject was discharged on 13 APR a* with ciprofloxacin and iodiform wound packing. At post-surgical visit on 02 MAY a* the umbilical wound was clean and dry with some exposed granulation tissue. There was no surrounding erythema, induration or fluctuance. Wound was healing well and no further packing was necessary. Lodocaine viscous was provided as a topical treatment for burning pain. The event resolved on 02 MAY a*. The investigator considered that there was no reasonable possibility that the wound infection may have been caused by investigational product.

Investigator text:

Patient had a Laparoscopic cholecystectomy on 10 APR a* on an outpatient basis which was a planned surgery. Patient returned to the ER on 12 APR a* with complaints of abd. pain, fever, nausea and vomiting. Patient was admitted to the hospital on 12 APR a* with a wound infection which had a positive wound culture of proteus. Patient was treated with Ciprofloxacin. Patient had a small fluctuance infra umbilical which was I & D'ed. Patient was discharged on 13 APR a* on Ciprofloxacin and with orders for iodiform wound packing bid. Patient had a post-surgical visit on 02 MAY a* at which time umbilical wound was clean and dry with some exposed granulation tissue. There was no surrounding erythema, induration or fluctuance. Wound was healing well and no further packing was necessary. Lodocaine viscous was provided as a topical treatment for burning pain. Patient is to return in 4 weeks for wound check unless it is completely healed.

Protocol Id: ING111762
Investigator Number: 081150
Subject Number: 000587
Treatment Number: 7044
Case Id: Z0016020A
Suspect Drugs: Raltegravir
Serious Events: Orchitis

*a*: The year
This 56-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 02 AUG.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject has no relevant medical history. Concomitant medications included atazanavir and tenofovir disoproxil fumarate.

On 14 APR, 256 days after the start of investigational product, the subject developed grade 3 or severe orchitis. The subject presented with acute right testicle pain and was hospitalised on 18 APR. Blood cultures from 21 APR were positive for gram positive cocci. The subject was treated with vancomycin, piperacillin sodium and morphine. Treatment with blinded trial medication was continued. The event resolved on 30 APR and the subject was discharged. The investigator considered that there was no reasonable possibility that the orchitis may have been caused by investigational product.

Investigator text:

Subject presented to [deleted] Hospital ED with acute right testicle pain. He was ultimately admitted. He was inpatient from 18 APR-30 APR. He was treated with IV Vancomycin, Zozyn and Morphine. He was continued on all his other medications. Continued dosing some of the blinded IP. Limited information available at this time. Medical records requested. Will update as more information is available. 31 JUL site still awaiting for medical records.

Protocol Id: ING111762
Investigator Number: 084204
Subject Number: 009972
Treatment Number: 30664, 30664
Case Id: Z0015277A, Z0015277B
Suspect Drugs: Raltegravir
Serious Events: Hepatitis, Pancreatitis acute

This 56-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 28 FEB.

The subject was randomized to receive RAL 400 mg twice daily.
Medical conditions at the time of the event included extrahepatic biliary ductal dilatation and gallstone.

On 19 APR a*, 51 days after the start of investigational product, the subject developed grade 3 or severe acute biliary pancreatitis.

The subject developed epigastric pain which worsened and the subject was hospitalised on 25 April a*. The subject showed no signs of sepsis. Treatment with investigational product was interrupted on 26 April a*. Laboratory test results dated 26 April a* showed white blood cell count at 17900 mm3 (normal range 3600 to 11000); neutrophils at 16110 mm3 (normal range 1540 to 7600); activated partial thromboplastin time 23 secs (normal range 25 to 45); aspartate aminotransferase 151 U/L (normal range 14 to 36); alanine aminotransferase 307 U/L (normal range 9 to 52); gamma glutamyl transferase 1346 U/L (normal range 12 to 43); alkaline phosphatase 226 U/L (normal range 38 to 126); bilirubin total 6.5 mg/dL (normal range 0.2 to 1.3); lipase 1008 U/L (normal range 23 to 300) and amylase 140 U/L (normal range 30 to 110). On 27 April a* an abdominal computed tomography with oral and intravenous iodinated contrast showed an hepatic granuloma and distal common bile duct ectasia compatible with choledocholithiasis. On 28 April a* laboratory test results showed bilirubin total at 2 mg/dL (normal range 0.2 to 1.3); bilirubin direct at 1.33 mg/dL (normal range 0 to 0.3); ALT 87 U/L; GGT 1097 U/L; alkaline phosphatase 172 U/L; lipase 120 U/L (normal range 0 to 60). The subject was started on ciprofloxacin, metronidazole, omeprazole, metoclopramide and dipyrone (prn).

On 30 April a* laboratory test results showed bilirubin direct at 0.42 mg/dL; GGT 933 U/L and alkaline phosphatase 139 U/L. Investigational product and concomitant antiretroviral therapy were restarted. Ciprofloxacin, metronidazole, metoclopramide and dipyrone were discontinued.

On 01 May a* lipase was at 151 U/L (normal 0-60). On 2 May a* the subject underwent an abdominal ultrasound that showed choledocholithiasis with significant dilation of the extrahepatic bile ducts and intrahepaticas. The gallbladder had a scleroatrophic aspect with various calculations inside. An hepatic granuloma in VII was seen. On 03 May a* laboratory test results showed AST at 80 U/L (normal 15-46); bilirubin total at 13.28 mg/dL (normal 0.2-1.3); bilirubin direct at 8.72 mg/dL (normal 0-0.3); ALT 155 U/L (normal 11-69); GGT 205 U/L (normal 12-58); alkaline phosphatase 308 U/L (normal 38-126); amylase 288 U/L (normal range 25 to 115) and lipase at 263 U/L (normal 0-60). On 04 May a* laboratory test results showed haemoglobin 10.8 g/dl, neutrophils 10648.8 mm3, WBC count 13600 mm3. The subject was treated with Zosyn (piperacillin and tazobactam) for cholangitis from 05 May a* to 12 May a*.

On 15 May a*, laboratory test results showed ALT 72 U/L, amylase 137 U/L, bilirubin direct 2.82 mg/dl, bilirubin total 3.75 mg/dl, GGT 907 U/L. On 20 May a*, laboratory test results showed alkaline phosphatase 131 U/L, amylase 119 U/L, bilirubin direct 1.95 mg/dl, bilirubin total 2.48 mg/dl and GGT 533 U/L.

*a*: The year

*新薬承認情報提供時に置き換え
On 25 May a*, the subject underwent an open cholecystectomy with bile duct injury requiring chest tube placement in the biliary tract.

On 28 May a*, laboratory test results showed bilirubin direct 1.03 mg/dl, bilirubin total 1.76 mg/dl, GGT 307 U/L, haemoglobin 10.9 g/dl, WBC count 16000 mm3.

The subject recovered well after the surgical procedure and was discharged on 30 May a* with a drain in the biliary tree. The event resolved on 05 July a*. The investigator considered that there was no reasonable possibility that the acute biliary pancreatitis may have been caused by investigational product.

Investigator text:

Patient with ultrasonographic diagnosis of cholelithiasis on 31 MAR a*. Ultrasound of the abdomen showed dilatation on 31 MAR a* via the distal extra-hepatic bile duct primary, due to gallstones. During the 8 week visit, 24 APR a*, a patient with epigastric pain beginning in 19 APR a* and opened an adverse event. There was worsening epigastric pain and was admitted on 25 APR a* at the Hospital [deleted] diagnosed with mild biliary pancreatitis. Informed by the attending physician of the hospital that the framework is stable and the patient shows no signs of sepsis. Event classified as serious adverse events grade 3 as required hospitalization. On 25 MAY a* patient underwent open cholecystectomy with bile duct injury requiring chest tube placement in the biliary tract. Patient recovered well after surgical procedure and was discharged on 30 MAY a* with the drain in the biliary tree. I look forward assessment of general surgery to remove the drain and end SAE. -

The subject has no relevant medical history. Concomitant medications included abacavir sulphate and Kaletra.

On 11 JUN a*, 104 days after the start of investigational product, the subject developed grade 3 or severe hepatitis. The subject presented at the site on 11 JUN a* complaining of uncontrollable vomiting. The subject was hospitalised on 11 JUN a* with sweating, several episodes of vomiting and poor general condition, weakness. Laboratory tests performed on 11 June a* showed ALT 962 U/L (normal 11-69), AST 393 U/L (normal 15-46), bilirubin direct 0.93 mg/dl, GGT 199 U/L (normal 12-58), hematocrit 32.5%, lymphocytes 1726.4 mm3, monocytes 1494 mm3, neutrophils 13296.6 mm3, sodium 119 mEq/l, WBC count 16600 mm3. The subject was diagnosed with hepatitis. The subject was started on dipyrrone, Tylex, bromopride, metoclopramide, dimeticone, sodium chloride and clonazepam.

On 12 June a*, laboratory test results showed ALT 699 U/L, AST 170 U/L, bilirubin direct 0.80 mg/dl, hematocrit 33.2%, neutrophils 13169.2 mm3, sodium 128 mEq/l, WBC count 16400 mm3.

Treatment with raltegravir was discontinued on 12 June a* and the subject was withdrawn from the study.

a*: The year
A CT of abdomen was performed on 15 June a* with no new findings. Laboratory test results dated 15 June a* included ALT 228 U/L, albumin 3.3 g/dl (NR 3.5-5), AST 51 U/L, bilirubin direct 0.33 mg/dl (NR 0-0.3), creatinine 0.5 mg/dl (NR 0.8-1.5), GGT 182 U/L, hematocrit 29.4% (NR 36-47), haemoglobin 10.5 g/dl (NR 11.5-16.4),

The event resolved on 18 June a*. The investigator considered that there was a reasonable possibility that the hepatitis may have been caused by investigational product.

Follow up information received on 19 JUN a* from the clinical team:

A lab sample was collected on 12 JUN a* and sent to the study central lab as an UNS visit showed significant hyponatremia (119 mg/dL), ALT of 751 U/L (15.6 x ULN), and AST of 225 U/L (5.4 x ULN). Total bilirubin was 28 umol/L (ULN=22)

Follow up information received on 20 JUN a* from the clinical team:

The subject did not take antiretroviral medication from 7 to 10 JUN a*. The subject took antiretroviral medication on 11 JUN a* prior to seeking medical attention. When she was admitted she did not present with abdominal pain. She had vomiting and malaise only and was not presenting with jaundice.

During hospitalisation, she was treated with sodium replacement fluid replacement, improved clinically and presented decrease in transaminases while observed as an inpatient. On 18 JUN a*, she was discharged from hospital and is scheduled to have an UNS visit at the on 21 JUN a*.

Follow up information received on 24 JUN a* from the clinical team:

Repeat labs on 21 June were largely within normal limits, except the ALT was 65 (ULN 48). Hepatitis B surface antigen and Hepatitis C ab were negative at Screening and remain negative upon repeat in June. The drugs of abuse screen was also negative but was obtained 2 weeks after her hospital admission

Follow-up information received on 26 JUN a* via query response:

The symptoms sweating, several episodes of vomiting and poor general condition, weakness started on 11 JUN a*.

The IP was interrupted on 07 JUN a*. The subject used the IP on 11/Jun/a* and these were interrupted again on 12 JUN a*.

Follow up information receive from the medical monitor on 08 JUL a*:

The possible role of complications related to the recent cholecystectomy or to the recent endoscopic procedures were considered unlikely in sight of the CT results and the subject was diagnosed with hepatitis. Relationship to ART regimen was considered.
The subject denied use of over-the-counter medication prior to the admission. The subject does not have a reference of alcoholism either.

Follow-up subsequently retrieved from the liver CRFs included:

The subject was not pregnant.

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the previous week. The subject did not consume alcohol.

The subject had no liver disease medical conditions, no drug related liver disease conditions and no other relevant medical conditions.

There were diagnostic imaging tests performed on 15 JUN a*. The liver imaging method was computerized tomography. The images were optimal for technical adequacy. The liver was normal for size, texture was normal and diffuse and/or geographic fatty infiltrate grade was not applicable - no fatty infiltration. Ascites was not present, focal hepatic lesions were characterized by a nonspecific calcified lesion in the right lobe of liver. There were no gallstones or gallbladder lesions - the subject had undergone a cholecystectomy on 25 MAY a*. Biliary ductal lesions - the ductal wall showed thickening or oedema. No portal / hepatic vein abnormalities were seen. There were no liver biopsies performed.

Investigator text:

On 11 JUN a* patient arrives to the site complaining of uncontrollable vomiting. At this time we concluded that it was related to a SAE previously reported (pancreatitis). She was hospitalized and after result of exams it was concluded that the EA (vomiting) had no relationship with the previous SAE (pancreatitis). Subject didn't use alcohol, no reports of dietary changes, denies new sexual partners. Since menopause. She had no fever at any time. Admitted on 11 JUN a* with sweating, several episodes of vomiting and poor general condition, weakness.

Protocol Id: ING111762
Investigator Number: 081321
Subject Number: 001138
Treatment Number: 30601, 30601
Case Id: Z0015367A, Z0015367B
Suspect Drugs: Amitriptyline, Dolutegravir
Serious Events: Depression, Overdose, Suicide attempt

This ■-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks.
in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 10 JAN.

This subject was randomised to receive oral DTG 50 mg once daily.

Medical conditions at the time of the event included depression and insomnia. Concomitant medications included duloxetine, temazepam, alprazolam, Kaletra, etravirine, amitriptyline hydrochloride, lorazepam, rosvastatin calcium, lisinopril, Hydrochlorothiazide + metoprolol tartrate, esomeprazole, triamcinolone acetonide, tadalafil, vitamin d and cyanocobalamin.

On 26 APR, 107 days after the start of investigational product, the subject developed grade 2 or moderate worsened depression. The subject was hospitalised on 26 APR. The subject was treated with duloxetine, risperidone and ziprasidone hydrochloride. Treatment with blinded trial medication was continued. The event resolved on 01 MAY. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by investigational product and that the event was possibly due to a death in the subject's family.

Investigator text:

Subject #001138 came in to see us for worsening of depression due to a death in his family. We referred him to [deleted] Centre. He was referred to [deleted] Psychiatric Facility by [deleted]. The subject made it to [deleted] on 26 APR where he elected to stay in-patient during the transition of his psychiatric medications. There was no suicide attempt.

On 04 JUN, 146 days after the start of investigational product, the subject developed grade 3 or severe attempted suicide and grade 3 or severe drug overdose. Medical conditions at the time of the event included depression and insomnia. Concomitant medications included amitriptyline, duloxetine, lurasidone, memantine hydrochloride, alprazolam, Kaletra and etravirine. The subject ingested 20-30 tablets of amitriptyline (Elavil) while drinking whisky. The subject phoned his partner and informed him of his actions. His partner drove the subject to the hospital and the subject was hospitalised. Associated symptoms included confusion, disturbed concentration, transient visual hallucinations, stupor and drowsiness. Treatment with blinded trial medication was continued. A non-contrast CT scan of the head showed no evidence for haemorrhage, mass effect, hydrocephalus or shift, but there was mild parenchymal volume loss. A drug screen was positive for benzodiazepines. The events resolved on 12 JUN. The investigator considered that there was no reasonable possibility that the attempted suicide and drug overdose may have been caused by investigational product and that the events were possibly due to the concomitant medication, amitriptyline.

Investigator text:
1) Suicidal ideation: Subject has documented past depression and/or other psychiatric conditions, psycho social stressors.

2) Suicidal ideation, behaviour or self-harm in the past: Yes. Two prior suicide attempts.

3) Is there a reference to current use of alcohol or illicit drugs? Yes, current alcohol use. No current illicit drug use.

4) Is there a family history of suicidality or psychiatric disorders? Unknown.

5) Did subject provide details on plans, preparations, specific intent towards suicide? Subject did not provide details on plans, preparations or intent towards suicide but did telephone his partner after ingesting the tablets and drinking 8oz of whiskey to inform him of what he did.

6) Did subject confirm that his intention was to cause his death and was aware that the amitriptyline dose ingested could be fatal? Subjects attempt was intentional and he was aware that the dose of amitriptyline could be fatal.

7) Signs/symptoms associated to amitriptyline overdose observed: Confusion, disturbed concentration, transient visual hallucinations, stupor, and drowsiness.

8) Clarify treatment applied and evolution: Patient was in-patient psychiatric care with counselling/group counselling and medications. Patient was discharged home when deemed competent by psychiatrist to make decisions regarding his welfare, was not a danger to self or others and after denying any self-harm ideation.

9) Clarify use of Namenda to treat depression: Namenda is listed in the medical records we received when this subject was having his psychiatric medications adjusted for worsening of depression. No indication for another use although one would suspect the patient may have had symptoms of dementia.

This 23-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 27 JAN to 28 MAR b*. The subject switched to the open-label phase and received oral DTG at 50 mg per day from 28 MAR b*.

This subject was randomised to receive oral DTG 50 mg once daily.

The subject has no relevant medical history. Concomitant medications included atazanavir and tenofovir disoproxil fumarate.
On 01 MAY b*, 460 days after the start of investigational product and 34 days after the start of open-label DTG, the subject developed grade 3 or severe varicella zoster virus. The subject developed problems with rash on right side of neck on 01 MAY b*; started with vesicles in his neck, which extended to multiple vesicles up at shoulder. The subject was hospitalised. The vesicles were PCR positive for varicella zoster virus. The subject was treated with acyclovir. Treatment with open-label DTG was continued. The event resolved with sequela (small wounds in his neck) on 11 MAY b*. The investigator considered that there was no reasonable possibility that the varicella zoster virus may have been caused by investigational product and DTG.

Investigator text:

1 MAY b* problems with rash in neck right side. Started with vesicles in his neck, this extended to multiple vesicles up at shoulder. When he went home he had some small wounds in his neck.

Protocol Id: ING111762
Investigator Number: 084496
Subject Number: 009425
Treatment Number: 30620
Case Id: Z0016372A
Suspect Drugs: Raltegravir
Serious Events: Disseminated tuberculosis

This 21-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 01 FEB .

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included diabetes mellitus. The subject had no other pre-study history of CHF.

On 08 MAY a*, 97 days after the start of investigational product, the subject developed grade 3 or severe disseminated tuberculosis. The subject was hospitalised. The subject was treated with frusemide, thiamine, heparin, captopril, Amoxicillin + clavulinate K, azithromycin, rifampicin, isoniazid, pyrazinamide, ethambutol hydrochloride, levofloxacin and digoxin. He had a physical examination consistent with heart failure, but the ECG and echocardiography (ECO) did not confirm this hypothesis. His ECG QTc is normal, the ECO had atrium and ventricle cameras normal, and cardiac enzymes were also normal. Biopsies were performed and histopathology showed granulomatous necrosis. Treatment with blinded trial medication was interrupted on 10 AUG a* and re-started on 14 AUG a*. He was being treated as disseminated.

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
tuberculosis (with pulmonary, pleural, pericardial and peritoneal invasion) as they awaited final results of cultures for microbiological confirmation, and this diagnosis was confirmed on 10 AUG a*. The heart failure was probably due by pericardial involvement. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the disseminated tuberculosis may have been caused by investigational product.

Follow-up information received on 14 SEP a*:

This subject has been evaluated in outpatient regime since 04/SEP/a*, using HAART and tuberculosis drugs without rifampicin. He is better and doesn't have any medical problems. All clinical events were related with disseminated tuberculosis.

Investigator text:

The symptoms initiated on July 9th with progressive dyspnoea with serosanguinolent secretion without fever. The sub investigator decided to initiate antibiotic for a respiratory infection with amoxicillin/ clavulanic acid. Today, during the regular week 24 visit, the patient was not better and the sub investigator suspect of congestive heart failure. Decided to admit at the hospital to clarify this hypothesis. The subject is still hospitalized with the same SAE, not with a new SAE. His clinical conditional is unclear until now. He had a physical examination consistent with heart failure, but the ECG and echocardiography (ECO) did not confirm this hypothesis. His ECG QTc is normal, the ECO had atrium and ventricle cameras normal, and cardiac enzymes was also normal.

At the moment, the clinical team is investigating different causes for his clinical conditional and tuberculosis treatment was started empirically. They are awaiting the results of biopsies performed and the rheumatologic team is also evaluating this case.

The study drugs was just stopped today despite I’ve already asked this conduct since the first day, but his ALT and AST are normal and other hepatic exams too.

After discussing this case with the monitoring study, we decide that the subject will not be discontinued from the study until we clear this condition.

Protocol Id: ING111762
Investigator Number: 081322
Subject Number: 001128
Treatment Number: 30611
Case Id: Z0015586A
Suspect Drugs: Raltegravir
Serious Events: Iridocyclitis

This [year]-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily.
daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 26 JAN. 

This subject was randomised to receive oral RAL 400 mg twice daily.

Concomitant medications included darunavir, tenofovir disoproxil fumarate and ritonavir. The subject had no known risk factors.

On 16 MAY, 111 days after the start of investigational product, the subject developed grade 2 or moderate anterior uveitis. Associated symptoms included redness of both eyes and pain behind both eyes. The subject was hospitalised on 18 MAY and diagnosed with bilateral uveitis, cause unknown. A lumbar puncture and MRI of the brain (with and without contrast) were both normal. The subject was treated with acyclovir and prednisone acetate eye drops. Treatment with investigational product was continued. The subject was discharged on 21 MAY. The event resolved on 14 JUN.

The investigator considered that there was no reasonable possibility that the anterior uveitis may have been caused by investigational product.

Investigator text:

Subject had redness of both eyes and pain behind both eyes. He was admitted to hospital on 18 MAY and was diagnosed with bilateral uveitis, cause unknown. Subject is responding to prednisone eyes drops and was discharged from hospital on 21 MAY. Subject continues to recover and will be following up with ophthalmology on 12 JUN.

Protocol Id: ING111762
Investigator Number: 084204
Subject Number: 001963
Treatment Number: 30667
Case Id: Z0015831A
Suspect Drugs: Dolutegravir
Serious Events: Abdominal pain

This 1-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 28 FEB.

This subject was randomised to receive oral DTG 50 mg once daily.

a*: The year
Medical conditions at the time of the event included epigastric pain. Concomitant medications included abacavir sulphate and fosamprenavir.

On 22 MAY a*, 84 days after the start of investigational product, the subject developed grade 2 or moderate abdominal pain. Abdominal ultrasound was normal. The pain intensified and the subject was hospitalised on 05 JUN a* to investigate the cause of the pain, including performing CT and endoscopy, results of which were deemed “unchanged”. Laboratory test results dated 05 JUN a* included amylase 152 U/L (NR 25-115), BUN 18 mg/dl (NR 19-43), creatinine 0.7 mg/dl (NR 0.8-1.5), GGT 76 U/L (NR 12-58), lipase 123 U/L (NR 0-60). Laboratory test results dated 06 JUN a* included amylase 151 U/L, eosinophils 7% (NR 2-4), lipase 123 U/L, lymphocytes 52% (NR 19-39), and monocytes 9% (NR 4-8). The subject was treated with hyoscine butylbromide, omeprazole and tramadol hydrochloride. Treatment with blinded trial medication was continued. The event resolved with sequelae on 14 JUN a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the abdominal pain may have been caused by investigational product. The increased lipase and amylase were thought to be due to the use of the background regimen ART and not the IP.

Investigator text:

Patient refer abdominal pain since 22 MAY a*, abdominal USG was normal. Once he presented increased of pain intensity, he was hospitalized on 05 JUN a* to proceed Computed tomography and high Endoscopy digestive. The result of abdominal CT was unchanged, and the patient was discharged on 14 JUN a*. Subject maintains abdominal pain with after discharge/ Increased lipase associated with abdominal pain, related to ARV background therapy. Lipase are normal since 14 JUN a*. No other associated symptom.

Protocol Id: ING111762
Investigator Number: 084071
Subject Number: 002014
Treatment Number: 3163
Case Id: Z0015793A
Suspect Drugs: Dolutegravir
Serious Events: Lung infection

This 49-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 17 NOV 2015.

This subject was randomised to receive oral DTG 50 mg once daily.

a*: The year
Medical conditions at the time of the event included biological hepatitis and biological inflammatory syndrome. Concomitant medications included paracetamol.

On 24 MAY b*, 189 days after the start of investigational product, the subject developed grade 3 or severe bacterial pneumopathy. The subject was hospitalised. Symptoms between 25 MAY b* and 03 JUN b* included a hacking cough with chest pain, fever, shivering, asthenia, anorexia, macroscopic hemature, diffuse abdominal pain, diarrhoea, vomiting, interscapular bilateral lumbar pain. The subject was treated with spiramycin, Spasfon, zolpidem, Claforan, tramadol hydrochloride and Augmentin. Treatment with investigational product was interrupted on 01 JUN b* and re-started on 04 JUN b*. Results of an abdominal ultrasound of 03 JUN b*: liver increased by size (20 cms before the right kidney), homogeneous without focal lesion, see bilaires fine. No vascular anomaly. Vesicle bilaire not distended. Kidneys are considerable and of morphology normal no dilation. Normal bladder. The event resolved on 28 JUN b*. The investigator considered that there was no reasonable possibility that the bacterial pneumopathy may have been caused by investigational product.

Investigator Text:

Macroscopic hematuria and fever for 7 days. Left lumbar pain Febrile patient in 39.5 C. No sign of shock, warm extremities.

some purposes sibilant, not of crepitant. Flexible calves. Vomiting water more galire 3 days and this day ago. Anorexia for 7 days supple abdomen. No pain in the lumbar percussion. Supple nape of the neck. 04 JUN b* Likely hepatic infringement.

Protocol Id: ING111762
Investigator Number: 084019
Subject Number: 002730
Treatment Number: 40592
Case Id: Z0015861A
Suspect Drugs: Dolutegravir
Serious Events: Chest pain

This 50-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 09 FEB .

This subject was randomised to receive oral DTG 50 mg once daily.

The subject's past medical history included acute myocardial infarction. Medical conditions at the time of the event included coronary disease and arterial hypertension.
Concomitant medications included clopidogrel, atorvastatin calcium, atenolol, aspirin, enalapril, lamivudine-hiv and atazanavir.

On 02 JUN a*, 114 days after the start of investigational product, the subject developed grade 3 or severe precordialgia. The subject was hospitalised. The subject is underwent cardiac catheterization on 25 AUG a* (at another hospital) but the final report was not yet received. Treatment with blinded trial medication was continued. The event resolved on 12 JUN a*. The investigator considered that there was no reasonable possibility that the precordialgia may have been caused by investigational product.

Investigator text:

patient with the diagnosis since August e* chronic coronary artery disease probably related to HIV. has arterial hypertension since may / 91 and MHX of Acute Myocardial Infarction on 28 AUG e* with revascularization did with the placement of two stents. This AE is SAE due to HOSPITALIZATION. We are waiting the Cardiac Catheterism for further clarifications. On the hospitalization the patient kept stable and she is waiting the other hospital to call for the cardiac catheterism.

Protocol Id: ING111762
Investigator Number: 083117
Subject Number: 002224
Treatment Number: 1047
Case Id: Z0016162A
Suspect Drugs: Raltegravir
Serious Events: Coronary artery disease

This 3-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 11 AUG.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject's past medical history included smoking and suspicion of transient stroke. There was no previous history of ischemia or ischemic cardiopathy.

On 25 JUN b*, 319 days after the start of investigational product, the subject developed grade 3 or severe coronary artery disease. The event was clinically significant (or requiring intervention). Acute chest pain on 25 JUN b* at rest was suggestive of a cardiac origin. ECG performed on 26 JUN b* showed normal result. Cardiac exercise test performed on 26 JUN b* confirmed the ischemic origin of the chest pain. Cardiac catheterization performed on 02 JUL b* confirmed multiple significant coronary...
arteries stenosis. On 02 JUL b*, an angioplasty with stenting was done with success. No relapse of chest pain since then. Treatment with blinded trial medication was continued. The event resolved on 02 JUL b*. The investigator considered that there was no reasonable possibility that the coronary artery disease may have been caused by investigational product.

Investigator text:

Acute chest pain on 25 JUN b* at rest suggestive of a cardiac origin. On 02 JUL b*, an angioplasty with stenting was done with success. No relapse of chest pain since then.

Protocol Id: ING111762
Investigator Number: 083989
Subject Number: 002712
Treatment Number: 30599
Case Id: Z0016269A
Suspect Drugs: Raltegravir
Serious Events: Pneumonia

This 34-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 09 JAN 2020.

This subject was randomised to receive oral RAL 400 mg twice daily.

Medical conditions at the time of the event included bronchitis and secondary epilepsy. Concomitant medications included lamivudine-hiv, atazanavir and ritonavir.

On 03 JUL a*, 176 days after the start of investigational product, the subject developed grade 2 or moderate pneumonia. The subject was noted to be vomiting and had a fever (body temperature 38.5 degrees C). The subject was hospitalised. Chest x-ray performed on 10 JUL a* showed image compatible with right lobar pneumonia. The subject was treated with ceftriaxone, clarithromycin, fenoterol hydrobromide and ipratropium bromide. Chest x-ray performed on 24 JUL a* showed small nodules on the left lower cervical lymph nodes, bilateral hilar, laminar atelectasis sparse. Treatment with blinded trial medication was continued. The event resolved on 28 JUL a* and the subject was discharged. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by investigational product.

Investigator text:

Patient with vomit since 03 JUL a*, fever (38.5C). A chest x-ray was made and was noticed image compatible with right lumbar pneumonia. The hospitalization was due to
the necessity for administration of intravenous medication and not due to severity of the event. On 18 JUN a*, 19 JUN a* and 13 JUN a* the patient had negative results for the detection of BK in sputum. On 24 JUL a* a chest x-ray was made and was noticed small nodules in the left lower cervical lymph nodes, bilateral hilar, laminar atelectasis sparse. Patient improved clinically and radiologically and discharged on 28 JUL a*.

Protocol Id: ING111762
Investigator Number: 081200
Subject Number: 000784
Treatment Number: 1058
Case Id: Z0016257A
Suspect Drugs: Raltegravir
Serious Events: Headache

This 50-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 12 OCT.

This subject was randomised to receive oral RAL 400 mg twice daily.

The subject did not have any relevant medical history. The subject was also receiving Viread and darunavir/ritonavir.

On 06 JUL b*, 268 days after the start of investigational product, the subject developed grade 1 or mild headache. The subject also experienced general malaise and fatigue, but denied fever, chills or respiratory problems. The subject presented to the ER on 07 JUL b* with headache in right fronto-temporal with radiation to back of head and right side of neck, nausea but no vomiting. The subject was hospitalised. CT scan of head without contrast was negative for past or active bleeds or tumour; lumbar puncture result was negative. The subject was treated with diazepam, diphenhydramine, droperidol, hydromorphone hydrochloride, ketorolac trometamol, lorazepam, promethazine, sodium chloride, Norco, ibuprofen and lignocaine hydrochloride. Treatment with blinded trial medication was continued. The event resolved on 09 JUL b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the headache may have been caused by investigational product.

Investigator text:

7-6-b* started with headache and general malaise fatigue, denies fever or chills, no respiratory problems. HA in right fronto-temporal with radiation to back of head and right side of neck, nausea but no vomiting. Emergency room visit on 7-7-b* and
This 38-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 23 NOV.

The subject was randomised to receive RAL 400 mg twice daily. The subject was also receiving darunavir/ritonavir and tenofovir as part of his ART regimen.

Medical conditions at the time of the event included depression.

On 14 JUL, 234 days after the start of investigational product, the subject developed grade 4 suicidal ideation. The event was clinically significant (or requiring intervention). Treatment with investigational product was discontinued on 17 JUL and the subject was withdrawn from the study. The event resolved on 18 JUL. The investigator considered that there was a reasonable possibility that the suicidal ideation may have been caused by investigational product.

Investigator text:

The subject texted the study coordinator about recurrence and increase intensity of suicidal ideation over the weekend, with no specific plan. He was advised to report to the emergency room if he was planning to implement but he declined and texted he was feeling better after speaking and spending the night with a neighbour. Today, the Principal Investigator was notified and made the decision to withdraw the subject. There is no history of self harm behaviour; no current use of alcohol or illicit drugs; no known family history of suicidality or psychiatric disorders; there was no suicidal ideation before the start of the study.
Module 2.7.4 Summary of Clinical Safety

Suspect Drugs: Dolutegravir
Serious Events: Renal colic

This 39-year-old female subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naive, antiretroviral therapy-experienced adults. The subject received oral investigational product from 18 FEB.

This subject was randomised to receive oral DTG 50 mg once daily.

No medical history was reported. Concomitant medications included ritonavir, tenofovir and atazanavir.

Ultrasound performed on 06 AUG a* showed a renal calculus.

On 17 AUG a*, 181 days after the start of investigational product, the subject developed grade 2 or moderate renal colic. The subject also experienced grade 2 increased creatinine of 2.41 mg/dL (normal range 0.6-1.0), glycated haemoglobin 6.4% (normal range 4-6), fever and abdominal pain. The subject was hospitalised. Creatinine re-test performed on 17 AUG a* showed result of 0.81 mg/dl. Treatment with blinded trial medication was interrupted on 17 AUG a*. The subject was prescribed piperacillin / tazobactam, when hospitalized, but this wasn’t started due to lack of fever and pain; only observation and medication were required. The event resolved on 18 AUG a*. Treatment with blinded trial medication was re-started on 19 AUG a* after the creatinine result was not confirmed on retest. The investigator considered that there was no reasonable possibility that the renal colic may have been caused by investigational product.

Investigator text:
Worsening urinary infection (high tract) with increased creatinine and glicade hemoglobin, fever and abdominal pain. Started on 17 AUG a*. The Ultra sound performed on 06/08/a* show a renal calculus. The ARV's were stopped due to the Creatinine value (increased). was asked a local lab exames to decide the treatment dose with piperaciline / tazobactam. Until now we don’t have this exames results. as soon as possible this form will be updated. piperaciline / tazobactam this drug was not started.

9.6.4.2. Cases Reported Between 05 September to 26 October

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the safety data lock point for both the ING111762 Week 24 CSR and the ISO outputs, through to the final 26 October safety data lock point for the ISS, and...
includes all initial reports and follow up information received by the company through 26 October. The data included here are not represented in the clinical study report included in m5.3.5.1, nor in the ISO Tables and Figures produced for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials database in preparation of these narratives.

Protocol Id: ING111762
Investigator Number: 081168
Subject Number: 000658
Treatment Number: 1044
Case Id: Z0017334A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia

This 32-year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 29 July to 27 June and oral dolutegravir at 50 mg per day from 28 June.

The subject was randomized to receive GSK1349572 50 mg once daily.

On 16 October, 445 days after the start of investigational product, 111 days after the last dose, and 110 days after the start of open-label dolutegravir, the subject developed grade 3 or severe pneumonia. The subject was hospitalised. Treatment with dolutegravir was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by investigational product and dolutegravir.

Investigator text:

Just learned about this. No medical records available yet. Will update as we get more information. -

Protocol Id: ING111762
Investigator Number: 081200
Subject Number: 000784
Treatment Number: 1058
Case Id: Z0016257B
Suspect Drugs: Raltegravir
Serious Events: Anxiety

This 32-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 12 October.

b*: Following year
This subject was randomised to receive oral raltegravir 400 mg twice daily.

On 01 September b*, 325 days after the start of investigational product, the subject developed grade 2 or moderate anxiety. The subject was hospitalised due to left side pain/numbness. CT, MRI and EEG were all negative. The subject was treated with tramadol hydrochloride. Treatment with blinded trial medication was continued. The event resolved on 04 September b*. The subject did not have a prior history of anxiety, but she did state that several deaths in her family upset her. The investigator considered that there was no reasonable possibility that the anxiety may have been caused by investigational product.

Investigator text:

Admitted for left side pain/numbness. CT/MRI/EEG all negative. discharged with anxiety and told to f/u with PCP -

Protocol Id: ING111762
Investigator Number: 081069
Subject Number: 001070
Treatment Number: 30634
Case Id: Z0016991A
Suspect Drugs: Dolutegravir
Serious Events: Back pain, Mental status changes, Metastatic neoplasm

This -year-old male subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 16 February .

Concomitant medications included tenofovir and efavirenz.

On 11 September a*, 208 days after the start of investigational product, the subject developed grade 3 or severe metastatic carcinoma of abdomen and grade 3 or severe mental status changes. On 23 September a*, the subject developed grade 3 or severe back pain. CT scan in the ER revealed multiple masses compatible with unspecified metastatic cancer. The subject was hospitalised for evaluation of altered mental status, abdominal pain, weakness and generalized failure to thrive. Hypercalcemia was noted. The subject was able to deny any fever, chills, or systemic manifestation of sepsis. The subject was treated with Norco, polyethylene glycol, ondansetron hydrochloride, ibuprofen, sodium chloride, Vicodin and morphine. Treatment with investigational product was discontinued on 26 September a* and the subject was withdrawn from the study. Chemotherapy was not initiated due to poor prognosis of the tumour and the subject was transferred to hospice care. The mental status changes event resolved on 14 September a*. The metastatic carcinoma of abdomen and back pain were unresolved at time of reporting. The back pain was considered by the investigator to be probably due to lytic lesions in the spine. The investigator considered that there was no reasonable possibility that the back pain may have been caused by investigational product.

a*: The year
b*: Following year
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Module 2.7.4 Summary of Clinical Safety

possibility that the metastatic carcinoma of abdomen, mental status changes and back pain may have been caused by investigational product.

Diagnostics:

CT scan of abdomen/pelvis: Multiple small hypoattenuating nodules are noted. There is more confluence of abnormality is noted in the coronal plane in the dome of the diaphragm. The spleen has enlarged and measures 17.8 cm in diameter. There is probable adenopathy stranding in the fat in the porta hepatis near the head of the pancreas. CT of the head with contrast showed left lateral ventricle slightly larger than the right, might represent focal atrophy versus normal. CT guided liver biopsy waiting for the results. Tumour markers including AFP which was elevated at 12.2. CA19-9= 222, CEA= 8, Calcium level= 11 and parathyroid hormone= appropriately suppressed. Calcium normal level= 8.8- 10.2 mg/dL. CT guided liver biopsy results showed "metastatic adenocarcinoma of the liver".

Investigator text:

The patient was admitted for evaluation of altered mental status, abdominal pain, weakness and generalized failure to thrive. At ER, the attending physician was unable to obtain detail information from the patient. However, he able to deny any fever, chills, or systemic manifestation of sepsis. CT scan in the ER revealed multiple masses compatible with some type of metastatic cancer, prompting admission for further evaluation. A chemotherapy was planned however this was not initiated after further evaluation revealed poor prognosis of the tumour.

Protocol Id: ING111762
Investigator Number: 081061
Subject Number: 001081
Treatment Number: 1069
Case Id: Z0013647E
Suspect Drugs: Dolutegravir
Serious Events: Depression, Suicide attempt

This 35-year-old male subject was enrolled in a ViiV-sponsored, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The subject received oral investigational product from 07 November.

This subject was randomised to receive oral dolutegravir 50 mg once daily.

The subject's past medical history included possible amphetamine abuse. Medical conditions at the time of the event included alcohol abuse and generalized anxiety.
disorder. Concomitant medications included olanzapine, clonazepam, duloxetine, desvenlafaxine succinate, methylphenidate hydrochloride and modafinil.

On 28 August b*, 295 days after the start of investigational product, the subject developed grade 4 worsened depression. The subject was distressed after an argument on 28 August b*, and decided to attempt suicide by overdosing on vodka and methylphenidate on 01 September b*. The subject was hospitalised on 02 September b*. Treatment with investigational product was continued. Serum ethanol was 178 mg/dl (ref range <10 mg/dl). The subject was discharged on 06 September b*. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by investigational product.

Investigator text:

Pt left voice mail msg that he requested hospital admission on 2SEP b* for exacerbation of depression. Discharged from hospital on 6SEP b*, study visit sched for 10SEP b*. Will sign rec release at that time. Pt was distressed by phone argument w/mother on 8/28/b*. Decided to overdose on methylphenidate, vodka on 9/1/b*; signed himself into psych unit on 9/2/b*. Antidepressants changed; discharged on 9/6/b*, to follow up w/psychiatrist and ID specialist.

Protocol Id: ING111762
Investigator Number: 084019
Subject Number: 001977
Treatment Number: 30657
Case Id: Z0017236A
Suspect Drugs: Dolutegravir
Serious Events: Upper limb fracture

This 21-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product from 27 February a*. The subject was randomized to receive GSK1349572 50 mg once daily.

The subject was hospitalised. Treatment with blinded trial medication was continued. The subject was discharged on 29 August a*.

Investigator selected backbone therapy was tenofovir and atazanavir boosted with ritonavir.

On 28 August a*, 183 days after the start of investigational product, the subject developed grade 2 or moderate multiple fractures left arm. The subject was hospitalised. Treatment with blinded trial medication was continued. The subject was discharged on 29 August a*. The event was unresolved at time of reporting. The investigator
considered that there was no reasonable possibility that the multiple fractures left arm may have been caused by investigational product.

Investigator text:

the SAE hospitalization was finished on 29/08/a* but the AE Fractures is ongoing -

Protocol Id: ING111762
Investigator Number: 85074
Subject Number: 2214
Treatment Number: 7087
Case Id: B0835051A
Suspect Drugs: Raltegravir
Pregnancy

This 27-year-old female subject was enrolled in a ViiV-sponsored, blinded study for the treatment of human immunodeficiency virus infection. The subject received oral investigational product per day from 16 November.

This subject was randomised to receive oral raltegravir 400 mg twice daily.

Concomitant medications included Truvada. The subject had one previous pre-term pregnancy resulting in spontaneous abortion.

On 24-Sep-b*, 313 days after the start of investigational product, the subject was reported to be pregnant. Date of last menstrual period was 22 July b*. Estimated date of delivery was 28 April c*. Treatment with blinded trial medication was discontinued. There were no other additional factors reported that may have an impact on the outcome of this pregnancy. The subject's partner had no relevant medical or family history which may have an impact on the outcome of this pregnancy.

9.6.5. ING112961 SAE and Pregnancy Case Narratives

9.6.5.1. Cases Reported up to 26 October

The narratives included in this section correspond to the SAEs and Pregnancy cases included in the ING112961 Week 96 CSR (Cohort I and Week 48 for Cohort II) (with a data lock point of 26 October for safety data), which is included in m5.3.5.2. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.

Protocol Id: ING112961
Investigator Number: 065785
Subject Number: 001111

a*: The year
b*: Following year
c*: 2 years later

* 新薬承認情報提供時に置き換え
This [8]-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 03 November.

Concomitant medications included 0.9 % Normal Saline, potassium chloride and enoxaparin.

On 17 December a*, 44 days after the start of dolutegravir, the subject experienced lower extremity weakness and difficulty breathing. The subject was hospitalised. The event was considered disabling. A CT of head revealed a left frontal mass suspicious for meningioma. MRI showed a focal mass lesion involving the left frontal region. The subject was diagnosed with a grade 4 frontal central nervous mass. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The subject died on 26 March b*. Cause of death was reported as frontal central nervous mass. The investigator considered that there was no reasonable possibility that the cerebral frontal mass may have been caused by dolutegravir.

Follow-up information received from Clinical Study Team on 29 December a*:

The subject was admitted to hospital on 17 December a*, for altered mental status and syncope exhibiting slight confusion and memory lapses. The subject was negative for toxoplasmosis antibodies, but toxoplasmosis treatment and repeat MRI scan in three weeks were recommended. The subject was discharged in stable condition and transferred to a nursing facility on 23 December a* while awaiting follow-up with regard to brain lesion. The discharge diagnosis was consistent with a possible toxoplasmosis vs. lymphoma vs. meningioma.

Additional information received 10 February b*:

Concomitant medications included normal saline, potassium chloride, and enoxaparin (Lovenox). The subject had no relevant medical history.

Follow-up information received 30 March b*:

It was reported that the subject died due to the event of brain mass on 26 March b*. It was not known whether an autopsy was performed or not.

Follow-up information received from clinical study team:
The subject was confirmed not to have undergone any tests in addition to the ones already reported. Initial hospital plans were to do further work up on the subject's cerebral mass, but all those plans were eventually placed on hold because of the severity of illness and the subject having shortly passed away. No final conclusions could be drawn from the analysis of the subject's medical records.

Investigator comment: the best assessment was that the subject who had very advanced AIDS and severely prolonged immunosupression due to the lack of effective treatment options developed possibly a brain lymphoma. The radiologist could not rule out the alternative diagnosis of meningioma, based on the appearance of the lesions on CT and MRI scans. The investigator thought that last possibility was less likely, considering the overall clinical picture. There were some initial notes on the subject's hospital chart raising the possibility that he may have had toxoplasmosis, but this was safely ruled out again by the overall clinical picture. No other diagnosis considerations are or were being considered. The lesions in radiographic studies were not consistent with PML.

Investigator Text:

The office received a message on 12/17/a* from answering service stated that patient was admitted into the hospital via 911EMS due to lower extremity weakness and difficulty breathing.

*a*: The year
This [3]-year-old female subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 10 November.

The subject's past medical history included upper respiratory infection and uterine leiomyoma.

On 04 February b*, 86 days after the start of dolutegravir, the subject developed grade 3 shortness of breath, chest pain and coughing. The subject was hospitalised. Diagnostic tests performed included D-dimer, which resulted above the normal range. The subject was admitted for monitoring of airway and to rule out blood clot. The subject was treated with salbutamol sulphate and promethazine hydrochloride. Treatment with dolutegravir was continued. The event resolved on 25 February b*. RSV testing was positive one week after discharge. No other significant findings were described for the diagnostic tests performed, including CT scan. The investigator considered that there was no reasonable possibility that the shortness of breath may have been caused by dolutegravir.

Investigator Text:

Patient with 5-6 days of URI, and sudden onset of chest pain came to ED on 2-4-b* pm with shortness of breath, chest pain with coughing. Work-up continues. Medications are now being given, but held in the morning for a CT scan to be done first. RSV testing was positive one week after discharge, no other findings per test results found. Sent home with no treatments, was given albuterol nebulizer every 4 hours only while in hospital. She had a prescription for phenergan as well for nausea, but did not take this much at home either. She has had nausea frequently before she was hospitalized for this event.

On 08 April b*, 149 days after the start of dolutegravir, the subject had hysterectomy for uterine leiomyoma, requiring hospitalisation. The subject had a 10 year history of chronic abdominal pain.

The subject experienced metromenorrhagia, dysmenorrhea and progression of anaemia. On 05 February b* a transvaginal ultrasound was performed and showed fibroids. The subject elected to have hysterectomy. Haemoglobin value on 08 February b* was 9.8g/dl (normal range 12-15.6).
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The subject was treated with lignocaine hydrochloride, phenylephrine hydrochloride, midazolam, fentanyl, propofol, suxamethonium, cephalzin sodium, dexamethasone, vecuronium bromide, ondansetron hydrochloride, morphine, glycopyrronium bromide and neostigmine. Treatment with dolutegravir was continued. The event resolved on 16 April b*. The investigator considered that there was no reasonable possibility that the hysterectomy for uterine leiomyoma may have been caused by dolutegravir.

Diagnostic Assessments:

Ultrasound, transvaginal, 2/5/b*

Investigator text:

Patient had nearly 10-year history of chronic abdominal pain. Developed metromenorrhagia, dysmenorrhea. Anemia had progressed. Documented fibroids on ultrasound. Patient elected to have definitive surgical management (hysterectomy) after considering all possible treatment options. Anemia is improving. -

Protocol Id: ING112961
Investigator Number: 065791
Subject Number: 001171
Treatment Number: UNKNOWN
Case Id: Z0007963A
Suspect Drugs: Dolutegravir
Serious Events: Body fat disorder

This 32-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 06 October b*.

Concomitant medications included rosuvastatin calcium, valaciclovir hydrochloride, metformin hydrochloride, esomeprazole, oxandrolone, testosterone, darunavir, Truvada, didanosine and maraviroc.

On 02 February c*, 484 days after the start of dolutegravir, the subject developed grade 1 or mild visceral adipose inflammation. The subject presented to the ER with intensifying abdominal pain and was hospitalised. A CT scan of the abdomen was found to be normal with possible kidney stone. Liver function tests were normal. The investigator reported the subject had an old kidney stone which was not considered to be the cause of pain; it was not clinically significant. The subject was treated with prochlorperazine and Percocet. Treatment with dolutegravir was continued. The event resolved on 17 February c*. The investigator considered that there was no reasonable possibility that the visceral adipose inflammation may have been caused by dolutegravir.

b*: Following year

c*: 2 years later
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Follow-up information received via Clinical Study Team on 16 February c*

The investigator stated the "abdominal pain started on 02 February c* with some nausea. Temperature was as noted and routine labs were within normal limits. The pain improved and the subject was sent to urology for stone but they did not think that was the source of pain. An ultrasound of the abdomen was not done. The subject's pain then worsened and he was sent to the ER. The subject was reported to be fine but remains under investigation. He had no other symptoms (no fever, no urinary changes, no decreased appetite)." Concurrent medications included darunavir/ritonavir 600 mg/100 mg; maraviroc 150 mg twice daily; truvada once daily; videx EC 400 mg once daily; rosuvastatin; metformin; nexium and oxandrolone.

Follow up received from the Medical Monitor on 04 March c*

The investigator clarified that there was no evidence of pancreatitis, gallstones or other intra-abdominal pathology.

Investigator Text:

Has had abdominal pain which intensified and he went to ER and was admitted All diagnostic testing negative. Symptoms resolving without treatment -

Protocol Id: ING112961
Investigator Number: 067734
Subject Number: 001621
Treatment Number: UNKNOWN
Case Id: Z0001924A
Suspect Drugs: Dolutegravir
Serious Events: Neurosyphilis

This ■-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 22 September ■

On 27 September a*, five days after the start of investigational product, the subject developed grade 4 neurosyphilis. The subject was hospitalised. The subject was treated with prednisolone, cortisone, tetrazepam, tramadol hydrochloride and phenoxyethylpenicillin potassium. The subject had a lumbar puncture on 07 October a*, which analysis was compatible with neurosyphilis. Treatment with investigational product was continued. The event resolved on 23 October a*. The investigator considered that there was no reasonable possibility that the neurosyphilis may have been caused by investigational product.

Investigator text:

a*: The year
c*: 2 years later
LOMBAR PONCTION HAS BEEN REALISED ON 07 OCT AND ON LCR DETECTION OF NEUROSYPHILIS TREATED BY PENICILLIN 24 MILLIONS DURING 14 DAYS (START DATE OF TREATMENT IS 08 OCT a*).

a*: The year
This 63-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 20 October.

Medical conditions at the time of the event included arthralgia and chronic renal failure. Concomitant medications included tiaprofenic acid and aspirin.

On 21 June, 548 days after the start of dolutegravir, the subject developed grade 4 acute renal failure. The subject was hospitalised. Renal biopsy showed an acute tubular necrosis with significant glomerular compromise. Treatment with dolutegravir was interrupted on 23 June. The event resolved on 28 June when serum creatinine was 130 umol/l and the subject was discharged. The event did not reoccur. The investigator considered that there was no reasonable possibility that the acute renal failure may have been caused by dolutegravir and that the event was possibly due to the concomitant medication, namely tiaprofenic acid and aspirin.

Follow up received from medical monitor on 28 June:

It was confirmed that the subject was discharged from hospital on 28 June with a diagnosis of acute renal failure in the context of known chronic renal failure. Creatinemia has decreased to 130 umol/l on 25 June. The renal biopsy showed an acute tubular necrosis with no relationship to HIV treatments but with probable renal hypoperfusion due to dehydration, low blood pressure and non-steroid anti-inflammatory treatment. A magnetic resonance angiography is scheduled to rule out a renal arterial stenosis.

Follow up received on 08 July from the Clinical team:

The transvenous kidney biopsy report documented medical history of acute renal failure, acute tubular necrosis and thrombotic microangiopathy. A cortical sample of 5mm, including 9 glomeruli, was observed using multiple staining techniques including Masson trichrome, Jones, PAS, and HE. Permeable glomeruli with slight volume increase, and hypertrophy within thin mesangial tubes were seen. Capillary lumen was free. Glomeruli walls were thin and supple. There were no endo or extracapillary proliferations. Fibrous area and Bowman's capsules were thickened. Almost 50% of the surface of the cortical parenchyma was crossed by broad fibrous structures, with slight...
inflammatory infiltrate. In the areas with fibrosis, the tubes were mainly atrophic, with thick "vitreous". Some of them were atrophic, pseudo-thyroidal like. However, most of them presented with dilated lumen due to flattened epithelial cells, endotheliform, with some naked basal cell membranes. Renal tubules had neither epithelial dystrophy, nor crystals, nor epithelial cytoplasmic anomalies. Inter lobular arteries and small arteries were normal. There was no vascular thrombosis. Analysis by immunofluorescence, was performed including five permeable glomerulus and four sclerous ones. In conclusion, the results showed acute tubular necrosis in the context of interstitial fibrosis with important tubular and glomerular disease. There was no glomerulopathy with deposits.

A magnetic resonance angiography was also performed and showed kidney with preserved topography, shape, and cortical thickening. There was a right 19mm mid renal simple serous cyst of anterior lip. There was no description of sinusal infiltrates, dilation of pyelocalyx, retroperitoneal infiltrates. or increased lymph nodes. Permeability of renal veins was normal. The aorta had good diameter, with no abnormality of serous membranes. Renal arteries were permeable and there were no infiltrates. In conclusion, there were no obvious lesions of renal arteries.

Follow-up information received on 26 August c* via query response:

Final diagnosis is of an acute renal failure with acute tubular necrosis with known background chronic renal failure. Multiple causes contributed to this, including use of non steroid anti inflammatory, hypotension due to antihypertensive treatment, and dehydratation. There were no signs of investigational drug toxicity.

Investigator Text:

sudden increase of creatinemia (grade IV) requiring investigation in hospitalization

Renal biopsy shows an acute tubular necrosis with a tubular and glomerular important impact. No implication of HIV treatments taken by patient but probably renal hypoperfusion with low blood pressure. Non steroid anti inflammatory pills taken by patient could be also implicated. Hospital discharge on 28th June with creatinemia=130 umol/l. during hospitalisation all treatment against hypertension were temporarily interrupted. -

Protocol Id: ING112961
Investigator Number: 068188
Subject Number: 001680
Treatment Number: UNKNOWN
Case Id: Z0003348A, Z0003348B, Z0003348C
Suspect Drugs: Cyclophosphamide + doxorubicin + vincristine + prednisone, Dolutegravir
Serious Events: Febrile bone marrow aplasia, Febrile bone marrow aplasia, Immunoblastic lymphoma

c*: 2 years later
This -year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg per day from 13 October .

On 11 January b*, 90 days after the start of dolutegravir, the subject developed grade 4 immunoblastic lymphoma. The event was clinically significant (or requiring intervention). Immunoblastic lymphoma was diagnosed by results of a gingival biopsy. The subject was treated with CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone) chemotherapy. Treatment with dolutegravir was continued. The subject died on 11 March b* due to immunoblastic lymphoma. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the immunoblastic lymphoma may have been caused by dolutegravir.

Investigator text:

immunoblastic lymphoma diagnosed after a biopsy (oral tumefaction) SAE per protocol

On 14 February b*, 124 days after the start of dolutegravir, the subject developed grade 4 febrile aplasia. The subject was hospitalised. Concomitant medications included (CHOP) chemotherapy (administered for lymphoma, diagnosed in December a* - not reported as a serious adverse event). Treatment with dolutegravir was continued. Diagnostic tests on 14 February b* revealed white blood cell count 1.020 x10^9/l (normal range 4-10.5), haemoglobin 92g/l (normal range 130-175), platelet count 40 x 10^9/l (normal range 130-400). Blood cultures collected on 14 February b* resulted negative. The subject was treated with lenograstim. The event resolved on 15 February b*. The investigator considered that there was no reasonable possibility that the febrile aplasia may have been caused by dolutegravir and that the event was possibly due to the concomitant medication, cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP) chemotherapy, which was stopped as a result.

Investigator text:

the patient had 39.5C at home on the 13 feb and was hospitalized with aplasia on the 14 feb. He was discharged on the 15 feb b* -

On 05 March b*, 143 days after the start of dolutegravir, the subject developed a new episode of grade 4 febrile aplasia. Diagnostic tests on 05 March b* revealed haemoglobin 95 g/l (normal range 130-175), platelet count 56 X10^9/l (normal range 150-400), white blood cell count 0.210 x 10^9/l (normal range 4-10.5). CSF analysis from the same date showed EBV DNA of 2700 copies/ml. Lumbar puncture was again performed on 08 March b* showing lymphocytes that corresponded mainly to CD3 lymphocytes, with no cells compatible with lymphoma. The results of an 09 March b* chest CT scan were consistent with pulmonary lymphoma. On 11 March b*, haemoglobin 105 g/l (normal range 130-175), platelet count 33 X10^9/l (normal range 150-400), white blood cell count 0.040x 10^9/l (normal range 4-10.5). The subject was...
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treated with acyclovir, Tazocilline, tobramycin, oxycodone hydrochloride, morphine, red cells bag, platelet concentrate, pegfilgrastim, ketoprofen, Bactrim, phytenadione, midazolam hydrochloride, Tienam and frusemide. Treatment with dolutegravir was discontinued and the subject was withdrawn from the study. The subject died on 11 March b* due to febrile aplasia. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the febrile aplasia may have been caused by dolutegravir.

Investigator Text:

the patient had a febrile aplasia and died on the 11th of March b*

Protocol Id: ING112961
Investigator Number: 068032
Subject Number: 002110
Treatment Number: UNKNOWN
Case Id: Z0008926A
Suspect Drugs: Dolutegravir
Serious Events: Gastroenteritis viral

This 37-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg twice per day from 26 July a*. Medical conditions at the time of the event included intermittent episodes of diarrhea.

On 27 October a*, 93 days after the start of dolutegravir, the subject developed grade 2 or moderate viral gastroenteritis. The subject went to the emergency room with episodes of liquid stools with nausea, vomiting and abdominal pain. The subject was hospitalised. A colonoscopy and parasite faecal test were performed after hospitalisation and were normal. Treatment with dolutegravir was continued. The event resolved on 28 October a*. The investigator considered that there was no reasonable possibility that the viral gastroenteritis may have been caused by dolutegravir.

Follow up received from clinical team on 13 April b*: The investigator clarified that the subject was hospitalised due to diarrhoea. The subject had light dehydration. The diarrhoea lasted 48 hours. Clostridium difficile toxin was also investigated and the results were negative. The diagnosis was acute diarrhoea probably caused by a viral infection.

Investigator text:

Patient went to emergency room with episode of liquid stools with nausea, vomits and abdominal pain. No fever. Episode was autolimited after 48 hours. Diagnosis: Acute diarrhoea. -

a*: The year
b*: Following year
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<table>
<thead>
<tr>
<th>Protocol Id:</th>
<th>ING112961</th>
</tr>
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<td>Suspect Drugs:</td>
<td>Dolutegravir, Frusemide</td>
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<tr>
<td>Serious Events:</td>
<td>Anaemia, Haemochromatosis, Hepatic fibrosis, Hypoalbuminaemia, Hypokalaemia</td>
</tr>
</tbody>
</table>

This 61-year-old female subject was enrolled in a ViiV-sponsored, open-label, Phase IIb pilot study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg twice per day from 28 September.

Medical conditions at the time of the event included hepatitis C. Baseline hematology test indicated mild anemia (haemoglobin of 10.8 g/dL) Concomitant medications included buprenorphine hydrochloride.

On 30 May b*, 244 days after the start of dolutegravir, the subject developed grade 3 or severe secondary hemochromatosis. On 22 June b*, the subject developed grade 4 fibrosis secondary to hepatitis C. After cirrhosis was suspected by fibroscan assessment (14.5 kpa), the subject was hospitalised on 22 June b* for liver biopsy and staging, as well as to assess hemochromatosis (suspected on hepatic RMN with iron surcharge measurement) and explore infectious disease linked with splenomegaly and hyperbilirubinemia. The subject was treated with deferasirox. Treatment with dolutegravir was continued. The events were unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the secondary hemochromatosis, secondary hepatic fibrosis and hepatitis C may have been caused by dolutegravir.

Follow-up information received from medical monitor on 04 July b*:

The subject's ALT (76) and bilirubin (142) had increased slightly at the week 32 of study.

Follow up received from the Medical Monitor on 08 July b*:

The pathology report of the liver biopsy (4 pieces, 25mm length, 4 portal zone + 1 piece 8mm 2 portal zone) documented: a Metavir score A2F2-3, secondary hemochromatosis, and no stenosis. Infectious analysis on liver biopsy resulted negative for BAAR, microsporidiae, cryptosporidiae, Entamoeba histolytica (PCR), toxoplasmosis (PCR), and leishmaniosis (PCR), Mycology and amebiasis test results were pending.

The origin of this hyperbilirubinemia was documented as mixed, as conjugated hyperbilirubinemia may be a result of the patient’s active chronic hepatitis C, secondary...
hemochromatosis (JAk2 neg), and chronic hemolysis. Immunoglobulin infusions were planned to improve auto-immune anaemia (coombs +IgG anti erythroglobin). The research on the schizocytes was to be retested as it was negative previously and the sample may have suffered from extreme temperatures as detailed on the result. Anisocytosis 3+, crenated cells, hypochromasia, microcytosis, poikilocytosis and teardrop red blood cells were considered linked to the myelofibrosis induced HIV infection, which was part of the subject’s medical history. The subject’s haemoglobin was stable around 8.4 g/dL without transfusion and platelets have improved (130 000 vs 60000/mm3 at screening).

Follow-up information received on 15 July b*:

The liver biopsy was planned to further explore the etiology of hyperbilirubinemia grade 4, without clinical symptoms.

Follow-up information received on 18 July b*:

Hyperbilirubinemia was grade 3 before the subject performed a liver biopsy. Hyperbilirubinemia was grade 3 before hospitalization, Follow up AST was 49 iu and ALT was 32 iu.

Investigator text:

liver biopsy programmed to assess hepatic staging, as cirrhose was suspected on fibroscan assessment (14.5 kpa) and to assess hemochromatosis (suspected on hepatic RMN with iron surcharge measurement) and explore infectious disease linked with splenomegaly and hyper bilirubinemia -

Medical conditions at the time of the event included leg edema. Concomitant medications included frusemide.

On 29 August b*, 335 days after the start of dolutegravir, the subject developed grade 3 or severe anemia. On 12 September b*, the subject developed grade 2 or moderate hypoalbuminemia. On 13 September b*, the subject developed grade 3 or severe hypokalemia. The subject experienced asthenia. The subject was hospitalised. Laboratory test results dated 12 September b* included haemoglobin 6.8 g/dl (normal range 11.5-15.5). Laboratory test results dated 13 September b* included potassium 2.7 mmol/l (normal range 3.5-5). Laboratory test results dated 14 September b* included bilirubin direct 172 umol/l (normal range unknown), bilirubin total 323 umol/l (normal range 0-21) and prothrombin time 50% (normal range 70-100). The subject was treated with potassium salt, spironolactone, albumin and blood. Treatment with dolutegravir was discontinued on 14 September b* and the subject was withdrawn from the study. Hypokalemia and hypoalbuminemia resolved on 14 September b*.

The anemia was ongoing at time of reporting. The investigator considered that there was no reasonable possibility that the hypokalemia, anemia and hypoalbuminemia may have
been caused by dolutegravir and that the hypokalemia was possibly due to the concomitant medication, namely frusemide, and study participation.

Follow-up information received on 07 October b* via query response:

The event is hypokalemia. The furosemid is the concomitant drug which caused the SAE.

Follow-up information received on 19 October b* via email:

Legs edema was a non-serious adverse event.

Investigator text:

Asthenia was the prior symptom to admission persistant anemia despite of blood transfusion

Protocol Id: ING112961
Investigator Number: 065813
Subject Number: 002410
Treatment Number: UNKNOWN
Case Id: Z0008958A
Suspect Drugs: Dolutegravir
Serious Events: Chest discomfort

This [•]-year-old male subject was enrolled in a ViiV-sponsored, open-label, Phase IIb pilot study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg twice per day from 06 July [•].

The subject's past medical history included heart palpitation and myocardial infarction. Medical conditions at the time of the event included diabetes, gastroesophageal reflux disease, hyperlipidemia and hypertension.

On 11 April b*, 279 days after the start of dolutegravir, the subject developed grade 1 or mild substernal chest discomfort. The subject was hospitalised. Treatment with dolutegravir was continued. The event resolved on 13 April b*. The investigator considered that there was no reasonable possibility that the substernal chest discomfort may have been caused by dolutegravir.

Follow up received from clinical team on 13 April b*: The subject was hospitalised with substernal chest discomfort described as throbbing. The subject reported to the coordinator that cardiac enzymes were normal and no new abnormalities were noted on the EKGs. The subject's medical history included likely non-alcoholic fatty liver disease.

Investigator text:

b*: Following year
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Subject discharged from hospital without evidence of acute coronary syndrome. All cardiac enzymes were normal. Patient was continued on all pre-admission meds, including study investigational drug. Patient remains asymptomatic. All outside hospital records (discharge summary, cardiology consult, emergency room notes, chest x-ray, hospital labs) were reviewed by site Principal Investigator (Dr. [redacted]). In Dr.'s assessment, subject experienced non-cardiac chest pain with spontaneous resolution, plus an undocumented episode of tachyarrhythmia. Subject was evaluated by Dr. [redacted] on 4/21/b*, and is scheduled to follow up with cardiologist.

Protocol Id: ING112961
Investigator Number: 065815
Subject Number: 002430
Treatment Number: UNKNOWN
Case Id: Z0005743A, Z0005743B
Suspect Drugs: Dolutegravir
Serious Events: Demyelinating polyneuropathy, Diabetes mellitus

This [redacted]-year-old male subject was enrolled in a ViiV-sponsored, open-label, Phase IIb pilot study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir 50 mg twice daily from 23 August [redacted].

Medical conditions at the time of the event included chronic inflammatory demyelinating polyneuropathy.

On 14 September a*, 22 days after the start of dolutegravir, the subject developed grade 2 or moderate chronic inflammatory demyelinating polyneuropathy. The subject was hospitalised. The subject had a long history of polyneuropathy but his gait suddenly worsened and he had increasing falls. The subject was treated with regular immunoglobulin intravenously. Treatment with dolutegravir was continued. His physical examination was most consistent with upper motor neuron disease, i.e. HIV myelopathy. He had an MRI of the brain and spine done which showed no gross abnormalities such as lymphoma or PML. The diagnosis was most likely HIV myelopathy, worsened by immune reconstitution inflammatory syndrome (IRIS). The subject's creatinine was 1.6 (unit not confirmed). The event resolved on 19 September a*. The subject was discharged from hospital on 20 September a*. The investigator considered that there was no reasonable possibility that the chronic inflammatory demyelinating polyneuropathy may have been caused by dolutegravir.

Investigator text:

He has had a long history of polyneuropathy but his gait suddenly worsened and he had increasing falls. Hence, we had him evaluated by Neurology. His physical examination was most consistent with upper motor neuron disease, i.e. HIV myelopathy. He had an
MRI of the brain and spine done last night. It has not been read officially, however I looked at it with the neurology team and no gross abnormalities such as lymphoma or PML were found. He is being aggressively worked up but our diagnosis right now is most likely HIV myelopathy, worsened by IRIS.

I will keep you closely updated as we get more information, but we are very comfortable that this is not drug related (other than it causing IRIS).

We plan to continue the subject on the study regimen. His creatinine increased overnight to 1.6 but we will aggressively hydrate him and I anticipate it will come down. If not, we will let you know. Subject was released from hospital on Sept 20th following 5 day tx with daily IVIG infusion.

Medical conditions at the time of the event included diabetes mellitus.

On 09 November a*, 78 days after the start of GSK1349572, the subject developed grade 3 diabetes mellitus. The subject had been experiencing increased polyuria and polydypsia for the past week. In the emergency room (ER), the subject was non-toxic and his preliminary laboratory data included results showing ph 7.45 (venous blood gases), lactate of 2.4 (unit not confirmed), and glucose of 492 (Bedside; unit not confirmed). The blood sugar in the urologist's office was 562 (unit not confirmed). The subject was hospitalised. Treatment with dolutegravir was continued. The subject was discharged from hospital on 12 November a* with glucose measuring 267 mg/dl and he had transitioned to Insulin therapy with Lantus and Novolog. The event resolved on 12 November a*. The investigator considered that there was no reasonable possibility that the diabetes mellitus may have been caused by investigational product.

Investigator text:

Subject admitted with newly diagnosed diabetes mellitus and a blood sugar in his urologist's office of 562. Patient has been experiencing increasing polyuria and polydypsia for the last one week. Subject was discharged on 11-12- a* with Glucose of 267 mg/dl and has transitioned to Insulin therapy with Lantus and Novolog.
(ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg twice per day from 01 November.

The subject's past medical history included methicillin resistant staphylococcus aureus (MRSA).

On 28 September b*, 331 days after the start of dolutegravir, the subject developed grade 2 or moderate MRSA skin abscess. The subject cut himself with a razor on 28 September b*. The subject woke up on 29 September b* with a severe throbbing pain over the cut on his chin. He still went to work, but the pain progressed and then he became nauseous. The subject was hospitalised. The large abscess on his chin was drained by ENT and grew out MRSA. The subject was treated with Trimethoprim/sulfamethoxazole. Treatment with dolutegravir was continued. The subject was discharged on 03 October b* on double-strength Bactrim. The event resolved with sequelae (3-4 loose bowel movements per day) on 23 October b*. The investigator considered that there was no reasonable possibility that the MRSA skin abscess may have been caused by dolutegravir.

Investigator text:

He had cut himself with a razor on 9/28/b* and when he woke up on 9/29/b* he had severe throbbing pain over the cut on his chin. He still went to work, but the pain progressed and then he became nauseous and sought care at where he was admitted and the large abscess on his chin was drained by ENT and grew out MRSA. He was discharged on 10/3/b* with Bactrim double strength twice per day and home care to do packing of the wound. He feels well, except for 3-4 loose bowel movements a day. Per subject report on 10-17-b*. He feels infection is resolved and has completed tx. Per subject, loose stools due to Bactrim were resolved by Oct 23rd.

Protocol Id: ING112961
Investigator Number: 065791
Subject Number: 002463
Treatment Number: UNKNOWN
Case Id: Z0010500A
Suspect Drugs: Dolutegravir
Serious Events: Completed suicide

This -year-old male subject was enrolled in a ViiV-sponsored, open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day from 26 September to 16 May b*.

Medical conditions at the time of the event included depression. Concomitant medications included lexapro, Adderall, metoclopramide hydrochloride, montelukast sodium, esomeprazole, vardenafil, zolpidem tartrate, tesamorelin acetate, darunavir, ritonavir and etravirine.

b*: Following year
On 16 May b*, 232 days after the start of dolutegravir, the subject committed suicide. The subject had lost his job and apartment. The subject died on 16 May b* due to completed suicide by drug intoxication and intoxication with ethylene glycol. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the subject committed suicide may have been caused by dolutegravir.

Follow-up information received on 21 August b* via email:

The subject had no known history of suicidal ideation or attempts. He never expressed any anxiety. The subject did not use drugs or ethanol. There was no known family history of psychiatric disorders and/or suicide attempts. The subject has never expressed any suicidal thoughts to the study staff prior to his death. He was concerned about housing, job etc, but he was working on his PhD. He was actively making plans to return to South Beach and to get another job. He was working part-time as a teacher of English to no-English speaking pupils. He had also just bought a new car. Not the usual activities for some one planning on suicide. There were the psychosocial stressors of losing his job and apartment.

Investigator text:

subject missed appointment and phone disconnected. Contacted emergency contact and was informed patient committed suicide on 16 May b*. Subject has lost his job and his apartment recently. had a history of depression. 08-01-b* per the death certificate and medical examiner's office the cause of death was ethylene glycol and drug intoxication.

9.6.5.2. Cases Reported Between 27 October to 08 June

For this study, with a completed interim statistical analysis more than six months prior to the planned submission date, a new safety data cut was taken for reporting in this ISS. The narratives included in this section correspond to the SAEs and Pregnancy cases reported from: the safety data lock point for the ING112961 Week 96 CSR (Cohort I and Week 48 for Cohort II); up to the 08 June cut-off date for inclusion of data from this study in the Integrated Safety Outputs, and includes all follow up information received by the company through 26 October. The data included here are not represented in the clinical study report(s) included in m5.3.5.2; however SAEs cumulative to 08 June for this study are included in the ISO Tables and Figures produced for the ISS, which are located in m5.3.5.3 along with the ISS.
This 51-year-old male subject was enrolled in a ViiV-sponsored open-label study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg twice per day from 26 July.

On 19 January, 542 days after the start of dolutegravir, the subject developed grade 1 or mild respiratory tract infection. The subject also experienced a cough, fever of 39 degrees Celsius, dyspnoea and thoracic pain. The subject was hospitalised. Further investigations showed: thoracic X-ray: normal; ECG: normal. Pneumococcus and Legionella in urine: negative. The subject was treated with levofloxacin and acetylcysteine. Treatment with dolutegravir was continued. The event resolved on 25 January. The investigator considered that there was no reasonable possibility that the respiratory tract infection may have been caused by dolutegravir.

Investigator text:

Mild respiratory tract infection that was controled with antibiotics during hospitalitation and resolved without problems patient present cough, fever 39 degrees C, dyspnoea and thoracic pain -
This 43-year-old male subject was enrolled in a ViiV-sponsored, open-label, Phase IIb pilot study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance.

The subject received oral dolutegravir at 50 mg twice per day from 16 August 2019.

Medical conditions at the time of the event included hypercholesterolemia, hypertriglyceridemia and tobacco addiction. Concomitant medications included pantoprazole.

On 22 December b*, 493 days after the start of dolutegravir, the subject developed grade 4 bivessel coronary disease. The subject was hospitalised and the event was life-threatening. ECG was performed and showed negative T wave from V1 to V4 and in aVL lead. The echocardiogram revealed a basal inferior hypokinesia. The subject was treated with aspirin, metoprolol, atorvastatin calcium, clopidogrel and omega-3 marine triglycerides. Treatment with dolutegravir was continued. The event resolved with sequelae on 29 December b*. The investigator considered that there was no reasonable possibility that the bivascular coronary disease may have been caused by dolutegravir.

Follow-up information received from medical monitor on 05 January c*:

Concurrent medical history confirmed current tobacco use (smoker). There was no family history of heart attack or stroke before age 55. Framingham 10 year risk at baseline was 11% and the subject had no concurrent or past myocardial infarction history. Concomitant ART at the time of the event included emtricitabine +tenofovir (Truvada) and atazanavir+ritonavir (Reyataz).

Investigator text:

On the 22 December b* occurrence of angina pectoris. ECG showed negative T wave in the V1-V4 and AVL derivations. Concomitantly echocardiogram evidenced a basal inferior hypokinesia. Patient was admitted into cardiology intensive care. 27 December b*: percutaneous coronary intervention and stent application in the left descendent anterior artery. No postoperative complications. -
This 41-year-old male subject was enrolled in a ViiV-sponsored, open-label Phase IIb pilot study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir at 50 mg twice per day from 13 September.

The subject’s medical history was significant for current hypertension.

Concomitant medication included Truvada, darunavir, etravirine and ritonavir.

On 01 November b*, 414 days after the start of dolutegravir, the subject developed grade 1 or mild coronary artery disease. The subject began to experience angina under exertion in mid February of b*. The subject then developed angina on 31 October b* and underwent stress test on 01 November b*. Catheterization revealed coronary artery disease. The subject was hospitalised and underwent a five-vessel bypass on 09 November b*. The subject was treated with metoprolol, atorvastatin calcium, clopidogrel bisulphate and nitroglycerine. Treatment with dolutegravir was continued. The event resolved on 26 January c*. The cardiologist performed an additional catheterization and angioplasty on 01 May c* to repair a faulty bypass graft. The investigator considered that there was no reasonable possibility that the coronary artery disease may have been caused by dolutegravir.

Follow up information received on 09 November b* from medical monitor:

Medical history was significant for past hepatolobiliary disorder, past respiratory, thoracic and mediastinal disorder, past vascular disorder, current eye disorder, current neoplasms benign, malignant and unspecified, current skin and subcutaneous tissue disorder, and current hypertension (day 1 ABP 136/69 mmHg). Day 1 ECG tracings were normal. The subject's concomitant medicines included metformin, metoprolol, Lipitor, Plavix, and Nitrostat. AEs of Diabetes Mellitus (09-Nov-a*) and Angina (01-Oct-b*) were listed as ongoing.

Follow up information received on 11 November b* from site:

The subject had developed angina and underwent a stress test last week, which was abnormal. He then underwent a cardiac catheterisation which showed significant coronary artery stenosis. He underwent a five-vessel bypass on 09 November b*. He is
recovering well post-operatively. The cause of his coronary artery disease is multi-
facitorial given his risk factors of hypertension, diabetes mellitus and family history of
coronary artery disease.

Investigator text:

Subject saw PMD for complaint of chest pain Grade 1 on exertion. He was referred to
cardiologist who prescribed medication and schedule subject for catheterization
procedure. He will be hospitalized for procedure.

Subject began to experience angina under exertion in mid February. Cardiologist
performed an additional catheterization and angioplasty on May 1st, c* to repair faulty
bypass graft.

This 2-year-old male subject was enrolled in a ViiV-sponsored, Phase IIb pilot study to
assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy
(ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The
subject received oral dolutegravir at 50 mg twice per day from 01 November .

The subject had no family history or relevant medical history or risk factors. Concomitant
medications included Truvada, atazanavir and filgrastim.

On 08 April c*, 524 days after the start of dolutegravir, the subject developed grade 3
or severe B-cell lymphoma. He presented to hospital with increased neck fullness,
abdominal pain and shortness of breath. He underwent an excisional lymph node biopsy
with pathology findings of aggressive diffuse large B-Cell lymphoma. PET scanning
showed multiple FDG-avid lymph nodes throughout the neck, chest, abdomen and pelvis
with splenic involvement. On 26 April c* he underwent lumbar puncture with
intrathecal methotrexate. The subject was treated with E-Poch Regime: etoposide
phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide and doxorubicin
hydrochloride (hydroxydaunorubicin). Cytoxan was dose reduced by 50% because of his
CD4 and Rituximab was given on Day 6 for concern for tumor lysis syndrome. He
tolerated the chemotherapy well and was discharged home. On 06 May c*, the subject
developed grade 2 or moderate febrile neutropenia and grade 2 or moderate diarrhea.
The subject was re-admitted on 06 May c*. He improved with oral Vancomycin
despite negative C diff studies. He was started on Neupogen and discharged home on 11

* 新薬承認情報提供時に置き換え
May c*. Febrile neutropenia and diarrhea resolved on 11 May c*. Treatment with dolutegravir was continued.

Subject received Cycle 2 of chemotherapy on 18 May c* with neupogen. His interim PET/CT on 05 June c* showed significant response to treatment and no metabolically active disease in the neck, chest, abdomen or pelvis. Cycle 3 was administered on 08 June c*. His discharge was held due to syncopal episode then due to fever. No culture growth resulted and his was discharged on PO antibiotics. Subject developed bony pain, severe, due to neupogen. Agent was held on a daily basis in response to symptoms and ultimately discontinued as his WBC/ANC remained adequate. The B-cell lymphoma was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the B-cell lymphoma and febrile neutropenia and diarrhea may have been caused by dolutegravir.

Diagnostic test results:

Exiçõesonal lymph node with pathology findings of aggressive diffuse large B-Cell lymphoma. PET scanning showed multiple FDG-avid lymph nodes throughout the neck, chest, abdomen, and pelvis with splenic involvement.

Follow-up lab tests performed on May 15th included the following abnormal results:
WBC 26.4x10E3/uL (High), HGB 11.90g/dL (Low), LDH 418 IU/L (High), Myelocytes 3.00% (High), HCT 35.2% (Low), RDW 15.2% (High), Neutrophils 22.2x10E3/uL (High), Neutrophils % 81%(High), NRBC 1.00% (High), Monocytes 1.10x10E3/uL (High), Lymphocytes% 5.00% (Low)

Follow-up information received on 14 May c* via query response:

E-poch regimen = etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, and doxorubicin hydrochloride (hydroxydaunorubicin)

Follow-up information received on 29 May c* via query response:

Re: event outcome: Subject just started chemotherapy for lymphoma and we anticipated this to be a long treatment.

Neutropenic fever and diarrhea have been added as SAEs and were a complication from the treatment for lymphoma.

Investigator text:

[ ] yo M with HIV, urgent care evaluation after ER evaluation for neck/throat swelling.

He is s/p excisional lymph node biopsy of the R neck. Pathology showed diffuse large B-cell lymphoma. He presents with increased neck fullness, abdominal pain, and SOB. Neck swelling has increased since last visit. Patient tolerated chemotherapy well. He was given a cycle of R-EPOCH. Cytoxan was dose reduced by 50% because of his CD4 and c*: 2 years later
Rituximab was given on Day 6 for concern for tumor lysis syndrome. He tolerated chemo well and was discharged to home. He was readmitted on May 6, c* with neutropenic fever and diarrhea. He improved with po Vanco despite negative C diff studies. He was started on neupogen and discharged home on May 11th, c*.

Subject received Cycle 2 of chemotherapy on May 18th with neupogen. His interim PET/CT on June 5th showed significant response to tx and no metabolically active disease in the neck, chest, abdomen or pelvis. Cycle 3 was administered on June 8th. c*. His discharge was held due to syncopal episode then due to fever. No culture growth resulted and he was discharged on PO ABx. Subject developed bony pain, severe, due to neupogen. Agent was held on a daily basis in response to symptoms and ultimately discontinued as his WBC/ANC remained adequate.

9.6.5.3. Cases Reported Between 09 June to 26 October

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the cut-off date for the Integrated Safety Outputs up to the final 26 October safety data lock point for the ISS, and includes all initial reports and follow up information received by the company through 26 October. The data included here are not represented in the clinical study report(s) included in m5.3.5.2, nor in the ISO Tables and Figures produced for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials’ database in preparation of these narratives.

Protocol Id: ING112961
Investigator Number: 068032
Subject Number: 001807
Treatment Number: UNKNOWN
Case Id: Z0017176A
Suspect Drugs: Dolutegravir
Serious Events: Thyroiditis

This 3-year-old male subject was enrolled in an open label, Phase IIb pilot study to assess the antiviral activity of a dolutegravir containing regimen in antiretroviral therapy (ART)-experienced, HIV-1-infected adult subjects with raltegravir resistance. The subject received oral dolutegravir, 50 mg once daily, from 26 October.

Medical conditions at the time of the event included hyperthyroidism. Concomitant medication included Truvada, maraviroc, darunavir, carbimazole and propranolol.

On 25 September d*, 1065 days after the start of dolutegravir, the subject developed grade 3 or severe thyroiditis. The subject developed flu symptoms fever 38-38.5C, asthenia and weakness. The subject was hospitalised on 29 September d*. The subject was treated with prednisone and cloxacillin sodium. Treatment with dolutegravir was continued. The event resolved on 05 October d* and the subject was discharged from
hospital on this date. The investigator considered that there was no reasonable possibility that the thyroiditis may have been caused by dolutegravir.

Diagnostics:

Cervical ultrasound: Enlargement of the thyroid gland was observed. Pain when area is palpated and an increase in vasculature was observed in Doppler study. Ganmagraphy: enlarged thyroid gland was observed

Investigator text:

On 25/09/d* patient started with flu symptoms. The day after patient started having fever (38-38.5°C), astenia and weakness. On 29/09/d* is admitted in the hospital and after a few tests carried out a thyroiditis is suspected. Diagnostic: Thyrotoxicosis (in the diagnostic process).

Final Diagnose was Thyroditis. Patient is discharged from hospital on 05/oct/d*

9.6.6. ING112574 SAE and Pregnancy Case Narratives

9.6.6.1. Cases Reported up to 18 June

The narratives included in this section correspond to the SAEs and Pregnancy cases included in both the ING112574 Week 24 CSR (with a data lock point of 18 June for safety data), which is included in m5.3.5.2, and in the ISO outputs. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.

Protocol Id: ING112574
Investigator Number: 086858
Subject Number: 000001
Treatment Number: UNKNOWN
Case Id: Z0014532A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia

This -year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 17 June.

As of 17 June a* the subject had 590 CD4+ cells/mm³ with 72,577 c/mL plasma HIV-1 RNA.

Concomitant ART medications comprised Truvada (from pre-study), with darunavir/ritonavir and etravirine since 24 June a*.

a*: The year

d*: 3 years later
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Module 2.7.4 Summary of Clinical Safety

The subject had TB pneumonia in February a*. Medical conditions at the time of the event included diarrhea.

As of 26 January b* the subject had 750 CD4+ cells/mm$^3$ and <40c/mL HIV-1RNA.

On 01 March b*, 258 days after the start of dolutegravir, the subject developed grade 3 or severe pneumonia aggravated. The subject was hospitalised. The subject was treated with azithromycin, salbutamol sulphate and levofloxacin. Treatment with dolutegravir was continued. The event resolved on 22 March b*. The investigator considered that there was no reasonable possibility that the pneumonia aggravated may have been caused by dolutegravir.

Diagnostics:

Chest X-ray conducted. Subject had started antibiotics by then. All cultures negative (performed: fluid culture, direct TB detection, AFB culture, MRSA screen, fluid culture, blood culture, Cryptococcus AG-bld, gram stain, respiratory culture), all negative. Per sub-I [deleted], presumed pneumonia treated and had started antibiotics before all tests were performed.

Follow-up information received on 13 March b* via query response:

Subject had TB pneumonia in FEB b*. Cultures pending, so unknown whether this is a continuation of that.

Follow-up information received on 27 March b* via query response:

Presumed pneumonia. However, subject had started antibiotics by the time all cultures were performed.

Additionally, the subject was noted to have travellers diarrhea for 5 days, beginning a few days before the onset of the pneumonia symptoms. He was in Rio de Janiero at the time of onset of both diarrhea and respiratory symptoms.

Investigator text:

This subject travelled out of the country to South America, symptoms of diarrhea started during the trip. The patient then complained of symptoms of pneumonia, during his trip on 01MAR b*. The site was contacted by the local hospital pharmacy requesting a list of the subject's medication. The Principal Investigator confirmed 05MAR b* at 4pm PST that the subject was hospitalized locally with pneumonia, type unknown, and culture pending. Diarrhea, Travellers. Location when the pneumonia, worsening of symptoms started: Rio de Janiero, Brazil. This pneumonia is worsening of the AE Pneumonia and the condition was not present prior to study start. -

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
This 30-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 14 June.

At 14 June the subject's CD4+ cell count was 80 cells/mm³ with plasma HIV-1 RNA of 12,802 c/mL.

As concomitant ART, the subject received Truvada and darunavir/ritonavir from prior to Screening and with etravirine added from 21 June.

The subject's past medical history included abdominal liposuction. Medical conditions at the time of the event included face lift [elective] and scar revision from previous calf implant surgery [elective].

As of 12 July, the CD4+ cell count was 130/mm³ with 52 c/mL of HIV-1 RNA.

On 27 July, 43 days after the start of dolutegravir, the subject developed grade 3 or severe pulmonary embolism and grade 3 or severe pleural effusion. The subject experienced shortness of breath and chest pain. The subject was hospitalised. An echocardiogram showed normal ejection fraction; CTA showed bilateral pulmonary embolus with prominent right pulmonary artery and a right greater than left effusion and consolidation for which the subject received antibiotic treatment. The pulmonary embolism was treated with anticoagulants warfarin sodium and enoxaparin, and fluids. Further imaging ruled out DVT. A flex bronchoscopy with right lung washing was performed on 13 August. Treatment with dolutegravir was continued. The events resolved on 10 November. The investigator considered that there was no reasonable possibility that the pulmonary embolism and pleural effusion may have been caused by dolutegravir.

Diagnostics:

Chest X ray showed atelectasis, effusion or air space disease

Follow up information received on 26 September via answer query report:

The investigator stated that the subject had not yet fully recovered.

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*a*: The year

*b*: Following year
Module 2.7.4 Summary of Clinical Safety

Follow-up information received on 27 March b* via answered query report:

Pneumonia was not diagnosed.

Investigator text:

This INT year old patient presented with shortness of breath and chest pain with recent liposuction. Surgery diagnosed a pulmonary embolus. A consultation with critical care pulmonologist was obtained and the patient was treated with anticoagulation fluids. Further imaging did not reveal deep vein thrombosis. An Echocardiogram showed NORMAL ejection fraction. A CTA showed bilateral pulmonary embolus with prominent right pulmonary artery and a right greater than left effusion and consolidation for which the patient received antibiotic treatment. A flex bronch with right lung washing was performed on 13AUG a*.

Protocol Id: ING112574
Investigator Number: 086858
Subject Number: 000007
Treatment Number: RUN-IN
Case Id: Z0012068A
Suspect Drugs: Dolutegravir
Serious Events: Pyrexia

This INT-year-old male subject was enrolled in a ViiV-sponsored, open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day from 31 August.

At 31 August a* the subject’s CD4+ cell count was 160 cells/mm$^3$ with 29,701c/mL plasma HIV-1 RNA.

As concomitant ART, the subject received maraviroc and Kaletra from prior to Screening to 6 September a*, both replaced by Truvada, enfuvirtide and darunavir/ritonavir from 7 September a*.

On 7 September a* the CD4+ cell count was 180 cells/mm$^3$ with 784c/mL HIV-1 RNA.

Medical conditions at the time of the event included chills, fever and headache. Concomitant medications included paracetamol.

On 15 September a*, 15 days after the start of dolutegravir, the subject developed grade 3 or severe worsening of acute febrile illness. The subject was hospitalised due to ongoing fever up to 104F, chills and headache over the past two months. The subject was treated with levofloxacin and metronidazole. Treatment with dolutegravir was continued. The event resolved on 01 December a*, without further clarification or diagnosis. The

a*: The year
b*: Following year
investigator considered that there was no reasonable possibility that the worsening of acute febrile illness may have been caused by dolutegravir.

Plasma HIV-1 RNA remained below 40c/mL from 29 September a* throughout the duration of the event.

Diagnostics:

CT Scan of the head and sinuses - unremarkable; Total Iron 23 (ref 30-160 mcg/dl); LDH 238 (ref <260 U/L); creatinine 1.4 (ref 0.4-1.2 mg/dL); albumin 3.2 (ref 3.5-5.5 g/dL); AST 64 (ref 0-35 U/L); ALT 59 (ref 0-45 U/L); WBC 7.1 (ref 4-11 1000/UL); prothrombin time 15.2 (ref 11.9-14.4 sec); plasma d-dimer 1220 (ref <250 ng/ML); blood and CSF cultures unremarkable

Investigator text:

The patient is a -year-old male brought in by his PMD, Dr. [deleted], for ongoing fever, chills and headache that have been present for the past 2 months. These symptoms are constant. The patient's fevers have gone up as high as 104. The patient endorses vomiting. He had a CT scan of the head and sinuses performed by Dr. [deleted] yesterday, which was unremarkable. Dr. [deleted] is here speaking with him at the bedside. He has been referred for admission. The patient was given Tylenol in triage.

This -year-old subject was enrolled in a ViiV-sponsored open label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 04 April a*. At 04 April a* the subject’s CD4+ cell count was 110 cells/mm³ with 1331c/mL plasma HIV-1 RNA.

For concomitant ART, the subject was receiving zidovudine/lamivudine since prior to Screening with darunavir/ritonavir added 11 April a*.

On 05 April a*, one day after the start of dolutegravir, the subject developed grade 2 or moderate cerebral vascular accident age indeterminate. The subject presented to the ER
complaining of visual changes. The subject reported he had been experiencing these changes for several days and had experienced them in the past. Evaluation in the ER showed a CVA of indeterminate age. The subject was hospitalised for observation. Treatment with dolutegravir was continued. The event resolved with sequelae on 09 April a*; the subject continues to experience visual disturbances and memory loss. The investigator considered that there was no reasonable possibility that the cerebral vascular accident age indeterminate may have been caused by dolutegravir.

Follow-up information received on 13 June a* via query response:

Nature of sequelae: subject continues to experience visual disturbances and memory loss.

Subject stated that he had history of some visual changes but none documented in the medical record. Given his memory loss and resulting altered mental status, we can only document his complaints of disturbed peripheral vision.

Investigator text:

Patient presented to ER with complaint of visual changes. Patient stated that he had been experiencing these changes for several days and had experienced them in the past. Evaluation in the ER showed a CVA of indeterminate age. More information pending. No drug therapy given for SAE. Patient was hospitalized for observation given event was age indeterminant.

Medical conditions at the time of the event included (hard-to-control) hypertension and triple coronary artery bypass grafting (coronary artery disease). Concomitant medications included cocaine.

On 23 May a*, 49 days after the start of dolutegravir, the subject developed grade 3 or severe hypertensive emergency and grade 1 or mild congestive heart failure. The subject presented to the Emergency Department with worsening dyspnea on exertion for more than a week and hypertensive urgency (BP 180s/120s). The subject was hospitalised. Chest X-ray showed mild pulmonary edema; BNP of 1282; echocardiogram showed improvement in EF of 40%. The subject was treated with frusemide and lisinopril. Treatment with dolutegravir was continued. The events resolved with sequelae (increasing dyspnea on exertion) on 25 May a*. The investigator considered that there was no reasonable possibility that the hypertensive emergency and congestive heart failure may have been caused by dolutegravir and that the hypertensive emergency was possibly due to cocaine inhalation and mild CHF.

Follow-up information received on 13 June a* via query response:

Sequelae described as increasing dyspnea on exertion

Investigator text:
Patient presented to Emergency Department with complaint of shortness of breath. Was admitted with hypertensive emergency possibly related to cocaine inhalation and mild CHF. Additional information will be submitted when available. Patient presented with worsening dyspnea on exertion for more than a week and hypertensive urgency (BP 180s/120s). Has a history of hard-to-control hypertension. Acknowledged smoking cocaine 3 days prior to presentation. CXR showed mild pulmonary edema. Troponins, chemistries, and coags WNL and BNP of 1282. Treatment involved adjustment of antihypertensive medications. Patient was discharged home.

This -year-old male subject was enrolled in a Viiv-sponsored open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 13 September .

As concomitant ART, the subject received Truvada and stavudine from prior to Screening to the onset of the event, 17 January b*, when these ARTs were stopped. The enfuvirtide that had been added from 20 September a* was also stopped 17 January b*. Enfuvirtide and stavudine were re-started 31 January b*.

At 13 September a* the subject’s CD4+ cell count was <20 cells/mm with 28,685c/mL plasma HIV-1 RNA. Although the subject initially responded to dolutegravir with a nadir viral load of 5459c/mL at 11 October a*, the HIV-1 RNA rebounded to 25,083c/mL on 10 November reaching 35,549c/mL 9 January b* prior to event onset.

Medical conditions at the time of the event included diabetes and hypertension. Concomitant (non-ART) medications included metformin hydrochloride, Bactrim DS, azithromycin, valaciclovir hydrochloride, Benicar HCT, sertraline hydrochloride, bupropion hydrochloride, omeprazole, sitagliptin phosphate, minoxidil, frusemide, carvedilol.

On 17 January b*, 126 days after the start of dolutegravir, the subject developed grade 2 or moderate dehydration, grade 2 or moderate nausea vomiting (viral syndrome) and grade 2 or moderate renal insufficiency. The subject presented to the ER with shortness of breath, chest pressure and low blood pressure. The subject was hospitalised. The subject underwent cardiac catheterization on 23 January b*, which was normal. Myocardial infarction was ruled out. The subject was treated with Augmentin. Treatment with dolutegravir was interrupted on 17 January b*. The events resolved on
28 January b*. Treatment with dolutegravir was re-started on 31 January b*. The investigator considered that there was no reasonable possibility that the dehydration, nausea vomiting (viral syndrome) and renal insufficiency may have been caused by dolutegravir. The dehydration was due to vomiting from viral syndrome; renal insufficiency was caused by dehydration.

Follow up information received on 25 January b* via medical monitor:

The subject did not have an MI and had a normal cardiac catheterization on Monday, Jan 23. The diagnosis was dehydration from nausea and vomiting due to a viral syndrome with renal insufficiency. He is supposed to be discharged today and was to restart his study meds/HIV meds when he returned home.

Investigator text:

The patient developed shortness of breath, chest pressure and low blood pressure. He was sent to the ER. All HIV and study meds were held. The subject had cardiac catheterization on Jan 23, b* which was normal. He did not have an MI. The subject was dehydrated due to vomiting from viral syndrome. Subject also had renal insufficiency due to dehydration, which resolved. Subject still hospitalized and has not yet restarted his HIV/study medication. The subject was rehydrated. All symptoms resolved and the subject was released from the hospital 28 Jan b* and restarted HIV meds 31 Jan b*. -

Protocol Id: ING112574
Investigator Number: 086888
Subject Number: 000545
Treatment Number: UNKNOWN, UNKNOWN
Case Id: Z0014282A, Z0014282B
Suspect Drugs: Dolutegravir
Serious Events: Dehydration, Gastroenteritis viral, Oesophageal candidiasis

This -year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 02 November a*.

At 01 November a* the subject’s CD4+ cell count was <20 cells/mm³ with 52,623c/mL plasma HIV-1 RNA. By 23 January b*, the CD4+ cells had increased to 70cells/mm³ with HIV-RNA<40c/mL.

Concomitant medications included ondansetron hydrochloride, benzylpenicillin. Truvada had been administered since prior to Screening while darunavir/ritonavir and etravirine were commenced 9 November a*.

a*: The year
b*: Following year
CONFIDENTIAL
Module 2.7.4 Summary of Clinical Safety

On 13 February b*, 103 days after the start of dolutegravir, the subject developed grade 2 or moderate viral gastroenteritis. The subject presented to the ER on 15 February b* with fever, diarrhea, nausea and vomiting. The subject was hospitalised. The subject was treated with intravenous fluids. Treatment with dolutegravir was interrupted. Dolutegravir was unable to be dosed from 14-15 February b* due to vomiting. Laboratory test results dated 15 February b* showed WBC count of 15.90 (normal range 3.50-10.80). Stool studies and chest X-ray were unremarkable. Treatment with dolutegravir was interrupted and re-started on 16 February b*. The event resolved on 17 February b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the viral gastroenteritis may have been caused by dolutegravir.

Diagnostic tests:

WBC 15.90 on 15 February b*. Chest X-ray on 15 February b* w/ minor linear scarring or platelike atelectasis at the lung bases. Stool studies were negative per d/c summary. Normal range for WBC is 3.50-10.80

Investigator text:

Subject presented to ER with symptoms of fever, diarrhea, nausea and vomiting. Unable to dose IP 14-15 February b* due to vomiting. Stool studies and chest xray performed in hospital which were unremarkable. IP restarted on 16 February b* with no further problems. Discharged on 17 February b*. Next scheduled research visit is on 21 February b* -

The subject's past medical history included pneumonia. Medical conditions at the time of the event included hepatitis C. Concomitant medications included, darunavir and ritonavir, dapsone, Lomotil and Atropine + diphenoxylate.

As of 22 February b*, the subject’s CD4+ cell count was 60 cells/mm³ with <40c/mL plasma HIV-1 RNA

On 02 March b*, 121 days after the start of dolutegravir, the subject developed grade 3 or severe candida esophagitis and grade 3 or severe dehydration. The subject presented to the ER with one-week history of fever, nausea, vomiting and abdominal pain, and a two-day history of watery diarrhea. The subject reported fevers up to 103 degrees F for one and a half weeks and having 5-6 bowel movements daily for the past two days and complained of diffuse abdominal pain but worse in the right upper quadrant. He had difficulty swallowing due to a sore throat and thrush and developed erythematous pruritic rash in upper extremities and chest and back on 08 March b* with generalized body ache. The subject was hospitalised. The subject was treated with fluconazole, metronidazole, clotrimazole, ciprofloxacin hydrochloride, famotidine and anti-emetic. Treatment with dolutegravir was continued. The events resolved on 15 March b*. The investigator considered that there was no reasonable possibility that the candida esophagitis with dehydration may have been caused by dolutegravir.

b*: Following year
Diagnostics:

WBC 14.16; H and H 12.2 and 35.8; platelets 244. All other test(s) pending. Normal ranges WBC-3.50-10.80; Hemoglobin-13.60-17.0; Hematocrit 42.0-52.0; platelets 140-400.

Follow-up information received on 27 March b* via query response:

Subject has a history of intermittent rash

Investigator text:

Presents to ER with 1-wk history of fever, nausea, vomiting, abdominal pain and a 2day history of watery diarrhea. Int fevers up to 103 for 1 1/2 wk and having 5-6 bowel movement once daily for the past 2 days. c/o diffuse abdominal pain but worse in the RUQ. Difficulty swallowing because of a sore throat and thrush. Developed erythematous pruritic rash in upper extremities and chest and back on 8 March b* w/ generalized body ache. -

Protocol Id: ING112574
Investigator Number: 086853
Subject Number: 000566
Treatment Number: UNKNOWN
Case Id: Z0010578A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia

This male subject was enrolled in a ViiV-sponsored, open-label Phase III study to evaluate the effectiveness of dolutegravir in HIV-1 infected, ART-experienced subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice daily from 06 July. At this time the subject’s CD4+ cell count was 20 cells/mm³ and the plasma HIV-1 RNA 195,737c/mL.

Medical conditions at the time of the event included human immunodeficiency virus. Concomitant medications included insulin. The subject received Truvada from prior to Screening until 12 July a*, stavudine and tenofovir disoproxil fumarate were commenced 13 July a* but interrupted 14 July a*. Both drugs were restarted 19 July a*.

On 13 July a* the CD4+ cell count was 30 cells/mm³ and the plasma HIV-1 RNA 1619c/mL

On 14 July a*, eight days after the start of dolutegravir, the subject developed grade 2 or moderate community-acquired pneumonia. The subject was admitted to the ER with complaints of flank pain, shortness of breath and fever of 102F. The subject reported
developing chills, dizziness and headaches after HIV medications were changed on 13 July a*. On the following day, he also developed shortness of breath with non-productive cough. The subject was hospitalised. Laboratory test results dated 15 July a* included albumin 2.8 g/dl (NR 3.2-5), BUN 26 mg/dl (NR 8-25), creatine 2.2 mg/dl (NR 0.76-1.46), fasting blood glucose 185 mg/dl (NR 70-99), hematocrit 36.7% (NR 41-50), haemoglobin 11.9 g/dl (NR 13.8-17.2), lymphocytes 6% (NR 16-46), neutrophils 81% (NR 40-75), protein total 9.6 g/dl (NR 6-9), pCO2 23 mmHg (NR 35-45). The subject was treated with prednisone, Bactrim DS, ceftriaxone and azithromycin. He only received 2 days each of ceftriaxone and azithromycin. Treatment with dolutegravir was interrupted on 14 July a*. The event resolved on 18 July a*. Dolutegravir was re-started 19 July a*. The investigator considered that there was no reasonable possibility that the community-acquired pneumonia may have been caused by dolutegravir.

Diagnostics:

UA: small blood, negative leukocyte esterase, negative nitrates, micro, 3-5, RBCs, 6-10 white blood cells, amorphous crystals, ABG 66,Urine strep pneumonia antigen-negative, Legionella-Negative, PCP respiratory cultures-negative, Cryptococcal Antigen- Negative, AFB Smear-Negative, Blood Cultures-Negative, Urine Cultures-Negative, Histoplasmosis Urine Antigen- Results unknown, A1c-8.1. Chest x-ray showed a right-sided infiltrate compared to the x-ray from March.

Investigator text:

Subject stated that he started having chills, dizziness and some headaches after his HIV medications were changed on 13-Jul-a*, his Day 8 study drug visit. The subject also developed shortness of breath with a non-productive cough. -

Protocol Id: ING112574
Investigator Number: 086853
Subject Number: 000568
Treatment Number: UNKNOWN
Case Id: Z0011909A
Suspect Drugs: Dolutegravir
Serious Events: Alanine aminotransferase increased, Drug eruption, Hyperbilirubinaemia

This —-year-old male subject was enrolled in a ViiV-sponsored, open-label study to evaluate the effectiveness of dolutegravir in HIV-1 infected, ART-experienced subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice daily from 31 August As of 31 August a* the subject’s CD4+ cell count was 20cells/mm³ with 197,051c/mL plasma HIV-1 RNA.

Concomitant medications included cetirizine hydrochloride, and multivitamins.

a*: The year
As concomitant ART, the subject had received Truvada from prior to screening to 6 September a*. Etravirine with darunavir / ritonavir were administered from 7 September a* to 15 September a*.

On 15 September a*, 15 days after the start of dolutegravir, the subject developed grade 3 or severe drug reaction rash. On 19 September a*, the subject developed grade 2 or moderate elevated alanine aminotransferase and grade 3 or severe hyperbilirubinemia. The events were clinically significant (or requiring intervention). All laboratory test results were within normal range on 07 September a* (day 8 visit). Laboratory test results dated 19 September a* included alanine aminotransferase 223 u/l (NR 0-48), alkaline phosphatase 392 u/l (NR 20-125), aspartate aminotransferase 67 u/l (NR 0-42), bilirubin direct 2.6 mg/dl (NR 0-0.4), bilirubin total 4.5 mg/dl (NR 0-1.3), creatinine 1.67 mg/dl (NR 0.76-1.46). The subject was treated with triamcinolone acetonide and promethazine hydrochloride. Treatment with dolutegravir was discontinued on 15 September a* and the subject was withdrawn from the study. At this point the subject had 40 CD4+ cells/mm$^3$ and <400c/mL HIV-1 RNA.

Repeat laboratory test results dated 22 September a* included ALT 76 U/L, alkaline phosphatase 448 U/L, AST 25 U/L, bilirubin total 0.9 mg/dl, eosinophils 3.7% (NR 0-7). On 29 September a*, ALT was 45 U/L, alkaline phosphatase 324 U/L, AST 28 U/L, bilirubin total 0.6 mg/dl and eosinophils 7.8%. Alkaline phosphatase was a non serious adverse event. The hyperbilirubinemia resolved on 22 September a*. The drug reaction rash and elevated alanine aminotransferase resolved on 29 September a*. The investigator considered that there was a reasonable possibility that the drug reaction rash, elevated alanine aminotransferase and hyperbilirubinemia may have been caused by dolutegravir.

Received by email from investigator on 22 September a*:

The investigator also reported that the subject's previous ARV regime included Truvada and Isentress (raltegravir). It appears the subject had been left on this failing regime for an extensive period of time as it appears he may have acquired an extensive number of integrase mutations. During the monotherapy phase, the subject had no issues, then at the completion of the monotherapy phase Prezista (darunavir) /Norvir (ritonavir) plus Intelence (etravirine) were added. Shortly thereafter the subject had what appeared to be a hypersensitivity reaction with extensive rash, fever, flu like symptoms and abnormal lab tests.

Follow-up information from medical monitor 12 October a*:

The alkaline phosphatase was still elevated (per Sep30 lab, value not reported).

Follow-up subsequently retrieved from the liver CRFs included:

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary

a*: The year
change in the previous week. The subject consumed alcohol. The average number of units consumed per week was two.

The subject had no liver disease medical conditions, no drug related liver disease conditions and no other relevant medical conditions.

There were no diagnostic imaging tests performed. There were no liver biopsies performed.

Investigator text:

The subject placed a call to the office on 19 September a* and stated that he had a fever, rash, nausea and vomiting since 15 September a*. The subject discontinued his study drug as well as his OBT on 15 September a*. The subject was seen in the office by a physician and his HIV meds were withdrawn permanently due to a drug reaction. The subject's rash did spread all over his body. The subject's OBT prior to 07 September a* was Truvada and Isentress. No other HIV therapy. The rash resolved on 29 September a*.

Protocol Id: ING112574
Investigator Number: 089489
Subject Number: 000663
Treatment Number: UNKNOWN
Case Id: Z0013781A
Suspect Drugs: Dolutegravir
Serious Events: Herpes zoster

This -year-old female subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 07 November a*.

At 7 November a* the subject had 60 CD4+cells/mm³ and 95,255c/mL plasma HIV-1 RNA.

The subject's past medical history included recurrent zoster. Concomitant medications included rizatriptan benzoate, trazodone hydrochloride, Septra DS and beclomethasone dipropionate. Since prior to Screening the subject also received etravirine, darunavir/ritonavir and Truvada. Enfuvirtide was added to this regimen on 15 November a*.

By 4 January b* the subject had 80 CD4+cells/mm³ and 1605c/mL plasma HIV-1 RNA.

a*: The year
b*: Following year
On 11 January b*, 65 days after the start of dolutegravir, the subject developed grade 3 or severe recurrent varicella zoster. The event was clinically significant (or requiring intervention). The subject developed peri-vaginal inflammation with burning pain in the afflicted area at the onset of the eruption. The subject presented at the ER on 14 January b*. The subject received intravenous acyclovir from 15 to 17 January b*. Treatment with dolutegravir was continued. The subject was discharged on 17 January b* and continued with oral acyclovir from 18 January b* until 25 January b*. The event resolved on 31 January b* and the subject commenced treatment with pregabalin. The investigator considered that there was no reasonable possibility that the recurrent varicella zoster may have been caused by dolutegravir.

Diagnostics:

Recurrent varicella zoster started 11 January b*. Subject was kept under observation at the emergency room from 14-17 January b*, received acyclovir i.v. 1 g t.i.d from 15-17 January b*, at discharge on 17 January, acyclovir oral t.i.d. Stop date 25 January b*

Additional information received on 18 January b*:

The subject was admittedly non-compliant around Christmas and New Year’s Eve, so, that most likely is the reason for the increase viral load at week 8,[1605c/mL, previously <40c/mL at 07 December a*] she has been counselled to be more compliant. The hospital cultures have not yet confirmed zoster (HSV) as cause of the peri-vaginal inflammation, but, it is assumed to be zoster reactivation. She had burning pain in the afflicted area at the onset of the eruption, on 11 Jan b*.

Investigator text:

varicella zoster started 11 January b* - 31 January b* -

Protocol Id: ING112574
Investigator Number: 091282
Subject Number: 001001
Treatment Number: RUN-IN, UNKNOWN, UNKNOWN
Case Id: Z0011196B, Z0011196C, Z0011196D
Suspect Drugs: Dolutegravir
Serious Events: Bowen’s disease, Progressive multifocal leukoencephalopathy, Pyrexia

This 30-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 02 August 2018.
Module 2.7.4 Summary of Clinical Safety

At 2 August a* the subject had <20 CD4+cells/mm$^3$ and 170,395c/mL plasma HIV-1 RNA.

Medical conditions at the time of the event included bowens skin lesion/skin cancer/squamous cell carcinoma in situ. Concomitant ART medications were darunavir/ritonavir, etravirine and stavudine since prior to Screening. T-20 added 10 August a* and maraviroc added 11 January b*..

By 27 September a* the subject had 70 CD4+cells/mm$^3$ and 86 c/mL plasma HIV-1 RNA.

On 04 October a*, 63 days after the start of dolutegravir, the subject developed grade 3 or severe worsening of bowen's lesions on temple and inferior lip. The subject was hospitalised and underwent excision of the Bowen disease lesion on left temple and inferior lips. Treatment with dolutegravir was continued. The event resolved on 11 October a*. The investigator considered that there was no reasonable possibility that the worsening of bowen's lesions on temple and inferior lip may have been caused by dolutegravir.

Follow-up information received on 04 November a*:

The investigator confirmed the event was not a pre-planned hospital admission before trial entry. The condition Bowen's lesions were due to HPV and are considered related to the subject's HIV condition.

Follow-up information received on 18 November a* via answered query report:

The investigator reported "Progressive worsening of Bowen lesions requiring exerese."

Investigator text:

exerese of bowen disease lesion on left temple and inferior lips. injury recovering

On 22 November a*, the subject had 160 CD4+cells/mm$^3$ and <40c/mL plasma HIV-1 RNA

On 21 December a*, 141 days after the start of dolutegravir, the subject developed grade 2 or moderate fever. The subject was hospitalised for evaluation. The subject was otherwise asymptomatic. Treatment with dolutegravir was continued. The event resolved on 30 December a*. The investigator considered that there was no reasonable possibility that the fever may have been caused by dolutegravir.

Follow-up information received on 16 January b* via answered query response:

Final diagnosis was reported as fever.

Follow-up information received on 27 January b* via answered query response:
The subject's fever was around 38.5 degrees C. The subject underwent infectious investigations consisting in blood tests, thoracic abdominal pelvic scanner, bronchial fibroscopy remained negative. No corrective therapy was administered for the event. The subject's immunosuppression was his main risk factor.

Investigator text:

moderate fever occuring on 21th of December and continuing the following days without symptoms leading to hospitalization for evaluation, given his deep immunosuppression

Concomitant medications included stavudine, darunavir, T-20 and etravirine.

On 11 January, 162 days after the start of dolutegravir, the subject developed grade 4 progressive multifocal leukoencephalopathy. The subject displayed slow psychomotor performances, temporospatial disorientation which appeared progressively after his first hospitalization (discharge on the 30 December a*). The subject was hospitalised. The subject was treated with sulphadiazine, pyrimethamine and sequential courses of foscarnet sodium. Treatment with dolutegravir was continued. The event resolved on 23 February b*. The investigator considered that there was no reasonable possibility that the progressive multifocal leukoencephalopathy may have been caused by dolutegravir.

Follow up information received on 12 January b* via medical monitor:

Concomitant medications included darunavir, etravirine and T-20 (enfuvirtide).

As of 17 January b* the subject had 210 CD4+cells/mm$^3$ and <40c/mL plasma HIV-1 RNA.

Follow-up information from site received on 27 January b* via answered query report:

Biopsy virus results of lumbar puncture: presence of JC virus by PCR: diagnosis of PML (progressive multifocal leukoencephalopathy) can be affirmed but not enough to explain all the images of RMN: cerebral biopsy is maintained to search an additional diagnosis. Signs and symptoms included slow psychomotor performances; temporospatial disorientation appeared progressively after his first hospitalisation discharge on 30 December a*. Subject has not yet specific treatment.

Follow up information received on 21 February b* via medical monitor:

The investigator reported "The subject has been hospitalized for a neurological syndrome with confusional signs without a clear diagnosis. The use of foscarnet is prohibited in the study but it has been essential to treat this subject with this molecule, given that his viral load in the CSF was high (12,300 cp/ml), higher than in the plasma, with presence of JC virus. So, foscarnet was introduced on 18 January and has been continued up to now. The last lumbar puncture shows a VL decrease to 500 cp/ml in the CSF. The last MRI done on 20 February shows a regression of cerebral lesions. His clinical status is also improving. Thus the benefit of foscarnet is clear and he must also continue dolutegravir
which has been very active in the control of his plasma viral load. If you consider that it is a protocol violation and that the subject must discontinue the protocol, we shall request an "ATU" of dolutegravir. (Expanded Access Program).

Follow up information received on 22 February b via medical monitor:

The subject had a protocol deviation. Despite this, it is fine to keep the subject in the study, due to the good plasma HIV response, and the lack of other therapeutic options. The investigator reported "Toxoplasmosis is not a confirmed diagnosis. We mentioned toxoplasmosis to justify the treatment by adiazine malocide that has been started at first step before having the different results of biological and radiological assessments. The subject did not respond to this treatment and the RMI was not in favor of a cerebral diagnosis so we can eliminate definitely this diagnosis. The most probable diagnosis is a reactivation of latent infection with JC virus, (Progressive multifocal leukoencephalopathy) (JC virus positive test by PCR in the first lumbar puncture) in a background of immune reconstitution-syndrome. There is no specific treatment of JC virus, but the use of antiretroviral agents with good CNS penetration like foscarnet can decrease the HIV VL in CSF and thus contribute to decrease the brain inflammation due to the HIV encephalopathy which can be also responsible for this neurologic syndrome. Of course the subject is still taking DTG as well as all the drugs of his OBR and must continue to take it since it has been demonstrating a very good efficiency on his plasma VL as you have noticed. He no other susceptible drug according to his baseline resistance profile."

Diagnostics:

RMN done on 11 January b: several lesions predominating in right cerebral hemisphere. A cerebral biopsy is scheduled to establish diagnosis Diagnostic of Progressive Multifocal Leukoencephalopathy confirmed by JC virus positive test by PCR on Jan 11th. HIV encephalopathy (CSF VL 12300 cp/ml)

Investigator text:

slow psychomotor performances, temporospatial desorientation appeared progressively after his first hospitalization discharge on the 30 December a* foscarnet has been very efficient for neurologic disorders(SAE no 4). Our medical team has decided to go on treating the patient by sequential courses of foscarnet -

Protocol Id: ING112574
Investigator Number: 090884
Subject Number: 001013
Treatment Number: UNKNOWN
Case Id: Z0014786A
Suspect Drugs: Dolutegravir
Serious Events: Acute respiratory failure, Productive cough

a*: The year
b*: Following year
This 51-year-old male subject was enrolled in a ViiV-sponsored, open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir 50 mg twice daily from 31 August.

At this date the subject had 270 CD4+ cells/mm$^3$ and 897 c/mL plasma HIV-1 RNA. Medical conditions at the time of the event included chronic obstructive pulmonary disease.

As concomitant ART the subject received from prior to Screening until 7 September $a^*$ abacavir and fosamprenavir/ritonavir. From 7 September $a^*$, concomitant ART medications included Kivexa, etravirine and darunavir/ritonavir.

By 15 February $b^*$ the subject had <40 c/mL HIV-1 RNA and 250 CD4+ cells/mm$^3$.

On 01 March $b^*$, 183 days after the start of dolutegravir, the subject developed grade 3 or severe cough with sputum. On 14 March $b^*$, the subject developed grade 3 or severe acute hypoxicemic and hypercapnic respiratory failure. The subject was hospitalised. Laboratory test results dated 14 March $b^*$ included blood pH 7.35, body temperature 37.4°C (normal range 36.5-37.5), CRP 5 mg/l (lower normal 5), creatinine 63 mcml/l, oxygen saturation 84%, WBC count 6200/mm$^3$, pCO$_2$ 57 mmHg, pO$_2$ 52 mmHg. Laboratory test results dated 15 March $b^*$ included blood pH 7.29 mmHg, pCO$_2$ 65 mmHg, pO$_2$ 79 mmHg. Laboratory test results dated 22 March $b^*$ included blood pH 7.32 mmHg, pCO$_2$ 49 mmHg and pO$_2$ 61 mmHg (normal ranges not available). The subject was treated with Amoxicillin + clavulanic acid, moxifloxacin hydrochloride, Bactrim, ceftazidime sodium and erythromycin. Treatment with dolutegravir was continued. The events resolved on 22 March $b^*$. The investigator considered that there was no reasonable possibility that the acute hypoxicemic and hypercapnic respiratory failure and cough with sputum may have been caused by dolutegravir.

Follow-up information received via query response on 27 March $b^*$:

The subject's regular COPD medications and treatment medications for this SAE were not known.

Diagnostics:

legionnella and pneumococcal antigenuria negative, pneumocystis research is negative 14/03/b* thoracic chest normal 14/03/b*, thoracic scan: mediastinal lymph nodes, bronchoemphysema, micronodule. BAL no germs

Investigator text:
patient is hospitalized for an acute respiratory failure probably viral, past history of COPD, no germ found in the bronchoalveolar liquid, hypoxemia and hypercapnia.

Protocol Id: ING112574
Investigator Number: 090966
Subject Number: 001021
Treatment Number: UNKNOWN
Case Id: Z0015181A
Suspect Drugs: Dolutegravir
Serious Events: Nerve compression

This 77-year-old male subject was enrolled in a ViiV-sponsored, open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir 50 mg twice daily from 24 August.

As of 24 August, the subject had 140 CD4+ cells/mm$^3$ and 56,014 c/mL plasma HIV-1 RNA.

The subject's past medical history included herniated lumbar disc in k* (treated by surgical intervention in e* and by infiltration in a*). The subject has a history of sciatica since e*.

Concomitant medications included Bactrim, rosuvastatin calcium, metformin hydrochloride, bromazepam, paroxetine hydrochloride, lysine aspirin, omega-3-acid ethyl esters, colecalciferol, nebivolol hydrochloride, loperamide hydrochloride, hard paraffin, lercanidipine hydrochloride, desloratadine, paracetamol, esomeprazole, Ixprim.

Concomitant ART included maraviroc from prior to Screening, darunavir/ritonavir and etravirine from prior to Screening until 31 August, and saquinavir/ritonavir and Kivexa from 31 August onwards.

By 8 February, the subject had 170 CD4+ cells/mm$^3$ and 73 c/mL HIV-1 RNA.

On 20 March, 209 days after the start of dolutegravir, the subject developed grade 3 or severe compression of L5 nerve. The subject developed left foot paralysis as a complication of the pre-existing sciatica and herniated lumbar disc on 20 March.

The subject was hospitalised. RMN performed on 14 April showed increasing hernia L4-L5 with discal compression of the nerve's root. The subject underwent surgery for neurological decompression on 19 April. Treatment with dolutegravir was continued. The event resolved on 23 April.

The investigator considered that there was no reasonable possibility that the compression of L5 nerve may have been caused by dolutegravir.

Investigator text:

a*: The year
b*: Following year
e*: Last year
k*: 7 years ago
surgical operation performed on the 19th of April for neurological decompression. Subject has a history of sciatica since e* and a herniated lumbar disc in k*, which was treated by surgical intervention in e* and by infiltration in a*. Left foot paralysis developed as a complication of these 2 pre-existing conditions on 20Mar b*, requiring surgery for neurological decompression on 19April b* -

Protocol Id: ING112574
Investigator Number: 090963
Subject Number: 001031
Treatment Number: UNKNOWN
Case Id: Z0011984A
Suspect Drugs: Dolutegravir
Serious Events: Pneumococcal sepsis, Septic shock

This 70-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 23 August a*. At this date the subject had 39,361c/mL plasma HIV-1 RNA and 160 CD4+ cells/mm³.

As concomitant ART the subject received Kivexa, etravirine and darunavir/ritonavir from prior to Screening until 30 August a*. From 31 August a*, the subject received zidovudine and tipranavir/ritonavir. Tenofovir was also administered since prior to screening. Enfuvirtide administered from prior to screening was stopped 3 April b*.

On 23 September a*, 31 days after the start of dolutegravir, the subject developed grade 4 pneumococcal sepsis and grade 4 septic shock. The subject also experienced symptoms of asthenia, fever and chills with cough. The subject was hospitalised. The subject was treated with ceftriaxone sodium, spiramycin, gentamicin sulphate, amoxicillin trihydrate, Augmentin, amikacin sulfate and Tazocilline. Treatment with dolutegravir was interrupted on 22 September a*, and restarted on 27 September a*. The events resolved on 07 October a*. The investigator considered that there was no reasonable possibility that the pneumococcal sepsis and septic shock may have been caused by dolutegravir. The investigator also confirmed the multiple organ failure was considered a complication of the same SAE and is not two different events.

Diagnostic Results:
Positive hemoculture with pneumococcus

Follow-up information received from clinical study team:
The subject had never smoked tobacco.
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Module 2.7.4 Summary of Clinical Safety

Investigator text:

First symptoms: asthenia, fever and chills with cough the 22nd of September a*. Respiratory distress with fever and orthostatic hypotension on 23Sep a*. Septic shock due to pneumococcal sepsis with multiple organ failure.

Protocol Id: ING112574
Investigator Number: 090918
Subject Number: 001038
Treatment Number: UNKNOWN
Case Id: Z0014234A
Suspect Drugs: Dolutegravir
Serious Events: Herpes ophthalmic

This 30-year-old male subject was enrolled in a ViiV-sponsored, open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day from 17 October a*.

At 17 October a*, the subject had 450 CD4+ cells/mm³ and 3,159 c/mL plasma HIV-1 RNA.

From 24 October a* the subject received as concomitant ART, Truvada and indinavir. The indinavir was stopped 02 November a* and replaced with tipranavir/ritonavir from 08 November a*.

By 07 February b*, the subject had 500 CD4+ cells/mm³ and <40 c/mL HIV-1 RNA.

On 07 February b*, 113 days after the start of dolutegravir, the subject developed grade 2 or moderate herpes ophthalmic. The subject was hospitalised and the event was clinically significant (or requiring intervention). The subject was treated with prednisone, acyclovir and valaciclovir hydrochloride. Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the herpes ophthalmic may have been caused by dolutegravir.

Diagnostics:

Hypothesis of immune restoration syndrome or direct toxicity medicament. Ocular herpes. The diagnosis of intra-ocular herpes simplex was made with PCR on Friday March 2nd

Follow-up information received on 14 February b* via email:

Fundus: there is an interference with a diffuse choroidal aspect of multiple white dot syndrome type Birdshot retinopathy. A diagnosis of sarcoidosis may be possible.

a*: The year
b*: Following year
CONFIDENTIAL
Module 2.7.4 Summary of Clinical Safety

Follow-up information received on 13 March b* via query response:

Decrease of visual acuity. No other symptoms. Suspected immune reconstitution or direct toxicity to the drug. Sample taken 28 February b* in favour of ocular herpes.

Follow-up information received 13 March b* via medical monitor:

Subject reported that visual acuity reduced on 07 February, and prior to this the subject had good vision. The subject experienced no pain and no generalised signs or symptoms of illness. He was hospitalized twice: from Sunday Feb 26th to Tuesday Feb 28th he had biologic investigations, an abdomino-pelvic scanning, an eye sample taken for bacteriological and virology research, an internist advice was also performed. As we had a suspicion of IRIS we decided to start a steroid treatment. The diagnosis of intra-ocular herpes simplex was made with PCR on Friday March 2nd, we stopped steroids immediately and we started intravenous aciclovir on the same day. He came back home on Saturday March 3rd and still continues intravenous aciclovir. He had a new ophthalmic examination on March 12th, conclusion was improvement. He continues intravenous aciclovir until next Tuesday and then we will decide how to manage the follow up.

Follow-up information received on 06 June b* via query response:

Dated June 6, b*, the SAE is ongoing.

Investigator text:

Decrease of visual acuity. No other symptoms. Suspected immune reconstitution or direct toxicity to the drug. Sample taken 28 February b* in favor of ocular herpes. The diagnosis of intra-ocular herpes simplex was made with PCR on Friday March 2nd -

Protocol Id: ING112574
Investigator Number: 091510
Subject Number: 001058
Treatment Number: UNKNOWN
Case Id: Z0014166A
Suspect Drugs: Dolutegravir
Serious Events: Dysphagia

This 1-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 24 January a*.

As of 24 January a*, the subject had <20 CD4+cells/mm³ and 67,662 c/mL plasma HIV-1 RNA

a*: The year
b*: Following year
The subject's past medical history included esophageal candida. Medical conditions at the time of the event included HIV infection CDC category C3. Concomitant ART medications included Truvada from prior to Screening, Kaletra and maraviroc from prior to Screening to 04 February a* and darunavir/ritonavir, etravirine and T-20 from 04 February a*.

On 24 January a*, same day after the start of dolutegravir, the subject developed severe swallowing difficulties. The subject experienced alteration of general status with weight loss, decreased appetite, fever and chills, oral thrush and dysphagia with solid food. The subject was hospitalised. The investigator reported final diagnosis as swallowing difficulty, of unknown etiology, oesophageal endoscopy and biopsy were normal. For the event, the subject was treated with soft diet intake. Oesogastroduodenal endoscopy confirmed no oesophageal candidiasis, diagnosis was oro-pharyngeal candidiasis due to Candida glabrata. The subject was treated with fluconazole and mycamine. Treatment with dolutegravir was continued. The event resolved on 21 February a*. The investigator considered that there was no reasonable possibility that the swallowing difficulty may have been caused by dolutegravir.

Follow up information received 14 February a*;

The subject was randomised on the 24 January a*, and during that visit he was complaining of oral [thrush] and difficulty on swallowing with recent weight loss. So he was treated by Triflucan (fluconazole) 200 mg/d. The hospitalisation, on 4 February, was mainly for non improvement of oral thrush and the investigation of the alteration of general status. The subject was still having oral intake problems, Triflucan was stopped on the 4 February because of non improvement. The subject confirmed complete compliance to his antiretroviral treatment despite these symptoms; as we can see in the drop of his HIV-RNA level of > 1 Log in 14days [to 2640c/mL 7 February a*]. After examining the laboratory and radiological procedures that the subject has recently done during this hospitalisation- until now there was no documented opportunistic infection, Candida Glabrata was isolated from the oral thrush which is partially sensitive to Triflucan, The Oeso-gastro-duodenal endoscopy done came back normal, so he was shifted to Mycamine treatment on the 6 February for treatment of oropharyngeal candidiasis. Note that he had an oro-pharyngeal candidiasis in March h*.

Diagnostics:

Normal upper endoscopy, done on the 14th of February a*

Investigator text:

alteration of general status with weight loss, decreased appetite, fever and chills, oral thrush and dysphagia on solid food -

Protocol Id: ING112574
Investigator Number: 091262

a*: The year
h*: 4 years ago
This 45-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 03 November a*

As of 03 November a* the subject had 250 CD4+cells/mm$^3$ and 54,966 c/mL plasma HIV-1 RNA.

The subject's past medical history included Hodgkin's disease, interstitial pneumopathy, tuberculosis and zona ophthalmica. Concomitant ART medications included maraviroc administered from prior to Screening and Truvada from 10 November a*.

By 02 January b* the subject had 360 CD4+cells/mm$^3$ and <40c/mL HIV-1 RNA.

On 13 January b*, 71 days after the start of dolutegravir, the subject developed grade 3 or severe infectious pneumopathy. The subject was hospitalised on 13 January b* due to persisting fever and chills. Laboratory test results dated 14 January b* showed C-reactive protein 118.8 mg/l (normal range 0-8.2). Thoracic X-ray performed on 14 January b* showed a right basal pneumopathy with crackles sounds. The subject was treated with ceftriaxone, amoxicillin trihydrate, spiramycin, levofloxacin, Augmentin and paracetamol. Treatment with dolutegravir was continued. The event resolved on 19 January b* and the subject was discharged. The investigator considered that there was no reasonable possibility that the infectious pneumopathy may have been caused by dolutegravir.

Diagnostics:

Thoracic X Ray performed on 14 JAN b*. Also, testing for both Chlamydia pneumoniae and Mycoplasma pneumoniae were reported as “positive”

Investigator text:

Infectious episode on December that seemed to be resolved on week 8 visit (02JAN b*). The patient was hospitalized for persistence of fever and chills on 13 JAN b*. A new thoracic X-Ray performed and showed a right basal pneumopathy with crackles sounds. Antibiotherapy was provided. The patient left hospital on 19JAN b* without sequelae.
As of 27 February b*, the subject had 420 CD4+ cells/mm$^3$ and <40c/mL plasma HIV-1 RNA. –

The subject's past medical history included Hodgkin's disease in h*. Concomitant medications included amlodipine besylate.

On 15 March b*, 133 days after the start of dolutegravir, the subject developed grade 3 or severe lymphadenopathy due to recurrent Hodgkin's lymphoma. CT scan performed in March b* showed left cervical adenopathies with some measuring more than 1 cm. The subject was hospitalised on 22 April b*. The subject underwent exeresis on 23 April b*. Treatment with dolutegravir was continued. The event resolved on 23 April b*. The subject was discharged on 24 April b*. Implantable chamber with bone marrow was planned on 04 June b* for chemotherapy incoming in few days. The investigator considered that there was no reasonable possibility that the lymphadenopathy due to recurrent Hodgkin's lymphoma may have been caused by dolutegravir.

Follow-up information received on 14 June b* via query response:

Chemotherapy not yet started and subject comes to office on 20Jun b*

The outcome date should not be updated because lymph nodes have been removed and as they were malignant, the chemotherapy will start soon.

Follow up information received on 06 July b* from the clinical team:

On 05 July b*, the subject received chemotherapy consisting of nalfucan (days 1 - 7, 100 mg/m$^2$/day), cortancyl (days 1 - 14, 40 mg/m$^2$/day), vincristine (day 1, 1.5 mgm$^2$), doxorubicin (day 8, 35 mg/m$^2$), endoxan (day 1, 650 mg/m$^2$) and vinblastine (day 8, 6 mg/m$^2$). The subject was reported to be still taking dolutegravir and has no adverse events.

The subject's next chemotherapy cycle is due to start on 02 August b*.

He remains on IP through 15 Oct b* (Week 48 study visit)

Investigator text:

Hodgkin disease (Stage II) on h* with right cervical adenopathy. Patient treated by 4 cycles of chemotherapy with radiotherapy. Patient considered relief. On the last CT scan performed on March b* (4 years of the end of treatment), new left cervical adenopathies with some more than 1 cm. Exeresis performed on 23 Apr b* (hospitalisation of 22Apr b* to 24 Apr b*). Hodgkin disease recidive. Implantable chamber with bone marrow on 04June b* for chemotherapy incoming in few days. -
This 50-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice daily from 05 March.

As of 05 March a*, the subject had 40 CD4+ cells/mm^3 and 293,311 c/mL plasma HIV-1 RNA.

Concomitant ART included Kivexa from prior to Screening to 13 March a*, darunavir/ritonavir from prior to Screening to 28 September a*, Truvada from 13 March a*, maraviroc from 13 March a* and tipranavir/ritonavir from 13 March a*.

As of 01 Jun a*, the subject had 60 CD4+ cells/mm^3 and 341,852 c/mL plasma HIV-1 RNA.

The subject has no past medical history relevant to the reported event. Medical conditions at the time of the event included endocrine disorder.

On 01 June a*, 88 days after the start of dolutegravir, the subject developed grade 3 or severe acantholytic epidermoid carcinoma. The event was clinically significant (or requiring intervention). The subject was treated with methotrexate, tobramycin and Biseptine. Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the acantholytic epidermoid carcinoma may have been caused by dolutegravir.

The subject was withdrawn as a Protocol Defined Virological Failure on 28 September, a*.

Diagnostics:

Good evolution of the hurt of the straight right eyelid with the local injections of methotrexate. Project of surgical operation between July 22nd and July 27th. The patient gets better he feels in good shape.

Investigator text:

Hurt of the junction enters the eyelid inf right and the right cheekbone. Initially taken care by city dermatologist who had made the diagnosis of wart and had made at the end of April the beginning of May a session of cryotheraphy. Following this session, the
patient manipulated this hurt, aspect of abcess was noticed on May 4th with consultation in ophthalmology and stake under pyostacine.

No improvement and on the contrary, in a extremely fast way the hurt enormously set in volume, presenting an aspect very coming out with round aspect centered on a central crater more or less oozing. The patient was then revised in ophthalmology and a biopsy was made.

June 1st, result of the anapath was obtained : carcinoma epidermoid acantholytic.

An ophtalmo opinion was then taken to consider therapeutic surgical possibilities on this hurt, but the ophtalmologists stand back, at the same time considering the aspect potentially very ruining of the surgical movement which would be necessary, but also because they are perplexed concerning the speed of appearance of the hurt. They ask for a dermatological opinion.

Called Pr [deleted] who thinks a possible differential diagnosis on this hurt which could be of better forecast. He is going to examine photos, to see the patient and to re-discuss with [deleted] to take the better decision rule. If the diagnosis of carcinoma stays of current events, possibility also of methotrexate premises.

Protocol Id: ING112574
Investigator Number: 089452
Subject Number: 001201
Treatment Number: UNKNOWN
Case Id: Z0012771A
Suspect Drugs: Dolutegravir
Serious Events: Hepatitis acute

This 32-year-old male subject was enrolled in an open-label ViiV-sponsored study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 15 July.

As of 15 July a*, the subject had 80 CD4+ cells/mm³ and 154, 899 c/mL plasma HIV-1 RNA.

As concomitant ART the subject had received Truvada and darunavir/ritonavir from prior the Screening to 21 July a*. From 22 July a*, T-20 was administered until 7 November a* and maraviroc until 10 November a*. The subject received Kivexa from 7 to 10 November a*. Truvada was recommenced 19 November a*, maraviroc from 01 February b* and T-20 from 01 February b* until 07 April b*.

Medical conditions at the time of the event included previous hepatitis B.

a*: The year  
b*: Following year
By 07 November a*, the subject had 360 CD4+ cells/mm³ and 156 c/mL HIV-1 RNA.

On 07 November a*, 115 days after the start of dolutegravir, the subject developed grade 4 acute hepatitis. The event was clinically significant (or requiring intervention). Relevant laboratory test results dated 07 November a* included ALT 1493 U/L (normal range 0-48), AST 1485 U/L (normal range 0-42), bilirubin total 108 umol/l (normal range 0-22), HBV DNA increased >11000000 IU/ml (normal range 0-28). Laboratory test results dated 05 December a* included ALT 104 U/L, AST 169 U/L, HBV DNA decreased 927000 IU/ml. Laboratory test results dated 29 December a* included ALT 90 U/L, AST 127 U/L and bilirubin total 83 umol/L. The subject was treated with dextrose. Treatment with dolutegravir was interrupted on 10 November a*. The event resolved on 19 January b*. Treatment with dolutegravir was restarted on 01 February b*. The subject’s ALT, bilirubin and AST have remained within normal range since late January, b*. The investigator considered that there was no reasonable possibility that the acute hepatitis may have been caused by dolutegravir. According to the investigator, the withdrawal of Truvada may have lead to a reactivation of Hep B.

Diagnostics:

05 Dec a* Hepatitis b surf.AG = REACTIVE

Additional information received via medical monitor on 11 November a*:

Patient 1201 has been taking nebivolol since March a* as a second-line therapy for hypertension. Acetylcystein (prescribed during an episode of bronchitis for symptoms relief) has been stopped on 17 October.

Currently, Subject 1201 presents lypoatrophy and intra-abdominal testicular retention. We have modified hepatobiliary disorders recorded in medical history as "past" because the previous infections with HAV (year z*; no clinical documentation available and no IgG Antibodies detectable); HBV (y*; no clinical documentation available) and HCV were included.

On 7 November enfuvirtide was stopped (severe discomfort to subcutaneous administration) and substituted with abacavir/lamivudine (drug previously used; HLAB5701 negative).

Since yesterday [10Nov a*] all antiretroviral drugs (including dolutegravir) have been stopped.

At presentation patient was jaundiced and noted dark urine. Moreover he also reported nausea and asthenia.

Previous HBV and HCV infections were reported in the patient's medical history. Both these infections were spontaneously cleared but, at the last available HBV serology, no
antibodies for HBs or HBc were detectable. During the visit, he did not report any potential risk factor for these infections.

The abdominal US performed this morning [11Nov a*] showed a mild hepatomegaly with a dishomogeneous echostructure but without focal lesions. Moreover, an enlarged lymph node at the hepatic hilus was observed. No other pathological abnormalities were reported for the other intra-abdominal organs.

Patient presented jaundice but not a concomitant rash. Asthenia, nausea and jaundice started since 02 November.

Tox screen: positive for cannabinoids.

Additional information received from Medical Monitor on 08 December a*:

This 30 yr old Caucasian homosexual male was randomized on 15 July a* with a baseline HIV RNA load of 154,899 copies/mL, and a CD4 count of 88. He denies recent herbal drug exposure, recreational drug usage, and any recent travel. He works in fashion merchandising. The most recent HIV RNA (on 10 October, a*) at the week 12 study visit was < 50 copies/mL, and the CD4 count was 283.

His past medical history includes hepatobiliary disease (HAV, HBV, and HCV), respiratory, skin and soft tissue and ear and labyrinth disorders. Current medical conditions include hypertension, musculoskeletal (lipoatrophy / lipodystrophy) and reproductive body system issues (intra-abdominal testicle).

He was diagnosed with acute HAV in z*, acute HBV in y*, and HCV RNA (with viral load of 327,000) in q*. He reported that he was both HBs Ab and HBe Ab positive, after the y* acute HBV infection. Both Ab were also repeated in s*, and were positive, with a negative HBs Ag. Also reported was a negative viral load test for both HBV and HCV in November, h* and he was treated with Truvada in h*. He has had prior Truvada treatment interruptions without experiencing any acute hepatitis.

Conmeds include: acetylcysteine (oral) once daily starting October 5, a* and stopped 17 October (for an acute URTI), and a beta-blocker (nebivolol) starting March, a* (for hypertension).

ConART includes: Fuseon and maraviroc, both BID, and both started on 21 July, a* as part of optimized background regimen for the current study. He had previously been on Prezista and Truvada since July, f*.

On 10 October, a* the subject was asymptomatic. He presented to the site for his week 12 study visit. At that visit, his ALT was 98, and AST was 73. They had been within normal range previously. The bilirubin was normal at this time.

On 07 November, a*, he presented to the study site for a Week 16 visit, and was complaining of dark urine. The investigator thought he appeared to have jaundice. The
subject was instructed to stop IP, and a liver event lab kit was collected. He stopped his Fuzeon that day, due to injection site pain. He started Kivexa, on 7 November, a*, however, all study drugs were stopped on 10 November, a* in response to the elevated liver lab values.

The lipase is mildly elevated at the Week 16 visit, with a value of 76 (all prior lipase had been WNL). However, the ALT was, 1713 and the AST 1374. The total and direct bilirubin were: 100/60 (normal ranges 0-22/ and 0-6, respectively). The alkaline phosphatase was 168. CPK was within normal limits.

Liver safety panel labs were sent on 07 November, a*. The HBs Ag returned REACTIVE at this time (it was non-reactive at Day 1 on the 15 July, a*). His Hbc-IgM antibody and HBe- IgM were both non-reactive.

HCV RNA (by PCR) was not detectable, and screening tests for HAV, CMV, EBV and ANA were all negative.

Local labs (Italy) collected on 14 November revealed HBe Ag +( reactive), and confirmed HBs Ag +

ALT was 1821, AST 1179, and total bilirubin 11.84 (all essentially unchanged since the 07 November, a* labs). A prothrombin time (PT) was normal.

The subject was reported to be feeling mildly better, with less nausea and less asthenia. He remains off all medicines as of 16 November, a*.

On 18 November, the subject felt unchanged, however, the Investigator elected to admit him to the hospital for close observation, secondary to the lab values from that day. His total/ direct bilirubin values increased to 17.83/14.89. His ALT was 1652, AST was 1423 (both largely unchanged since the prior values on 14 November.)

The subject was started on oral Truvada on 19 November, a*, to treat the Hepatitis B

He was discharged from the hospital on 27 November.

LAB UPDATE:

HBV DNA PCR results from 07 November, a* were available on 18 November, a*. The count was 640,200,000 copies/mL

His syphilis screen (serum RPR) returned non-reactive.

Baseline (Day 1, collected 15 July, a*) HBV DNA by PCR was < 169 copies/mL (lower limit of testing). Hbc IgM from that date was also non-reactive. HBs Ab( total) was positive from a frozen Day 1 plasma sample, indicating that HBs IgG was present at baseline. This indicates that the current episode of Hepatitis B is most probably a reactivation.

a*: The year
As of 24 November, the site reported ALT and AST were decreasing at 852 and 931, respectively, and total bilirubin was largely unchanged at 16.97. He remained in hospital as of 25 November, a*, but was reported to be feeling well.

Labs collected on 05 December, a* were: total bilirubin 308, and direct bilirubin 158 (which are increased from 07 November, a* values). ALT was 104 and AST 169 (lower than previous values).

Hepatitis D virus total Ab (sample from 07 November, a*) was non-reactive.

Follow-up information received on 10 January b* via query response:

The patient had a previous B hepatitis. The withdrawal of Truvada may have lead to a reactivation of Hep B. At the moment the patient is waiting for the formal decision about the restart of dolutegravir antiretroviral regimen.

Follow-up information received on 01 February b* via answered query response:

The investigator confirmed the subject restarted dolutegravir on 01 February b*.

Additional information received from Medical Monitor on 12 March b*:

Liver laboratory results on 28 February b* were all within normal ranges.

Additional information received from Medical Monitor on 02 April b*:

On 26 March b* lab results included ALT 20, AST 32, and total bilirubin 12. HIV RNA was decreasing, but still above 50 copies/ml (it was 86), and his CD4 continue to increase slowly and is at 272.

Follow-up subsequently retrieved from the liver CRFs included:

The subject did not use herbals, complementary or alternative medicines, food supplements or illicit drugs. The subject did not fast or undergo significant dietary change in the previous week. The subject did not consume alcohol.

Medical conditions included past acute viral hepatitis A, past chronic hepatitis B and past chronic hepatitis C. The subject had current drug related liver disease conditions.

There were diagnostic imaging tests performed on 11 November a*. The liver imaging method was ultrasound - transabdominal. The images were optimal for technical adequacy. The liver was enlarged (hypertrophic) for size, texture was dishomogeneous, and diffuse and/or geographic fatty infiltrate grade was not applicable - no fatty infiltration. Ascites was not present, focal hepatic lesions were characterized s
hemangioma, no gallstones or gallbladder lesions, no biliary ductal lesions and no portal/hepatic vein abnormalities were observed. There were no liver biopsies performed.

Investigator text:

Preliminary Laboratory exams performed on 07/Nov/a* showed an acute hepatitis related to the reactivation of a previous HBV infection. The liver function slowly and progressively improved, particularly after the reintroduction of Truvada. At the exams January 3 the transaminases are slightly above the normal values, Bilirubin level has significantly improved, patient is HBV-DNA neg. -

Protocol Id: ING112574
Investigator Number: 089452
Subject Number: 001202
Treatment Number: UNKNOWN
Case Id: Z0012364A
Suspect Drugs: Dolutegravir
Serious Events: Epstein-Barr virus infection, Immune reconstitution syndrome

This 21-year-old male subject was enrolled in a ViIV-sponsored, open-label study study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 20 July a*.

As of 20 July a*, the subject had <20 CD4+cells/mm^3 and 104,203 c/mL plasma HIV-1 RNA.

The subject has no relevant medical history. As concomitant ART the subject received Truvada, etravirine and darunavir/ritonavir from prior to Screening to 26 July a*. From 27 July a* tenofovir, maraviroc and tipranavir/ritonavir were administered.

The subject developed fever and cough from 20 September a*. He was initially treated with Cefixime (400 mg once daily) and Azithromycin (500 mg once daily) for 7 days without any clinical benefit. He was admitted at the site's day hospital service on 04 October a*. Blood test showed C-reactive protein elevation at 120 mg/L (normal range 2-6). Chest x-ray and an abdominal ultrasound scan did not show any pathologic finding. C-reactive protein was 118 mg/L on 14 October a*.

By 12 October a* the subject had 230 CD4+cells/mm3 and <40 c/mL HIV-1 RNA.

On 18 October a*, 90 days after the start of dolutegravir, the subject developed grade 2 or moderate cryptogenic immune reconstitution syndrome and grade 1 or mild Epstein-Barr virus infection reactivation. The subject was hospitalised. Laboratory test results

*a*: The year
dated 20 October a* showed C-reactive protein of 99 mg/L. The subject was treated with ceftriaxone and levofloxacin. Treatment with dolutegravir was continued. At a visit on 09 November a*, the subject reported a significant improvement of the fever and cough, and C-reactive protein re-tested at 54 mg/L. The cryptogenic immune reconstitution syndrome resolved on 09 November a*. The Epstein-Barr virus infection reactivation was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the cryptogenic immune reconstitution syndrome and Epstein-Barr virus infection reactivation may have been caused by dolutegravir.

Follow-up information received 20 October a*:

The subject had ongoing respiratory and skin and soft tissue conditions; a past history of hepatobiliary (liver) issues, neoplasm and musculoskeletal/connective tissue conditions.

Follow-up information received from medical monitor on 27 October a*:

Subject was discharged from hospital on 21 October with the following diagnosis: possible immune reconstitution syndrome and EBV-DNA activation (1996 copies/ml) in HIV-infected patient with previous hepatitis B and squamous cell carcinoma at right vocal cord. All the imaging studies are negative; the patient is doing better.

Follow-up information received on 10 November a* via query response:

At the blood sample of the 09th November a*, C-reactive protein decreased and concomitantly fever and cough improved. We are waiting for the EBV DNA quantification.

Follow-up information received on 01 December a* via query response:

Resolution of fever and cough, C-reactive protein decrease to 54 mg/dl. We will perform a new blood tests for the next week. Clinically SAE could be considered resolved.

Follow-up information received on 01 February b* via answered query report:

Although the investigator previously responded that clinically the SAE could be considered resolved at the time of reporting on 01 February b*, the event outcome remained unresolved, the EBV DNA result was 1500 UI/ml. The subject was scheduled to undergo a thoracic-abdominal CT scan in a few weeks time.

Diagnostics:

CT scan abdomen - thorax - neck and brain: no pathologic lymphadenopathy. No other significant findings. EBV DNA: 1966 cp-ml

Investigator text:

a*: The year
b*: Following year
Since 20th September \textsuperscript{a*} occurrence of fever and cough. He was initially treated with cefixime (400 mg once daily) and azitromicin (500 mg qd) for 7 days without any clinical benefit. He was admitted at our Department's Day hospital service on the 04th October \textsuperscript{a*}. Blood test showed a C-Reactive protein elevation (120 mg/dL; normal values 2-6 mg/dL). A X-Ray Chest and an abdominal ultrasound scan did not show any pathologic finding. He was admitted in our Infectious Diseases ward yesterday (18 Oct \textsuperscript{a*}). At the visit performed on the 09th November \textsuperscript{a*} he reported a significant improvement of the fever and cough.

Protocol Id: ING112574
Investigator Number: 089452
Subject Number: 001203
Treatment Number: UNKNOWN, UNKNOWN, UNKNOWN, UNKNOWN, UNKNOWN
Case Id: Z0011368A, Z0011368B, Z0011368C, Z0011368D, Z0011368E
Suspect Drugs: Dolutegravir
Serious Events: Convulsion, Cytomegalovirus infection, Cytomegalovirus infection, Cytomegalovirus viraemia, Progressive multifocal leukoencephalopathy

This \textsuperscript{a∗} year-old female subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir 50 mg twice daily from 20 July \textsuperscript{a*}.

As of 20 July \textsuperscript{a*}, the subject had <20 CD4+ cells/mm\textsuperscript{3} and a particularly high viral load of 23,390,390 c/mL plasma HIV-1 RNA.

As concomitant ART the subject received: enfuvirtide from prior to Screening until 27 July \textsuperscript{a*} and again from 1 September to 7 November \textsuperscript{a*}, maraviroc from prior to Screening until 7 November \textsuperscript{a*}, Truvada from prior to Screening until 6 December \textsuperscript{a*}, atazanavir from 28 July \textsuperscript{a*} to 31 August \textsuperscript{a*}, stavudine and tipranavir/ritonavir from 14 November \textsuperscript{a*} until 16 February \textsuperscript{b*}.

On 17 August \textsuperscript{a*}, 28 days after the start of dolutegravir, the subject developed grade 3 or severe CMV systemic infection. The subject was hospitalised. Associated sign/symptoms included fever and grade 2 rashes.

The subject had blood tests performed on the 17 August \textsuperscript{a*} with evidence of CMV active replication: Agp65=14, CMV-DNA 7000 cp/ml. An ophthalmological evaluation preformed on the same date excluded a CMV retinitis. The subject did not have any relevant medical condition except the known HIV infection with <20CD4+ cells/mm\textsuperscript{3} and 9,687,850 c/mL HIV-1 RNA at this time point.

There was no organ dysfunction due to CMV localisation. The subject was treated with ganciclovir and prednisone. Treatment with dolutegravir was continued. The event

\textsuperscript{a∗}: The year
\textsuperscript{b∗}: Following year
resolved on 03 September a*. The investigator considered that there was no reasonable possibility that the CMV systemic infection may have been caused by dolutegravir.

Additional follow-up information received on 23 August a*:

A 7 year old female has a baseline CD4 of less than 20, and a baseline HIV RNA of 23,390,390 copies/mL (7.37 log 10). She has had minimal virologic response, with HIV RNA at Day 8 (7.26 log 10) or Week 4 (6.99 log 10).

Her CD4 remains less than 20 cells.

She has a reported systemic CMV infection with the following test results

Ag p65 CMV = 14
Blood CMV-DNA = 7000 copies/ml

Con-meds include Augmentin and atarax, concomitant antiretroviral therapy maraviroc (Celsentri) 300 mg BID and atazanavir 400 mg BID as OBR along with DTG.

Deletion report was received on 28 October a*:

Treatment medication of ganciclovir was deleted.

Investigator text:

On the blood tests performed on the 17th Aug a* evidence of CMV active replication: Agp65=14, CMV-DNA 7000 cp/ml. An ophthalmologist evaluation preformed on the same date excluded a CMV retinitis. Patient presented fever and associated a G2 skin rash. No organ dysfunction due to CMV localizzation. -

The subject's past medical history included toxoplasma gondii encephalitis.

As of 10 October a* the subject’s CD4+ cells remained <20/mm$^3$ with 4,021,232 c/mL HIV-1 RNA.

On 18 October a*, 90 days after the start of dolutegravir, the subject developed grade 2 or moderate seizure. The subject was hospitalised. MRI of the brain excluded active neurotoxoplasmosis. The cerebral lesion localized in the right frontal lesion was compatible with residual scarring of the previous neurotoxoplasmosis. EEG showed epileptogenic focus in the right frontal region. The subject was treated with levetiracetam, Cotrimoxazole and atovaquone. Treatment with dolutegravir was interrupted on 18 October a*, re-started on 25 October a* and permanently stopped on 05 November a*. The event resolved on 05 November a*. The investigator considered that there was no reasonable possibility that the seizure may have been caused by dolutegravir.
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Module 2.7.4 Summary of Clinical Safety

Follow-up information received via medical monitor on 24 October a*:

Subject had extensive past opportunistic infections that may explain these symptoms including cerebral toxoplasmosis, disseminated cryptococcosis, meningitis and disseminated CMV infection. Current OI prophylaxis includes valganciclovir, sulfamethoxazole-trimethoprim. Current conditions included fever.

Follow-up information received from medical monitor on 27 October a*:

Subject was discharged on 27 October a* with diagnosis of 'seizure in HIV-infected patient with right cerebral ischemia'. Occurrence of new CNS opportunistic diseases have been excluded by MRI. The patient is doing well, she is receiving levetiracetam. It was not known when the ischemic cerebral event occurred; the imaging is not consistent with an acute ischemic episode and the previous MRI (negative for a frontal right ischemic area) was performed years ago.

Follow-up information received on 28 November a* via query response:

Investigator confirmed right cerebral ischemia is not considered to be an SAE.

Diagnostics:

MRI brain: Exclusion of active Neurotoxoplasmosis. The cerebral lesion localized in the right frontal lesion is compatible with residual scarring of the previous neurotoxoplasmosis. EEG: epileptogenic focus in the right frontal region.

Follow-up information received on 23 February b* via answered query report:

The investigator confirmed dolutegravir was discontinued on 05 November a* due to virological failure and suspected allergic rash but not due to the SAE.

Investigator text:

Probable seizure on the 18th October a*. Firstly admitted to "Hospital in [redacted]" where she started levetiracetam, as seizure prophylaxis, and cotrimaticol for suspected neurotoxoplasmosis. She was discharged on the 20th October and admitted to our Hospital in the same day.

Medical conditions at the time of the event included human immunodeficiency virus and severe immunosuppression secondary to uncontrolled HIV infection. Concomitant medications included stavudine and tipranavir (Aptivus).

The subject was withdrawn from the study 07 November a*.

On 06 December a*, 139 days after the start of dolutegravir and 31 days after the last dose, the subject developed grade 3 or severe reactivation of systemic cytomegalovirus. Associated symptoms included ipovisus at left eye. The subject was hospitalised. The
subject was treated with foscarnet sodium for a total of 18 days with suppression of CMV agp65 and marked decrease of blood CMV DNA. The event resolved on 23 December a*. The investigator considered that there was no reasonable possibility that the reactivation of systemic cytomegalovirus may have been caused by dolutegravir.

Diagnostic text:

CMV/DNA = 86419 copies/ml Agp65 = 220 nuclei

Investigator text:

Diagnosis of CMV sistemic reactivation (symptoms; ipovisus at left eye). Patient was treated with Foscavir intravenous for a total of 18 days with suppression of CMV agp65 and marked decrease of blood CMV DNA

The subject's past medical history included severe immunosuppression related to uncontrolled HIV infection. Concomitant medications included Ascriptin.

On 08 December a*, 141 days after the start of dolutegravir and 33 days after the last dose, the subject developed grade 4 progressive multifocal leucoencephalopathy (PML). The subject had been admitted to the hospital with CMV reactivation and PML on 06 December a* with associated symptoms of ipovisus at left eye and mild fever. Brain CT scan showed large right frontal hypodensity and a smaller left frontal subcortical hypodensity. EEG revealed epileptiform alterations in the right cerebral hemisphere. Brain MR showed suspected progressive multifocal leucoencephalopathy in the right frontal-parietal region. The subject was treated with filgrastim, meropenem and valgancyclovir. The subject died on 16 February b* due to progressive multifocal leucoencephalopathy.

An autopsy was not performed. The investigator considered that there was no reasonable possibility that the progressive multifocal leucoencephalopathy may have been caused by dolutegravir.

Follow up information received on 10 January b*:

The primary reason for stopping dolutegravir were rash and itching, of course the concomitant presence of virological rebound made this decision easier.

Follow-up information received on 28 March b* via query response:

I confirm date of diagnosis 08 Dec a*

Follow-up information received 05 April b* via Answered Query Report:

The subject was not receiving any concomitant antiretroviral therapy at the time of this event. An autopsy was not performed.

a*: The year
b*: Following year
The patient was withdrawn from the study on the 07th November a*. She was admitted in our Hospital on 06th December a* for CMV reactivation and PML (symptoms: iritis at left eye and mild fever). The worsening of PML resulted in death on 16th February b*.

On 16 November a*, 119 days after the start of dolutegravir and 11 days after the last dose, the subject developed grade 2 or moderate cytomegalovirus infection reactivation. The subject was hospitalised due to fever related to reactivation of CMV systemic infection. The subject was treated with Piperacillin + tazobactam, vancomycin hydrochloride, fluconazole, filgrastim, bromazepam, ganciclovir and potassium chloride. The event resolved on 03 December a*. The investigator considered that there was no reasonable possibility that the cytomegalovirus infection reactivation may have been caused by dolutegravir.

Follow-up information received 05 April b* via Answered Query Report:

Body temperature on admission and discharge was unknown as was admitted to a different hospital.

Patient admitted to our hospital due to fever related to reactivation of CMV systemic infection.

- Protocol Id: ING112574
  - Investigator Number: 089452
  - Subject Number: 001214
  - Treatment Number: UNKNOWN, UNKNOWN, UNKNOWN
  - Case Id: Z0012049A, Z0012049B, Z0012049C
  - Suspect Drugs: Dolutegravir
  - Serious Events: Hepatic cirrhosis, Pleural effusion, Pneumonia, Renal failure acute, Streptococcal sepsis

This year-old male subject was enrolled in a Viiv-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 13 September a*. As of 13 September a* the subject had 170 CD4+ cells/mm$^3$ and 14,830 c/mL plasma HIV-1 RNA.

As concomitant ART the subject received lamivudine and darunavir/ritonavir from prior to Screening to 20 September a* and 4 December a*, respectively. From 21

a*: The year
b*: Following year
September a*, the subject received etravirine and maraviroc with interruptions between the 4 and 14 December a* and 15 January b* to 28 February b*.
Darunavir/ritonavir was added to the regimen 14 December a* with the same period of interruption from 15 January b*.

Medical conditions at the time of the event included cardiac failure. Concomitant medications included nitroglycerine, ramipril and carvedilol.

The subject had a past history of IV heroin use, diagnosed with HIV in s* and treated with Peg Interferon for acute HCV (genotype 4a) in n*. He had an acute myocardial infarction in April, a*. At that hospitalization, it was determined that the subject had progressive liver disease with cirrhosis. The subject was given a Child-Pugh score of 6 at that hospitalization.

The subject was noted to have congestive heart failure and worsening of chronic renal insufficiency in May, a*. During hospitalization 2000 cc of fluid was drained from his chest cavity. The subject was recently hospitalized (August, a*) for worsening of chronic renal insufficiency. The subject also had ascites at that visit.

On 29 September a*, 16 days after the start of dolutegravir, the subject developed grade 2 or moderate pleural effusion, detected on chest X-ray during pre-operative investigations. The subject was hospitalised on 29 September a*. The subject had presented for elective inguinal hernia repair, but was noted to have recurrent pleural effusions on the pre-operative assessment chest X-ray. The subject was noted to have ascites, but was afebrile and without shortness of breath (100% oxygen saturation on room air). His abdominal girth was 91 cm. The subject was treated with frusemide and canrenoate potassium which did remove fluid, however, it was noted that creatinine and metabolic acidosis increased as a result. Relevant laboratory tests included on admission 29 September a*: serum creatinine of 2.11 (normal range 0.5-1.25) which increased to 3.13 by 03 October a*. On 03 October a* the subject had low platelets at 70,000 (previously 74,000) and direct bilirubin was 1.3 (normal range 0.1-0.25) (previously 1.61 at admission). The subject was changed to oral diuretics, and observed. An abdominal ultrasound on 03 October a* revealed no acute pathology, and a large inhomogeneous liver and a large smooth spleen, with little fluid remaining in lungs or abdomen. The subject's abdominal girth had reduced to 86 cm. The subject remained afebrile without difficulty breathing. Treatment with dolutegravir was continued throughout the hospitalisation. The event resolved on 04 October a*. The investigator considered that there was no reasonable possibility that the pleural effusion may have been caused by dolutegravir.

Follow up information received on 17 October a* from site via email:

The subject was discharged from hospital on 04 October a* after having programmed the followings: nephrology consultation is planned for 18 October a* and echocardiography is planned for 24 October a*. On 11 October a* a lab retest for creatinine had a value of 2.49 mg/dl.

a*: The year
b*: Following year
n*: 11 years ago
s*: 16 years ago

* 新薬承認情報提供時に置き換え
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Module 2.7.4 Summary of Clinical Safety

Follow-up information received from clinical study team via investigator on 16 November a*:

The above subject, who was hospitalized in October for pleural effusion, complicated by renal insufficiency (which was already present at baseline on day 1, as noted below in the doctor's summary from the week 4 results), had his week 8 lab results return (collected on 10 November). His serum creatinine remains elevated at 223.8 (decreased slightly from week 4 on 14 October). His other lab results remain stable mildly elevated total bilirubin and lipase.

Investigator text:

During preoperative investigations conducted in another Hospital a Chest X-ray was performed. Radiological examination showed a right Pleural effusion. Patient was admitted in our Hospital on the 29th sep. a* -

Medical conditions at the time of the event included atopic dermatitis, chronic renal Failure, heart failure, hypertension and liver cirrhosis. Concomitant medications included etravirine, darunavir, ritonavir and maraviroc.

A second SAE began on 08 January b*, 117 days after the start of dolutegravir. The subject developed grade 3 or severe septicemia due to Streptococcus viridans and grade 3 or severe basal pneumonia. The subject was hospitalised. The subject had presented to the ER on 09 January b* due to diarrhea and hypotension. Chest X-ray and ultrasound scan of the abdomen showed a basal right pneumonia and massive peritoneal effusion. The subject was hospitalized at the nephrology department. Laboratory test results dated 09 January b* included creatine 3.52 mg/dl (normal range 0.5-1.25). On 17 January b*, the subject was transferred to infection diseases department where his diuretic treatment was optimized. The subject was treated with levofloxacin, Piperacillin + tazobactam, frusemide, canrenoate potassium, human albumin and amlodipine. Treatment with dolutegravir was interrupted on 15 January b*. The hypotension and diarrhea resolved on 09 January b*. The subject underwent peritoneal drainage on 25 January b* and ascites resolved on the same day. Septicemia due to streptococcus viridians and basal pneumonia resolved On 27 January b*. Treatment with dolutegravir was re-started on 08 February b*. The investigator considered that there was no reasonable possibility that the septicemia due to streptococcus viridans and basal pneumonia may have been caused by dolutegravir

Follow up information received on 10 January b*:

The subject had been [cautiously] admitted to hospital mainly because of the hypotension related to diarrhea in a subject with creatinine values above the normal range. On 10 January b* the subject's clinical condition was improving and the subject's blood pressure was normal.

\textsuperscript{a*}: The year 
\textsuperscript{b*}: Following year
He stopped ART treatment on 04 December a* and restarted on 14 December a*. On this date, the HIV RNA values were negative, [<40 c/mL] even off therapy.

Follow up information received on 02 February b* via email from site:

The subject, as reported at the study entry had HCV related cirrhosis. The actual start day of his (SAE of *viridans streptococcus*) illness was 08 January b* and 09 January b* was the date of the hospitalization. The presence of fever, cough, and chest pain was not reported by the subject at the admission: abdominal swelling was present when we accepted the subject on 17th January b* (within hospital transfer from nephrology to infectious disease departments). Probably the renal insufficiency worsened due to dehydration, not a hepato-renal syndrome. Blood culture was positive for *Streptococcus Viridans*. The subject received levofloxacin from 12 January b* and piperacillin-tazobactam was added on 17 January b*. The subject got the diagnosis of recurrent atopic skin lesion before entering the trial. It can be considered an AE while the main SAE was being treated. Ascites can be considered as an AE that occurred during the SAE event. 25 January b* was the end date for the ascites event as this was the date of removal of the peritoneal drainage.

Follow-up information received on 08 February b* via query response:

Patient had a history of blood hypertension; the finding of hypotension previously reported was probably imputable to the diarrhoea. Unknown if hypotension treated. Hypotension and diarrhea cause unknown.

The Subject had a third SAE of ascites secondary to chronic cirrhosis which began on 20 February, b*. This also entailed worsening of chronic renal insufficiency, which began on 23 February. Follow-up information received on 23 February b*:

Concomitant ART was stopped on the 15th January b*

On 08 February b*, the subject's viral load was 176,515 copies/mL. Follow up information received on 08 March b* via medical monitor:

The subject's baseline serum creatinine level was 209 umol/L and his screening Child-Pugh score was 6. On 05 March b*, the subject has withdrawn from the study due to noncompliance with HAART. He had been restarted by the PI on all ART on 08 February, b*, but he did not actually take ART (including IP) until he was readmitted to the hospital for the worsening ascites on 23 February. On this date of withdrawal, his creatinine level was 321 (units not specified, grade 3).

Follow up information received on 09 March b* via deletions report:

The SAE of exacerbation of atopic cutaneous lesion was deleted.

Follow up information received on 13 March b* from site via email:
Module 2.7.4 Summary of Clinical Safety

We think that the diagnosis of *S.viridans* septicaemia may reasonably summarize all the events. The septicaemia was considered primarily a pneumonia with sepsis which lead to the other events of diarrhea / hypotension.

Follow-up received on 02 May b* via deletion report:

Concomitant medication ritonavir was deleted by the investigator.

Diagnostics:


Investigator text:

“On the 09th January of b* for diarrhoea and Hypotension patient was admitted in to emergency departement of xxxx Hospital. Chest X Ray and Ultrasound scan of the abdomen showed a basal right pneumonia and massive peritoneal effusion. Patient was to admitted to the Nephrology department of the xxxx Hospital. On the 17th January patient was trasferred to our Infectious diseases department where diuretic treatment was optimized. The patient had a peritoneal drainage performed that was removed on the 25th January b*. Sign and symptoms; diarrhoea, hypotension, ascites, acute renal insufficiency”

Medical conditions at the time of the event included chronic renal failure and liver cirrhosis. Concomitant medications included darunavir (with booster drug ritonavir), maraviroc and etravirine.

On 20 February b*, 160 days after the start of dolutegravir, the subject developed grade 3 or severe ascites secondary to liver cirrhosis. The subject experienced worsening of ascites and lower limbs edema from 20 February b*. The subject was admitted to a day hospital service on 23 February b* and was treated with intravenous diuretics frusemide 20 mg and canrenoate potassium 200 mg. On 23 February b*, the subject developed grade 3 or severe acute kidney failure on chronic kidney disease. The subject was hospitalised on 24 February b*. The subject was treated with red blood cells (for anemia in previous myocardial infarction), frusemide, canrenoate potassium, albumin and ceftriaxone sodium. Treatment with dolutegravir was continued (until 04 March b* when stopped for non-compliance). The events resolved on 08 March b*. The investigator considered that there was no reasonable possibility that the ascites secondary to liver cirrhosis and acute kidney failure on chronic kidney disease may have been caused by dolutegravir.

Follow-up information received on 09 March b* via query response:
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Module 2.7.4 Summary of Clinical Safety

Anaemia was diagnosed on the 25th February b*. Myocardial infarction was diagnosed on the 13th April a* as reported in medical History.

Follow up information received on 13 March b* from site via email:

The second SAE was hepatitis C cirrhosis; the worsening of renal labs was before the reintroduction of iv diuretic therapy and in absence of antiretroviral drugs.

Diagnostics:

February 23, b*: Abdominal ultrasound scan: Increase (compared to a previous US performed on the 08th February b*) of the peritoneal effusion in particular in peri-hepatic and peri-splenic regions.

Follow up information received on 02 May b* via AQR.

During hospitalisation, due to worsening renal function, diuretic therapy was switched from parenteral to oral route of administration. No other therapy was administered.

Investigator text:

“From 20th February b* patient reffered the worsening of ascites and lower limbs edema. On the 23th February b* patient was admitted to our Day Hospital service were was treated with intravenous diuretics (Furosemide 20 mg and Potassium Kanreconate 200 mg). On the 24th February b* the patient was hospitalized in our departement “

Protocol Id: ING112574
Investigator Number: 089452
Subject Number: 001219
Treatment Number: UNKNOWN
Case Id: Z0014977A
Suspect Drugs: Dolutegravir, Etravirine
Serious Events: Pruritus, Rash

This -year-old female subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 14 March a*.

As of 14 March a* the subject had 150 CD4+cells/mm³ and 1218c/mL plasma HIV-1 RNA.

As concomitant ART the subject received tenofovir and maraviroc from prior to Screening until 21 March a*, and etravirine and Kaletra from 22 March a* until 2 April a*.

a*: The year
b*: Following year
Module 2.7.4 Summary of Clinical Safety

On 30 March a*, 16 days after the start of dolutegravir, the subject developed grade 2 or moderate rash on skin and grade 3 or severe itching. The subject was hospitalised. The subject was treated with chlorpheniramine, hydrocortisone sodium succinate, pantoprazole, sodium chloride, prednisone and hydroxyzine hydrochloride. Treatment with dolutegravir (and concomitant ART) was interrupted on 02 April, a*. The events resolved on 10 April a*. The investigator considered that there was a reasonable possibility that the rash on skin and itching may have been caused by dolutegravir and that the events were possibly due to the concomitant antiretroviral medication, etravirine.

Additional information received via medical monitor on 12 April a*:

The subject was discharged from hospital after treatment for seven days with IV solucortef (hydrocortisone), then oral prednisone. ALT was never elevated. Breathing difficulty /airways compromise was not objectively documented. Mild oral odema/dyspnea (grade 1) was reported. The investigator commented subject had been receiving Kaletra in the past, so it is unlikely that the rash may be attributed to this drug. The rash may be due to dolutegravir or etravirine (or both).

Follow up information received on 02 May a* via AQR:

The subject had a history of rash/itching (probable hypersensitivity to darunavir).

Follow up information received on 31 July a*:

As of 06 June, a*, the investigational product (IP and Kaletra only, without etravirine) have been restarted, under close in hospital observation the first 24 hours. The subject continues to do well as of time of reporting. Currently, both dolutegravir and etravirine are suspected to have possibly caused the SAE.

Follow up information received on 10 August a* via medical monitor:

Dolutegravir was restarted without any problems on 6 June a* and the rash has been attributed to etravirine use and not to dolutegravir.

Investigator text:

On 02 Apr a* the patient was visited on our day hospital service due to skin rash and itching occurred on 30/03/a*. During DH valuation was administered to the patient trimeton 10 mg and solu-cortef 500 mg intravenously. Patient referred a symptomatology improvement after administration of drugs and for this reason was discharged from DH service. All antiretroviral therapy was stopped. Today for the persistence of skin rash and itching she was hospitalized to our centre. Moreover mild oral involvement has been described (grade 1) -

Protocol Id: ING112574
Investigator Number: 089456
Subject Number: 001242

a*: The year

* 新薬承認情報提供時に置き換える
This 32-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 12 September a*.

As of 12 September a*, the subject had <20 CD4+ cells/mm³ and 407,487 c/mL plasma HIV-1 RNA.

As concomitant ART the subject received emtricitabine and Kaletra from prior to Screening until 19 September a*, Truvada, saquinavir/ritonavir and maraviroc were then administered from 19 September a* until 26 March b*. Darunavir/ritonavir was commenced 13 April b* after the study withdrawal visit on 12 April b*.

Subject had previous episode of gallbladder stones; an abdomen scan on 28 October e* revealed one gallstone.

By 27 February b* the subject had 40 CD4+ cells/mm³ and 138,562 c/mL HIV-1 RNA.

On 26 March b*, 196 days after the start of dolutegravir, the subject developed grade 3 or severe exacerbation of cholelithiasis. The subject presented to the ER due to a sudden abdominal pain. Ultrasound scan of the abdomen performed on 26 March b* detected gallbladder stone. The subject was hospitalised. Treatment with dolutegravir was discontinued on 26 March b*. The subject underwent surgery and laparoscopic cholecystectomy on 02 April b*. The event resolved on 05 April b*. The investigator considered that there was no reasonable possibility that the exacerbation of cholelithiasis may have been caused by dolutegravir.

Follow-up information received on 13 April b* via query response:

After revising subject's medical history, an abdomen ultrasound scan of 28 OCT e* was identified that reported a single gallbladder stone.

Follow-up information received on 26 April b* via query response:

Subject discontinued IP because adverse event. IP was not restarted because when subject was ready to re-start it was the day of the Withdrawal visit, due to virological failure prior to the onset of the SAE.

Investigator text:

a*: The year
b*: Following year
e*: Last year
Patient presented at the E.R. of another hospital because of sudden abdominal pain; gallbladder stone was detected and patient was hospitalized for clinical monitoring at the Surgical Ward.

Patient underwent surgery and laparoscopic cholecistectomy was performed on 02/APR/b*. Pateint was discharged on 05/APR/b*.

Protocol Id: ING112574  
Investigator Number: 089458  
Subject Number: 001264  
Treatment Number: UNKNOWN, UNKNOWN  
Case Id: Z0014560A, Z0014560B  
Suspect Drugs: Dolutegravir  
Serious Events: Constipation, Parotid gland enlargement

This 31-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir 50 mg twice daily from 24 January a*.

As of 24 January a* the subject had 70 CD4+cells/mm$^3$ and 74,097 c/mL plasma HIV-1 RNA

As concomitant ART the subject received Truvada from prior to Screening, daurinavir/ritonavir and enfuvirtide from prior to Screening until 31 January a* and Kaletra, etravirine and saquinavir from 31 January a*.

By 21 February a* the subject had 130 CD4+ cells/mm$^3$ and 68,375c/mL HIV-1 RNA.

On 07 March a*, 43 days after the start of dolutegravir, the subject developed grade 1 or mild fecal retention. The subject was hospitalised. The subject was treated with blood transfusion and enema. Treatment with dolutegravir was continued. The events resolved on 15 March a*. The investigator considered that there was no reasonable possibility that the fecal retention may have been caused by dolutegravir

During the hospital stay, they noted swelling of the parotid gland. He was to have that biopsied at a later time, but was withdrawn from the study on 01 June, a* due to virological failure before this information was obtained by the site..

Follow up information received from clinical on 07 March a*:

The subject's baseline (24 January a*) hemoglobin level was 100 (units not specified) and by the week 4 visit on 21 February a* it had fallen to 92.

Diagnostic Results:

a*: The year  
b*: Following year
Hemoglobin 07Mar a* 7.2 g/dl (12.2-17)
Hemoglobin 13Mar a* 10.5 g/dl
Hemoglobin 20Mar a* 10.9 g/dl

Investigator Text:

during the last night the patient experienced abdominal and gastric pain. He was then hospitalized in another centre, where they found faecal retention and anemia - Concomitant medications included Truvada, Kaletra, etravirine and saquinavir.

On 08 March a*, 44 days after the start of dolutegravir, the subject developed grade 1 or mild parotid gland swelling. The subject was already hospitalized at that time for treatment of his fecal retention. Biopsy of the parotid gland found some aggregates of typical acinar cells and numerous lymphocytes. No treatment was given as specific diagnosis has not been established. Treatment with dolutegravir was continued. The event resolved on 16 April a*. The investigator considered that there was no reasonable possibility that the parotid gland swelling may have been caused by dolutegravir.

Follow-up information received on 01 June a* via query response:

The subject didn't receive any SAE treatment and at the moment it's not possible to give a specific diagnosis of the event. We will follow up the subject

Investigator text:

during the last hospitalization it was found a swelling of the parotid glands wich is waiting of a biopsy -

Protocol Id: ING112574
Investigator Number: 090940
Subject Number: 001403
Treatment Number: UNKNOWN
Case Id: Z0015862A
Suspect Drugs: Dolutegravir
Serious Events: Ovarian mass

This -year-old female subject was enrolled in a ViiV-sponsored open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day from 13 December .

As of 13 December a*, the subject had <20 CD4+ cells/mm3 and 289,238 c/mL plasma HIV-1 RNA.

a*: The year
By 28 May b*, the CD4+ cell count had increased to 120 cells/mm³ with a decrease in plasma HIV-1 RNA to <40 c/mL.

On 27 May b*, 166 days after the start of dolutegravir, the subject developed grade 1 or mild ovarian mass. The subject was hospitalised. Treatment with dolutegravir was interrupted. The event resolved on 01 June b*. The investigator considered that there was no reasonable possibility that the ovarian mass may have been caused by dolutegravir. The subject had a known elevation of alkaline phosphatase before enrolment into the study, however, the ovarian mass was not identified until after she was enrolled, so it is considered an on study adverse event. Preliminary biopsy results suggested a benign process. She remains on study as of Oct 31, b*.

Follow-up information received on 14 June b* via answered query report:

The subject's investigational product was interrupted on 28 May b* and restarted on 29 May b*.

No relevant risk factors or medical conditions to be reported.

On macroscopic point of view the mass is related with a Kyst and not with a carcinoma nevertheless we are waiting for a pathology examination.

There isn't until now no references related to the concomitant medications provided to the patient during hospitalization. No relevant tests were performed before and during the hospitalization except the lab tests regarding week 24 visit

Investigator Text:

hospitalization due surgical intervention for caracterizing the ovarian mass that the patient had before the initiation of the trial. the patient is in good condition and it will be submitted to the intervention today- 28 may b*. without interruption of the medication until today.

Protocol Id: ING112574
Investigator Number: 090397
Subject Number: 001605
Treatment Number: UNKNOWN
Case Id: Z0015487A
Suspect Drugs: Dolutegravir
Serious Events: Cholecystitis acute

This  ■-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir 50 mg twice daily from 22 March ■. 

b*: Following year
As of 22 March a* the subject had 40 CD4+ cells/mm3 and 76,533 c/mL plasma HIV-1 RNA.

As concomitant ART the subject received lamivudine, maraviroc and darunavir/ritonavir from prior to Screening to 28 March a*. Truvada with tipranavir/ritonavir was then administered from 29 March a*.

Medical conditions included Calcifying chronic pancreatitis.

On 09 May a*, 48 days after the start of dolutegravir, the subject developed grade 3 or severe acute cholecystitis. The subject was hospitalised on 11 May a*, due to prolonged vomiting and fever which started on 09 May a*. A gallbladder ultrasound was performed and revealed suspected gallbladder inflammation. The subject was treated with Augmentin. Treatment with dolutegravir was continued. The event resolved on 16 May a*.

The investigator considered that there was no reasonable possibility that the acute cholecystitis may have been caused by dolutegravir.

Investigator text:

The patient was hospitalized on 11/05/a* due to prolonged vomiting and fever that started on 09/05/a*. After performing several tests, is suspected gallbladder inflammation. The final diagnostic is acute cholecystitis.

Protocol Id: ING112574
Investigator Number: 090818
Subject Number: 001802
Treatment Number: UNKNOWN
Case Id: Z0012793A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia

This hammad-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 17 August a*.

As of 15 August a*, the subject had 50 CD4+ cells/mm³ and 13,226 c/mL plasma HIV-1 RNA.

As concomitant ART the subject received tenofovir and darunavir/ritonavir from 25 August a*.
Medical conditions at the time of the event included human immunodeficiency virus. Concomitant medications included seasonal trivalent influenza vaccine dresden and zolpidem tartrate.

By 11 October a* the subject had 120 CD4+cells/mm$^3$ and $<40$ c/mL HIV-1 RNA.

On 05 November a*, 80 days after the start of dolutegravir, the subject developed grade 3 or severe pneumonia. The subject developed shortness of breath and fever. The subject was hospitalised on 06 November a*. Sputum culture detected Gram Positive Cocci in chains. Chest x-ray showed right lower base infiltrate; CT of chest showed right lower lobe pneumonia and left base atelectatic changes. The subject's body temperature was measured on 07 November a* at 100.1 F. The subject was treated with salbutamol sulphate, azithromycin, ceftriaxone and paracetamol. The subject interrupted treatment with dolutegravir on his own from 07 to 10 November a*. The event resolved on 10 November a*. The subject was discharged on 11 November a*. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by dolutegravir.

As of 11 November a*, the subject had 150 CD4+cells/mm$^3$ and 2009 c/mL HIV-1 RNA.

Follow-up information received on 16 November a* via query response:

CBC was done but the result was not clinically relevant.

To answer the query about CONART, the patient did not take all his HIV meds while hospitalized; hence, they are not included in the "Relevant Medication".

Investigator text:

We just learned today when the patient turned up for his study visit that he was admitted from 06Nov a* to 11Nov a* for pneumonia. S/Sx started on the 05Nov a* when the pt developed shortness of breath and fever. While hospitalized, he did not tell the hosp staff, including his attending physician that he has HIV, hence, the PI was not consulted for his admission. The pt did not call the site as well. The pt stopped the IP on his own from the 7th-10th. The pt was counselled intensely on the importance of compliance to study procedures and compliance to his HIV drugs. -

9.6.6.2. Cases Reported Between 19 June a* to 26 October a*

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the safety data lock point for both the ING112574 Week 24 CSR and the ISO outputs, through to the final 26 October a* safety data lock point for the ISS, and includes all initial reports and follow up information received by the company through 26 October a*. The data included here are not represented in the clinical study report a*: The year
This 54-year-old male subject was enrolled in a ViiV-sponsored open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day from 05 January 2019.

As of 04 January 2019, the subject had 180 CD4+ cells/mm\(^3\) and 9761 c/mL plasma HIV-1 RNA.

The subject's past medical history included status post myocardial infarction and tobacco dependence. Medical conditions at the time of the event included anxiety, arteriosclerotic heart disease, cardiomyopathy, hyperlipidemia, hypertension, hypoperfusion and shortness of breathing with exertion. Concomitant medications included alprazolam, acyclovir, diazepam and Bactrim DS.

Concomitant ART included etravirine and darunavir/ritonavir from prior to Screening to 09 January 2019. From 10 January 2019, the subject received Truvada, didanosine and tipranavir/ritonavir.

By 10 August 2019, the subject had 173 CD4+ cells/mm\(^3\) and <40 c/mL plasma HIV-1 RNA.

On 01 September 2019, 240 days after the start of dolutegravir, the subject developed grade 2 or moderate chest pain. The subject was hospitalised. The subject was treated with aspirin, nitroglycerine, carvedilol and atorvastatin calcium. Treatment with dolutegravir was continued. The event resolved on 02 September 2019. The investigator considered that there was no reasonable possibility that the chest pain may have been caused by dolutegravir.

Investigator Text:

Subject reported to ER on 01SEP 2019 with complaints of chest pain and dizziness. and weakness as well as shortness of breathe and nausea. pain scale was 6/10. Tests were performed and then he was admitted for observation. Discharged on 02SEP 2019. More to follow when it becomes available. Discharge summary not yet available. At time
of discharge symptoms had fully resolved. He stated that he experiences episodes of anxiety at least twice a week characterized by diaphoreses and dull chest pain lasting for about 10 minutes/episode. Was discharged on .25 mg of Xanax BID prn for anxiety for 1 week until he sees someone here in clinic for follow-up. He is also to schedule a Muga Scan ASAP. He saw Dr. [deleted] for follow-up last week in clinic and the Muga has been scheduled. Updates will be provided as they become available. 10/26/a* patient has improved since hospitalization. He has followed up with his cardiologists on a regular basis. He is adherent to all treatments. -

Protocol Id: ING112574
Investigator Number: 086897
Subject Number: 000521
Treatment Number: UNKNOWN
Case Id: Z0017386A
Suspect Drugs: Dolutegravir
Serious Events: Syncope

This male subject was enrolled in a ViiV-sponsored, open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir 50 mg twice daily from 01 March. As of 01 March a*, the subject had 148 CD4+ cells/mm$^3$ and 6196 c/mL plasma HIV-1 RNA.

The subject's past medical history included possible dehydration due to food poisoning on 20 October a*.

Concomitant ART included Truvada from prior to Screening and darunavir/ritonavir started on 08 March a*.

By 11 October a*, the subject had 199 CD4+ cells/mm$^3$ and 90 c/mL plasma HIV-1 RNA.

On 20 October a*, 233 days after the start of dolutegravir, the subject developed grade 2 or moderate syncope. He presented to the emergency department and he was hospitalised. He stated that while he was sitting he started to see black spots, was feeling light-headed, dizzy and nauseous and while trying to walk to the door he "passed out" and fell on the floor. The subject reported that he hit his head and was "out" for a few minutes, woke up with blood coming from his nose and he also experienced fecal incontinence. The subject denied post-ictal state. The subject was treated with intravenous fluid(s). The syncopal episode was most likely to be secondary to vasovagal. Treatment with dolutegravir was continued. The event resolved on 20 October a*.

The investigator considered that there was a reasonable possibility that the syncope may have been caused by dolutegravir.

a*: The year
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Investigator text:

pt. presented to emergency dept. with history of recent syncopal event. pt. states he had dinner out a few hours before the event. pt. states that while sitting he started seeing black spots, feeling light-headed, dizzy and nauseous. while attempting to walk to the door, he "passed out" - falling on the floor. He stated he hit his head, was "out" for a few minutes, woke up with blood coming form his nose and fecal incontinence. pt. denies post ictal state. syncopal episode was most likely secondary to vasovagal. pt. is currently asymptomatic. this event occurred on 10/20/a*. Pt. informed study staff on 10/22/a*.

Protocol Id: ING112574
Investigator Number: 086853
Subject Number: 000561
Treatment Number: UNKNOWN
Case Id: Z0016649A
Suspect Drugs: Dolutegravir
Serious Events: Haematochezia, Rectal haemorrhage, Rectal haemorrhage

This 40-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 21 June .

As of 21 June a*, the subject had 413 CD4+ cells/mm³ and 721c/mL plasma HIV-1 RNA.

The subject's past medical history included angiodysplasia of the colon. Concomitant medications included zolpidem tartrate, Hydrocodone APAP, duloxetine, potassium chloride, pantoprazole, bisacodyl, Nulytely, frusemide, iopamidol, midazolam hydrochloride, fentanyl, red blood cells, lignocaine hydrochloride and Heparin/saline.

Concomitant ART included Truvada from prior to Screening and darunavir/ritonavir from 28 January a*.

As of 22 May b*, the subject had 302 CD4+ cells/mm³ and <40 c/mL plasma HIV-1 RNA.

On 11 August b*, 417 days after the start of dolutegravir, the subject developed grade 2 or moderate hematochezia with rectal bleeding. The subject presented at the ER on 12 August b* with complaint of rectal bleeding, and was hospitalised. Haemoglobin tested on 12 August b* showed result of 6.8 g/dl (normal range 13.5-17.5). The subject was transfused with 3 units of packed red blood cells. Colonoscopy showed no bleeding. The subject underwent angiogram selection and vascular embolization on 13 August b*. The subject is scheduled for a nuclear medicine RBC scan. Treatment with

a*: The year
b*: Following year
dolutegravir was continued. The event resolved on 16 August b*. The investigator considered that there was no reasonable possibility that the hematochezia with rectal bleeding may have been caused by dolutegravir.

Diagnostics:

The subject went to the ER on 08-12-b* with complaint of rectal bleeding. The subject called the research office on 08-13-b* and gave the coordinator all information up until today. His Hgb was 6.8, the subject had a blood transfusion with 3 units of PRBC's and a colonoscopy that showed no bleeding. The subject is scheduled for a nuclear medicine RBC scan in the future. The patient had an angiogram selection and a vascular embolization done on 08-13-b*

Follow-up information received on 29 August b* via query response:

The subject was found to have an angiodysplastic area of the jejunum/duodenum that caused the bleeding.

Investigator text:

THE SUBJECT WENT TO THE ER ON 08-12-b* WITH COMPLAINT OF RECTAL BLEEDING. THE SUBJECT CALLED THE RESEARCH OFFICE ON 08-13-b* AND GAVE THE COORDINATOR ALL INFORMATION UP UNTIL TODAY. HIS Hgb WAS 6.8, THE SUBJECT HAD A BLOOD TRANSFUSION WITH 3 UNITS OF PRBC's AND A COLONOSCOPY THAT SHOWED NO BLEEDING. THE SUBJECT IS SCHEDULED FOR A NUCLEAR MEDICINE RBC SCAN IN THE FUTURE. The patient had an Angiogram Selection and an Vascular Embolization done on 08-13-b*. -

Protocol Id: ING112574
Investigator Number: 086853
Subject Number: 000567
Treatment Number: UNKNOWN
Case Id: Z0016604A
Suspect Drugs: Dolutegravir
Serious Events: Atrial flutter

This [blank] year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice per day from 08 July a*. The subject had 350 CD4+ cells/mm³ and 1662 c/mL plasma HIV-1 RNA.

a*: The year
b*: Following year
The subject's past medical history included heart attack and triple bypass. Medical conditions at the time of the event included coronary artery atherosclerosis.

Concomitant ART included Truvada from prior to Screening, darunavir/ritonavir from prior to Screening (with interruption between 14 July a* and 28 July a*) and etravirine from 15 July a*.

By 08 Jun b*, the subject had 270 CD4+ cells/mm³ and <40 c/mL plasma HIV-1 RNA.

On 02 August b*, 391 days after the start of dolutegravir, the subject developed grade 1 or mild atrial flutter. The subject presented at the ER with complaints of right-sided abdominal pain along with a productive cough. Heart rate was rapid, irregular and lasted for 4 hours. He also was complaining of difficulty urinating and felt constipated. The subject denied chest pain. The subject was hospitalised. Laboratory test results dated 02 August b* included BUN 22 mg/dl (NR 8-21), creatinine 1.5 mg/dl (NR 0.75-1.2) and WBC count 12.7 th/ul (NR 4-10). The subject was treated with diltiazem hydrochloride, metoprolol, enoxaparin, digoxin and amiodarone. Treatment with dolutegravir was continued. The event resolved on 03 August b*. The investigator considered that there was no reasonable possibility that the atrial flutter may have been caused by dolutegravir.

Diagnostics:

CARDIAC ENZYMES ARE UNREMARKABLE; CHEST X-RAY SHOWS NO OBVIOUS INFILTRATES OR EFFUSIONS. EKG SHOWS ATRIAL FLUTTER WITH 2:1 AV CONDUCTION AT 140 BEATS PER MINUTE.

Investigator text:

SUBJECT WENT INTO THE ER WITH COMPLAINTS OF CONTINUOUS COUGH, LOTS OF PHLEGM. HEART RATE WAS RAPID, IRREGULAR AND LASTED FOR 4 HOURS. HE ALSO WAS COMPLAINING OF DIFFICULTY URINATING AND FELT CONSTIPATED. THE SUBJECT DENIED CHEST PAIN. THE SUBJECT ALSO WENT TO THE ER WITH RIGHT-SIDED ABDOMINAL PAIN ALONG WITH A PRODUCTIVE COUGH.

Protocol Id: ING112574
Investigator Number: 090767
Subject Number: 001090
Treatment Number: UNKNOWN, UNKNOWN
Case Id: Z0015882B, Z0015882C
Suspect Drugs: Dolutegravir
Serious Events: Squamous cell carcinoma, Squamous cell carcinoma

a*: The year
b*: Following year
This 34-year-old male subject was enrolled in a ViiV-sponsored, open-label study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1-infected adult subjects with treatment failure on an integrase inhibitor containing regimen. The subject received oral dolutegravir at 50 mg twice daily from 05 March.*

As of 05 March*, the subject had 40 CD4+ cells/mm³ and 293,311 c/mL plasma HIV-1 RNA.

Concomitant ART included Kivexa from prior to Screening to 13 March*, darunavir/ritonavir from prior to Screening to 28 September*, Truvada from 13 March*, maraviroc from 13 March* and tipranavir/ritonavir from 13 March*.

As of 01 June*, the subject had 60 CD4+ cells/mm³ and 341,852 c/mL plasma HIV-1 RNA.

On 12 June*, 99 days after the start of dolutegravir, the subject developed grade 3 or severe lip epidermoid carcinoma. The subject was confirmed to have no signs and symptoms associated with the event. The event was clinically significant (or requiring intervention). Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the lip epidermoid carcinoma may have been caused by dolutegravir.

Follow-up information received on 16 October* via query response:

Epidermoid carcinoma ongoing

Investigator text:

new apparition of epidermoid carcinoma

As of 02 July*, the subject had 46 CD4+ cells/mm³ and 201,215 c/mL plasma HIV-1 RNA.

On 10 August*, 158 days after the start of dolutegravir, the subject developed grade 3 or severe epidermoid carcinoma of hand. The event was clinically significant (or requiring intervention). Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the epidermoid carcinoma of hand may have been caused by dolutegravir.

Follow-up information received on 19 September* via query response:

No signs/symptoms.

Not yet concertation with many physicians (oncologist, dermatologist and infectiologist) no concomitant treatment actually but I notified to the Ecrf the ARV therapy.
The subject was withdrawn from the study on 2 October a* for protocol defined virological failure.

Follow-up information received on 16 October a* via query response:

Date 16 Oct a*: epidermoid carcinoma ongoing. Epidermoid carcinoma ongoing diagnostics performed by oncologist during his consultation. No treatment; but surgery programmed to the end of this year.

Investigator text:

new apparition of epidermoid carcinoma

9.6.7. ING114915 SAE and Pregnancy Case Narratives

9.6.7.1. Cases Reported up to 21 May

The narratives included in this section correspond to the SAEs and Pregnancy cases included in the limited SAS safety outputs that were produced to describe the safety data up to the 21 May data lock point for the ISS. These SAEs and Pregnancy cases were also included in the ING114915 study synopsis, which is located in m5.3.5.4. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.

Protocol Id: ING114915
Investigator Number: 94677
Subject Number: 467702
Treatment Number: 
Case Id: B0811228A
Suspect Drugs: Darunavir plus Ritonavir
Serious Events: Acute sinusitis

This 60-year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received darunavir plus ritonavir from 08 February.

On 19 June a*, 132 days after the start of darunavir and ritonavir, the subject was hospitalised to rule out grade 1 or mild febrile neutropenia. Treatment with darunavir and ritonavir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the febrile neutropenia may have been caused by darunavir and ritonavir.

a*: The year
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Investigator Text:

Subject admitted to hospital for possible neutropenic fever. X-ray of chest was clear CAT scan showed sinusitis. Giving IV antibiotics (unknown at this time) and possibly Neupogen.

Follow up information received on 05 July a*:

The event term was updated from rule out neutropenic fever to chronic sinusitis. The intensity of the event was changed from grade 1 to grade 2. The event improved on an unspecified date.

Investigator text:

Had surgical treatment on June 25 without any complications, was discharged on June 26th without any medical problems. Put on Augmentin. Was given neupogen. Neutropenia resolved. White count back to normal. Was put on lisinopril.

Follow-up information received 09 July a*:

The subject was diagnosed with exacerbation of chronic sinusitis. The subject also experienced deviated nasal septum, chronic bilateral maxillary sinusitis with retained purulent secretions, and chronic bilateral ethmoid and sphenoid sinusitis with polyps. The subject was treated with hydrocodone bitartrate and acetaminophen (Norco) and amoxicillin/clavulanate potassium (Augmentin). The event was resolved on 26 June a*.

Follow-up information received 10 July a*:

The investigator confirmed that neutropenia was not a separate serious adverse event.

Follow-up information received 26 and 30 July a*:

SAE term was updated to Acute on chronic sinusitis. The subject was treated with oral Norco, oral Augmentin, IV Vancomycin, injection Neupogen, IV normal saline, injection Nystatin and ophthalmic drops Cosopt.

Investigator text:

Subject admitted to hospital for possible neutropenic fever. X-ray of chest was clear. CAT scan showed sinusitis. Giving IV Vancomycin. Had surgical treatment on June 25 without any complications, and was discharged on June 26th without any medical problems. Put on Augmentin. Was given Neupogen. Neutropenia resolved. White count back to normal. Was put on Lisinopril.

Follow-up information received on 02 October a*:

a*: The year
The subject was treated with Norco, Augmentin (oral), Vancomycin, Neupogen, normal saline, Nystatin, Cosopt and Tylenol.

Protocol Id: ING114915
Investigator Number: 
Subject Number: 475905
Treatment Number: 
Case Id: B0790756A
Suspect Drugs: Darunavir plus Ritonavir
Serious Events: Bronchitis

This 51-year-old male subject was enrolled in a ViiV-sponsored open-label Phase IIIB, randomized study of the safety and efficacy of GSK1349572 to darunavir/ritonavir in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral darunavir plus ritonavir at 800/100 mg per day from 05 March.

On 13 March a*, eight days after the start of darunavir and ritonavir, the subject developed grade 3 or severe bronchitis. The subject was hospitalised. Treatment with darunavir and ritonavir was continued. The event resolved on 15 March a*. The investigator considered that there was no reasonable possibility that the bronchitis may have been caused by darunavir and ritonavir.

Investigator Text:

Presented 12Mar a* with complaints of nausea, diarrhoea, abdominal pain x3 days. Noted to have fever and shortness of breath. Administered IV fluids and admitted for observation.

Event term changed to diagnosis. Discharged 15Mar a*. Symptom resolution 20Mar a*. Treated with antibiotics. Not related as others in subject household had been ill with same/similar symptoms.

Follow-up information received on 05 April a*:

The onset of event was updated to 09 March a*, four days after the start of darunavir and ritonavir. It was reported that at admission CBC was normal except for white blood cell: 4.1 thousand/mm3, lymph abs 0.9 thousand/mm3, 21%. It was confirmed that cultures were negative.

Additional information received 10 April a*:

Treatment medications included levofloxacin, ketorolac (Toradol), sulfamethoxazole-trimethoprim, acetaminophen oxycodone, acetaminophen, albuterol-iratropium, bisacodyl, calcium carbonate, clonidine, dextromethorphan/guaifenesin, diphenhydramine, morphine, ondansetron, and zolpidem.

Follow up information received on 01 May a*:

a*: The year
Relevant assessments included a chest x-ray on 12 March a* which found no radiographic evidence of acute cardiopulmonary process.

Follow-up information received on 10 October a*:

The subject was withdrawn from the study on 02 October a*. The subject was lost to follow-up as the subject was incarcerated.

This 35-year-old female subject was enrolled in an open-label ViiV-sponsored study a GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 07 February a*.

On 31 March a*, 53 days after the start of dolutegravir, the subject developed grade 2 or moderate hematemesis. The subject was hospitalised. Treatment with dolutegravir was continued. The event resolved on 31 March a*. The investigator considered that there was no reasonable possibility that the hematemesis may have been caused by dolutegravir.

Investigator Text:

Subject had an episode of hematemesis that lasted for 10 minutes on 31Mar a*. Subject was admitted to the hospital and released on 02Apr a* all records have been requested.

Follow-up information received 08 June a*:

The subject had a chest x-ray, ultrasound of gallbladder, and an EKG on 01 April a*, and all tests were normal. The subject had no relevant medical history or risk factors and received no treatment for this event. The event resolved on 02 April a*.

Follow-up information received 15 June a*:

On admission it was noted that the subject "ate rice and beans yesterday and immediately had nausea and vomited frank blood. She states that this has never happened to her previously. She sometimes has nausea after taking her HIV medication. She denies nausea and vomiting when she eats. She complains of vague epigastric discomfort, but no
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servere pain. She has gas-like pain to he lower abdomen. She has chronic diarrhoea secondary to her medications. She denies melena and frank rectal bleeding. She has chronic pain to her back, hands, and feet secondary to arthritis and takes Naprosyn for pain. She denies dysphagia and odynophagia." Differential diagnosis included Mallory-Weiss tear and peptic ulcer disease. At the time of reporting no endoscopy had been performed.

Follow-up information received 23 October a*:

The subject denied the differential diagnoses of Mallory-Weiss tear and peptic ulcer disease, and did not follow-up with GI.

Protocol Id: ING114915
Investigator Number:
Subject Number: 476908
Treatment Number:
Case Id: B0802853A
Suspect Drugs: Darunavir, Ritonavir
Serious Events: Herpes zoster disseminated

This 4-year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject was in the comparator arm and received darunavir 800 mg from 14 February and oral ritonavir 100 mg from 14 February a*.

Concomitant medications included perphenazine, fexofenadine hydrochloride and gabapentin.

On 10 May a*, 86 days after the start of darunavir and ritonavir, the subject developed grade 3 or severe disseminated shingles. The subject was hospitalised. Treatment with darunavir and ritonavir was continued. Treatment drugs included valaciclovir and oxycodone. The event resolved on 14 May a*. The investigator considered that there was no reasonable possibility that the disseminated shingles may have been caused by darunavir and ritonavir.

Investigator text:

SUBJECT WENT TO SITE'S ER ON 05 MAY a* W. C/O LEFT LOWER BACK PAIN X I WEEK (SUBJECT CONCERNED AS PAST MEDICAL HX INCLUDES RIGHT NEPHRECTOMY). DX W. NEUROPATHY AND D/C'D W. GABAPENTIN. 08 MAY a* PRESENTED FOR STUDY VISIT WK 12 & DX W. SHINGLES L

a*: The year
INNERASPECT OF THIGH AND LOWER BACK. May a* LESIONS SPREAD TO HEAD AND GENITALS. HOSPITALIZED DX DISS. SHINGLES

Follow-up information received on 22 May a*:

Concomitant medication also included fluticasone propionate (Flonase) for congestion due to allergy.

Follow-up information received on 23 May a*:

Medical history included chicken pox. The subject did not receive the varicella vaccination. Concomitant medications included labetalol, heparin and albuterol inhaler. The subject was also treated with diphenhydramine, Tylenol and Sarna cream. No relevant diagnostic tests were performed.

Protocol Id: ING114915
Investigator Number: 94773
Subject Number: 477302
Treatment Number: 
Case Id: B0786983A
Suspect Drugs: Dolutegravir
Serious Events: Hodgkin's disease

This male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 28 December .

On 16 February b*, 50 days after the start of dolutegravir, the subject developed grade 3 or severe anaemia and grade 3 or severe dehydration. The subject was hospitalised. Treatment with dolutegravir was continued. The events were unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the anaemia and dehydration may have been caused by dolutegravir.

Follow-up information received 05 March b*:

The final diagnosis was changed to Hodgkin's Lymphoma. Test results on 23 February b* included sodium 125 meq/l (normal range 136 - 145), albumin 2.4 g/dl (normal range 3.4 - 5.0), AST 94 u/l (normal range 15 - 37), haemoglobin 8.7 g/dl (normal range 13.5 - 18.0), haematocrit 25.7% (normal range 40.0 - 52.0), lymphocytes 14% (normal range 20 - 45), monocytes 16% (normal range 2 - 9), haptoglobin less than 1 mg/dl (normal range 40 - 240), iron 23 mcg/dl (normal range 65 - 175), and ferritin greater than 1650 ng/ml (normal range 22 - 322). The subject was treated with ondansetron,
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acetaminophen+hydrocodone (Norco), morphine, ceftriaxone, sodium chloride, meropenem (Merrem), pantoprazole (Protonix), potassium bicarbonate, and enoxaparin.

Investigator Text:

FEVER, N/V STARTED ON 19FEB b*. NO BM SINCE 15FEB b*. SEEN ON 20FEB b* FOR WEEK 8 VISIT. NRTI CHANGED TO TRUVADA D/T RECURRENT CONSTIPATION. RETURNED ON 23FEB b* WITH CONFIRMED FEVER, N/V.

HAD BM MOSTLY BLOOD, LITTLE STOOL. C/O LOWER ABDOMINAL PAIN. ADMITTED TO HOSPITAL FOR OBSERVATION AND CT. HGB DECREASED FROM 10.8G/DL ON 20FEB b* TO 8.7G/DL ON 23FEB b* AT ADMISSION TO HOSPITAL.

Follow-up received on 23 April b*:

Subject was also treated with ferrous sulphate, Vancomycin, Zithromax, Ethambutol, normal saline, Versed, Fentanyl, Propofol, Neosynephrine, Ancef, Lovonov, Solu-cortef, Zofran, Decadron, Benadryl, Demerol, Bleomycin sulphate, Doxorubicin, Dacarbazine and Vinblastine. Treatment with dolutegravir was discontinued permanently and the subject was withdrawn from the study. The event improved on an unspecified date.

Follow-up information received 25 April b*:

The event onset date was updated to 09 January b*; event resolved on 08 March b*. Dolutegravir was discontinued on 20 March b*.

Investigator text:

HOSPITAL ADMISSION 23FEB b* - 09MAR b*. ADMITTED INITIALLY FEVER AND GI COMPLAINTS; CT ABDOMEN AND PELVIS, KUB, EGD AND COLONOSCOPY SHOWED NO CLEAR ETIOLOGY FOR ABD COMPLAINTS AND FEVER.

WORK-UP FOR INFECTIOUS ETIOLOGY, TREATED WITH IV ANTIBIOTICS AND POSSIBLE MAC. BONE MARROW BIOPSY NORMAL. LYMPH NODES BIOPSY SHOWED HODGKIN'S LYMPHOMA, RECEIVED FIRST ABVD CHEMO. DISCAHGED IN GOOD CONDITION.

Follow up information received on 24 May b*:

The haemorrhoids, abdominal and pelvic lymphadenopathy and the hepatosplenomegaly were symptoms leading to the final diagnosis of hodgkin's lymphoma. Treatment with dolutegravir was continued during the SAE.

Follow-up information received 29 May b*:

b*: Following year
The event was recovering / resolving at the time of reporting.

Protocol Id: ING114915
Investigator Number: 
Subject Number: 484508
Treatment Number: 
Case Id: B0799254A
Suspect Drugs: Darunavir, Ritonavir
Serious Events: Pneumonia bacterial

This 68-year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily from 20 March.

The subject's past medical history included bacterial pneumonitis.

On 25 April, 36 days after the start of investigational product, the subject developed grade 3 bacterial pneumonia. The subject was hospitalised. Treatment with investigational product was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the bacterial pneumonia may have been caused by investigational product.

Follow-up information received on 07 May:

The subject underwent a chest X-ray which showed dyspneal left lung basis pneumonia. The event resolved on 30 April.

Follow-up information received 14 May:

The subject was treated with Augmentin.

Follow-up information received 25 May:

Relevant diagnostics included gasometry: which showed hypoxia and hypocapnia.

Follow-up information received on 30 May:

Study drugs darunavir and ritonavir were interrupted.

Follow up information received on 08 June:

Concomitant medications included Truvada.
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Module 2.7.4 Summary of Clinical Safety

Investigator text:

Augmentin (antimicrobial). Truvada before SAE and Truvada after 25 May.

Follow-up information received 20 June a*:

Medical history included pulmonary pneumocystosis. The subject was also reported as drinking one bottle of wine a day, and smoking 45 packs/year. Conclusion of translated hospital discharge letter noted "acute lobar lung disease of the left lower lobe, developing favourable under treatment with Augmentin and respiratory physiotherapy. Two nodules in the left lower lobe diagnosed by chance on a chest scan, as part of pre-therapeutic analysis within the antiretroviral treatment protocol, in an active smoke."

Protocol Id: ING114915
Investigator Number: 94847
Subject Number: 484704
Treatment Number: 
Case Id: B0814691A
Suspect Drugs: Dolutegravir
Serious Events:

This 24-year-old female subject was enrolled in a ViiV-sponsored open-label study study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir from 28 March 2017.

Concomitant medications included Truvada and dolirhume.

Approximately 12 weeks after the start of dolutegravir, the subject was found to be pregnant. Date of last menstrual period and estimated date of delivery were not provided at the time of reporting, though the subject was reported as being at five weeks gestation. Treatment with dolutegravir was discontinued. At the time of reporting the outcome of the pregnancy was unknown.

Follow-up information received on 28 August a*:

The subject's date of last menstrual period was reported to be 24 May a*, her estimated date of delivery was 27 February b*. The subject was using condoms as a method of contraception. Relevant laboratory tests and procedures included HCG positive on 21 June a*. Previous pregnancies included one pre-term pregnancy which resulted in a spontaneous abortion.

Follow-up information received 26 October a*:

a*: The year
b*: Following year
Treatment with dolutegravir was stopped on 29 June a*

Protocol Id: ING114915  
Investigator Number: 094847  
Subject Number: 484706  
Treatment Number:  
Case Id: B0806915A  
Suspect Drugs: Dolutegravir  
Serious Events: Congestive cardiomyopathy

This 28-year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects.

The subject received oral dolutegravir at 50 mg per day from 04 April a*. On 22 April a*, 18 days after the start of dolutegravir, the subject developed grade 3 or severe hospitalization for dilated cardiomyopathy. The subject was hospitalised. The subject received Triatec and Cardensiel as corrective therapy for the event. Treatment with dolutegravir was continued. The event resolved on 25 April a*. The investigator considered that there was no reasonable possibility that the hospitalization for dilated cardiomyopathy may have been caused by dolutegravir.

Follow up information received on 08 + 11 June a*:

The event term was changed from hospitalization for dilated cardiomyopathy to dilated cardiomyopathy. The event was unresolved at the time of reporting. The intensity of the event was changed from grade 3 to grade 2.

Investigator text:

No ethanol abuse. No smoking, no cardiovascular factor. After has atypical chest pain the patient underwent a cardiac ultrasound, it was found dilated cardiomyopathy with a dysfunction ventricular left.

Follow up information received on 12 June a*:

Investigator text:

Not HIV related. ECG Correct.

Follow up information received on 13 July a*:

The subject had no history of any viral antibodies.

a*: The year
Concomitant medications included tenofovir + emtricitabine.

Follow-up information received on 18 July a*:

The subject of Cameroonian descent, does not have cardiovascular risk factors, in particular he does not smoke. His past medical history included haemorrhoidectomy and also a positive HIV serostatus since p*. With regard to his virological status, his test results showed a CD4 count of 488/mm3 and a viral load of 22,000/ml prior to treatment.

The subject was hospitalized from 22 to 25 April a*. Following an episode of atypical chest pain, transthoracic echocardiography was performed, which found signs of dilated cardiomyopathy with left ventricular dysfunction of around 40-45%. The subject described a NYHA stage II dyspnoea without chest pain or syncope. The subject was therefore referred to CCN for evaluation. His current treatment consists of Truvada 1 tablet per day and dolutegravir as part of the study.

The clinical examination showed an arterial pressure of 136/90 mmHg, a heart rate of 70 bpm and an oxygen saturation of 100% on room air. Regular heart sounds, without murmurs or rubs. No signs of either left or right ventricular failure. Peripheral pulses were easily palpable. The ECG showed a regular sinus rhythm with incomplete left bundle branch block and a negative T-wave in the lateral leads. The chest X-ray was normal.

Laboratory results: creatinine 115 umol/l, blood electrolytes normal, AST and ALT normal, troponin normal, BNP 95 pg/ml, total cholesterol 1.74 g/l, HDL cholesterol 0.52 g/l, LDL cholesterol 1.11 g/dl, triglycerides 0.56 g/dl, haemoglobin 13.3 g/dl, MCV normal, WBC 3200/mm3, lymphocytes 2042/ml, haemostasis normal, prothrombin time and aPTT normal, fibrinogen 6.38g/l.

Transthoracic echocardiography found: the left ventricle (LV) is slight dilated (indexed LV end-diastolic diameter = 33mm/m2) and globally hypokinetic with an EF estimated at 41% using the biplane method. Numerous trabeculations (which could suggest non-compaction but not all the usual criteria are present). Filling pressures not elevated; systolic pulmonary artery pressure normal.

Work-up for the dilated cardiomyopathy consisted of: coronary angiography - normal. Heart MR: LVEF 31%, global left ventricular hypokinesia, delayed myocardial enhancement suggesting either sequelae of myocarditis, or fibrosis as a manifestation of an advanced stage of the subject's dilated cardiomyopathy. Holter ECG: pending. Investigation of sleep apnoea: no significant sleep apnoea syndrome, no need for any devices.

Treatment was initiated with an ACE inhibitor and a beta-blocker. The subject has been referred to CCN for treatment optimisation and exercise rehabilitation. Treatment on discharge consisted of Triatec 2.5, 1 tablet in the morning and Cardensiel 1.25, 1 tablet in the morning.

a*: The year
p*: 13 years ago
In an exercise stress test performed on admission to cardiac rehabilitation, the subject reached 76% of his predicted maximum heart rate, during the 120-Watt stage, with no chest pains or significant repolarisation changes. Continuous ECG monitoring showed quite a few ventricular extrasystoles, sometimes grouped. His blood pressure profile increased in a normal way. He had a peak VO2 of 19.3 ml/kg/min which was 68% of the predicted value, with a ventilatory threshold of 12.7 ml/kg/min, corresponding to a heart rate of 99bpm.

Follow-up information received on 20 July a*:

The event resolved with sequelae on 25 April a*. The dilated cardiomyopathy was considered to have viral etiology. The event had no relation with HIV infection.

Protocol Id: ING114915
Investigator Number: 485002
Subject Number: 485002
Treatment Number: B0816391A
Case Id: ING114915
Suspect Drugs: Dolutegravir
Serious Events: Pyelonephritis

This 3-years old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 14 March 2023.

The subject's past medical history included gastrointestinal disorder. Medical conditions at the time of the event included cardiovascular disorder, infection, insomnia, kidney disorder and skin disorder.

On 06 July a*, 114 days after the start of dolutegravir, the subject developed grade 3 or severe pyelonephritis. The subject was hospitalised. Treatment with dolutegravir was continued. The subject was treated with meropenem. The event resolved on 17 July a*. The investigator considered that there was no reasonable possibility that the pyelonephritis may have been caused by dolutegravir.

Investigator Text:

At noon of 05Jul a* patient started to feel unwell, developed high fevers and flank pain. Was admitted to the hospital in the evening of 05Jul a* for pyelonephritis and immediate antibiotics were initiated. Patient defervesced 09Jul a*.
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Module 2.7.4 Summary of Clinical Safety

Update 18.08. a* Patient feeling well, discharged from hospital. No interruption of study medication.

Follow up information received on the 24 July a*:

It was reported that there were no documented imaging tests available. However, the most likely reason for the pyelonephritis was active anal intercourse without a condom, which is a typical risk factor for urinary tract infection in men.

Follow-up information received on 31 July a*:

Investigator text: At noon of 05Jul a* patient started to feel unwell, developed high fevers and flank pain. Was admitted to the hospital on 06Jul a* for pyelonephritis and immediate antibiotics were initiated. On admission leukuria, urine culture 10E6 E. Cloacae. Leuko 15.400/UL, CRP 35 MG/L. Patient quickly defervesed on abx. 18.08. a* patient feeling well, discharged from hospital.

Follow up information received on 08 August a*:

The onset date of the event was updated to 05 July a*. The resolution date was confirmed as 17 July a*. Normal ranges provided for the leukocytes and CRP.

Follow-up information received 16 August a*:

The subject was treated with ciprofloxacin, paracetamol, jonosteril, and novaminsulfon.

Protocol Id: ING114915
Investigator Number: 129
Subject Number: 486003
Treatment Number:
Case Id: B080689A
Suspect Drugs: Abacavir sulfate + lamivudine, Darunavir plus Ritonavir
Serious Events: Drug hypersensitivity

This 21-year-old female subject was enrolled in a ViiV-sponsored open-label study of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral Darunavir plus Ritonavir 800 mg/100 mg once daily from 17 May a* and abacavir sulphate+lamivudine-hiv (Kivexa) from 17 May a*.

On 27 May a*, ten days after the start of investigational product, the subject developed grade 2 or moderate possible abacavir hypersensitivity reaction. The event was clinically significant (or requiring intervention). Treatment with investigational drug and unspecified was discontinued and the subject was withdrawn from the study. The subject
was treated with chloropyramine. The event improved on an unspecified date. The investigator considered that there was a reasonable possibility that the possible abacavir hypersensitivity reaction may have been caused by Kivexa and investigational drug.

Follow up information received on 08 June a*:

The only symptom of the suspected abacavir hypersensitivity was maculopapular rash.

Follow up information received on 11 June a*:

The subject had no history of any drug allergy.

The subject experienced a disseminated maculopapular rash. The subject also had erythema. The subject did not have a fever.

Follow up information received on 13 June a*:

The subject had no relevant medical history or risk factors.

The subject was randomised to receive Darunavir plus Ritonavir 800 mg/100 mg once daily.

The subject was withdrawn from the study on 31 May a*. The final outcome is unknown as the subject is not accessible.

Follow up information received on 27 July a*:

The last dose of investigational product was on 31 May a*. The site confirmed that chloropyramine was a treatment medication.

The relationship to investigational product was changed to 'no'.

The subject was lost to follow up and withdrawal.

Protocol Id: ING114915
Investigator Number: 486611
Subject Number: 486611
Treatment Number: B0807864A
Case Id: B0807864A
Suspect Drugs: Dolutegravir
Serious Events: Appendicitis

This 37-year-old male subject was enrolled in a ViiV-sponsored, open-label study of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral
 naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 11 April.

Concomitant medications included ranitidine hydrochloride and ketorolac trometamol.

On 18 May a*, 37 days after the start of dolutegravir, the subject underwent a grade 3 or severe appendectomy. The subject was hospitalised. Treatment with dolutegravir was interrupted. The event resolved on 22 May a*. The investigator considered that there was no reasonable possibility that the appendectomy may have been caused by dolutegravir.

Investigator text:

The patient was operator on due do an appendectomy. He was hospitalized from 05/18/a* to 05/22/a*.

Follow-up information received on 11 June a*:

Concomitant medications included paracetamol.

Follow-up information received on 12 June a*:

No relevant laboratory results were available from discharge summary.

Follow-up information received on 26 July a*:

SAE term was updated to appendicitis. The subject underwent appendectomy and received IV ranitidine 50 mg once only on 18 May a*, IV ketorolac 30 mg once only on 18 May a* and IV paracetamol 1000 mg once only on 18 May a*. Treatment with dolutegravir was interrupted on 18 May a*.

Follow-up information received on 12 September a*:

Dolutegravir treatment was re-started on 19 May a*. Laboratory test results included TA: 140/70, haematology: leukocyte 13580; biochemistry: BT 1.24; BD 0.37; Na 131, all other laboratory test results were normal.

9.6.7.2. Cases Reported Between 22 May to 26 October

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the safety data lock point for both the ING114915 study synopsis and the limited ISS SAS safety outputs, through to the final 26 October safety data lock point for the ISS, and includes all initial reports and follow up information received by the company through 26 October. The data included here are not represented in the study synopsis included in m5.3.5.4, nor in the limited SAS safety outputs produced for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials database in preparation of these narratives.
This 30-year-old male subject was enrolled in a ViiV-sponsored, open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 13 February.

The subject's past medical history included status post partial colectomy and small intestine obstruction.

On 05 July, 143 days after the start of dolutegravir, the subject developed grade 4 small intestine obstruction. The subject was hospitalised. Treatment with dolutegravir was continued. The event resolved on 07 July. The investigator considered that there was no reasonable possibility that the small intestine obstruction may have been caused by dolutegravir.

Investigator text:

Subject presented with small bowel obstruction in the setting of prior abdominal surgery. Conservative treatment with complete bowel rest and IV fluids.

Follow-up information received on 01 August:

Laboratory test results (WBC, haemoglobin, platelets and creatine) dated 05 July were within normal ranges. No further diagnostic tests (i.e. abdominal ultrasound) were performed. The subject was treated with IV sodium chloride 0.9% 125 ml solution (05-07 July), IV hydromorphone 0.1-0.3 mg (05-07 July), IV pantoprazole 40 mg (06-07 July) and IV ondansetron 4 mg (06-07 July).

Investigator text:

Subject presented with small bowel obstruction in the setting of prior abdominal surgery. Conservative treatment with complete bowel rest and IV fluids. Abdominal surgery done after having gunshot wound to the abdomen and is S/P colon resection with colostomy and subsequent reversal. Previous history of bowel obstructions. Presented to the emergency department with abdominal pain.
Follow-up information received 07 August a*:
No further tests were performed.

Follow-up information received 08 August a*:
The final diagnosis was reported as recurrence of small bowel obstruction.

Follow-up information received on 08 August a*:
On 07 August a*, 176 days after the start of dolutegravir, the subject again experienced grade 4 recurrent small bowel obstruction. The event was unresolved at the time of reporting. Treatment with dolutegravir was continued. The investigator considered that there was no reasonable possibility that the event was related to dolutegravir.

Investigator text:
Presented to emergency department with abdominal pain. Reported one episode of nausea and vomiting. No fever, haematemeses or haematochezia. Abdominal X-ray showed distended loops of bowel with air fluid levels. Suspicious for small bowel obstruction. Medical history of recurrent small bowel obstruction due to adhesions status post laparotomy after gunshot wound (z*). Admission 07 August a*; discharge 10 August a*.

Follow-up information received on 09 August a*:
Concomitant medications included pneumococcal 23-polyvalent vaccine, hydromorphone and oxycodone-acetaminophen.

On 08 August h*, the subject's diagnostic tests were as follows: lipase 14 IU/L (normal range 13-16), haemoglobin 15.5 g/dl (normal range 13.1 - 17.5) and white blood cells 8 K/CMM (normal range 4 - 10). The subject was treated with sodium chloride 0.9% solution, droperidol, heparin, pantoprazole, dextrose 5%-NaCl 0.9% solution.

Follow-up information received 16 August a*:
The second episode of recurrent small bowel obstruction was resolved with sequelae on 10 August a*.

Follow-up information received on 10 September a*:
Investigator text:
Clinically improved at discharge but follow-up abdominal X-ray showed worsening (sequelae) of small bowel obstruction. Surgery consult advised close follow-up and possible future elective surgery.

a*: The year
h*: 4 years ago
z*: 30 years ago
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Follow-up information received on 13 September a*

Concomitant medications updated.

Follow up information received on 27 September a*

Concomitant medications included ondansetron.

Investigator text:

Presented to the emergency room with syncope (Oceans case B0820712B). Due to the likeliness of some level of cardiac insufficiency with this he was admitted. He also experienced chest pain. Cardiac catheterization reported mild plaque and no significant obstructive coronary artery disease. Prior echocardiogram: depressed left ventricular systolic function with ejection fraction 30% and left ventricular enlargement.

Follow-up information received on 27 September and 02 October a*

On 25 September a*, the subject underwent exploratory laparotomy due to small bowel obstruction with small bowel resection and cholecystectomy. Treatment with dolutegravir was interrupted. The subject was discharged on 01 October a*.

Investigator text:

Surgery done for small bowel obstruction. This was planned after his last hospitalization for SBO. Surgery was performed and subject doing well. Subject discharged 01-Oct-a*.

Follow up information received on 08 October a*

During the surgery on 25 September a*, the subject also underwent extensive lysis of adhesions. The postoperative diagnosis was dense intraabdominal adhesions contributing to the history of multiple recurrent small-bowel obstructions and cholelithiasis.

The event term was amended for the SAE of recurrence of small bowel obstruction, (onset date: 07 August a*) from "recurrence of small bowel obstruction" to "recurrent small bowel obstruction postoperative laparotomy, dense intra-abdominal adhesions cholelithiasis." The outcome was amended from resolved with sequelae to resolved on 01 October a*. Treatment with dolutegravir was continued.

Follow-up information received on 15 October a*

The subject has had long-standing gallstone diagnosis since m* - there is no evidence of worsening since the subject started participating in the study. The event 'recurrence of small bowel obstruction' (onset date 07 August a*) has been updated to "recurrent small bowel adhesions'. Exploratory laparotomy secondary to recurrent small bowel adhesion was performed on 25 September a*. During surgery there was extensive lysis...

Concomitant medications included heparin.

On 01 September a*, 201 days after the start of dolutegravir, the subject developed grade 4 syncope. The subject was hospitalised. The subject was treated with a single dose oral aspirin 162 mg (indication: unstable angina). Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the syncope may have been caused by dolutegravir.

Investigator comments:

This subject was admitted to hospital on 01 Sep a* with syncope and chest pain. The subject underwent a cardiac catheterization on 04 Sep a*. The results of the catheterization are not yet known and the subject remains hospitalized at this time.

Follow-up information received on 13 September a*:

Concomitant medications included nicotine (inhaled) and nicotine patch.

The subject was treated with oral aspirin 162 mg and 325 mg, oral simvastatin 40 mg, oral potassium chloride 40 mEq, sublingual nitroglycerine 0.4 mg, IV sodium chloride 1000ml and oral carvedilol 3.125 mg.

Follow-up information received on 26 September a*:

Laboratory test results were within normal ranges.

Investigator text:

Presented to the emergency room with syncope. Due to the likeliness of some level of cardiac insufficiency with this he was admitted. He also experienced chest pain. Cardiac catheterization reported mild plaque and no significant obstructive coronary artery disease. Prior echocardiogram: depressed left ventricular systolic function with [text missing].

Follow up information received on 27 September a*:

The event term was updated from syncope to "syncope ruled out for cardiogenic vasovagal or neurogenic causes. Typical chest pain relieved with nitroglycerin". The event onset date was updated from 01 September a* to 30 August a*. The event resolved on 07 September a*.

Investigator text:

a*: The year
Surgery done for small bowel obstruction. This was planned after his last hospitalization for SBO. Surgery was performed and subject doing well.

Prior echocardiogram: depressed left ventricular systolic function with ejection fraction 30% and left ventricular enlargement.

Follow-up information received on 10 October a*:

Family history significant for coronary artery disease (father age 70), subject has history of hypertension; no cardiac disease. No history of seizures.

ECHO performed "prior to surgery before hospitalization". The subject was discharged on 01 October a*.

Follow-up information received on 15 October a*:

The syncope was confirmed to be of cardiac origin therefore the SAE term has been updated to 'cardiac syncope'.

The Echo was performed prior to the small bowel surgery. The subject was discharged on 07 October a*.

At an unknown time after the start of dolutegravir, the subject developed abdominal pain. The subject was hospitalised. The event outcome was unknown at the time of reporting. Investigator causality was unknown at the time of reporting.

Follow up information received on 08 October a*:

Concomitant medications included oxycodone-acetaminophen, heparin and nicotine.

On 04 October a* the subject experienced grade 3 abdominal pain. The event was unresolved at the time of reporting. Dolutegravir was continued. The investigator assessed the event as unrelated to dolutegravir.

Investigator text:

Subject presented with small bowel obstruction in the setting of prior abdominal surgery. Conservative treatment with complete bowel rest and IV fluids. Abdominal surgery done z* after having gunshot wound to the abdomen and is s/p colon resection with colostomy and subsequent reversal. Previous history of bowel obstructions. Presented to the emergency department with abdominal pain.

Presented with abdominal pain start 8/7/a*. Reported one episode of nausea and vomiting. No fever, haematemesis or haematochezia. Abdominal xray showed distended loops of bowel with air fluid levels. Suspicious for small bowel obstruction. Medical history of recurrent small bowel obstruction due to adhesions status post laparotomy after gunshot wound (z*). Adm 8/7/a*; disch 8/10/a*.

a*: The year
z*: 30 years ago
Presented to the emergency room with syncope. Due to the likeliness of some level of cardiac insufficiency with this he was admitted. He also experienced chest pain. Cardiac catheterization reported mild plaque and no significant obstructive coronary artery disease. Prior echocardiogram: depressed left ventricular systolic function with ejection fraction 30% and left ventricular enlargement.

Surgery done for small bowl obstruction. This was planned after his last hospitalization for SBO. Surgery was performed and subject doing well.

Presented to ED about one week status post (further text missing).

Follow-up information received on 15 October a*:

Investigator text: Presented to ED about one week status post small bowel adhesion removal.

Follow-up information received 25 and 29 October a*:

Medical history included cardiomyopathy. The final diagnosis was grade 4 postoperative ileus. Symptoms included abdominal pain, distention, nausea, and vomiting. The subject was treated with hydromorphone, neostigmine, glycopyrrolate, ondansetron, acetaminophen, enoxaparin, potassium chloride in dextrose 5%NaCl 0.45%, docusate sodium, sennosides, maalox plus, metronidazole, phenylephrine, lactated Ringers, vecuronium, sodium chloride 0.9%, cefazolin, rocuronium, propofol, lidocaine 2%, fentanyl, midazolam, droperidol, labetalol, ketorolac, oxycodone, hydrazine. The event was resolved on 18 October a*.

Protocol Id: ING114915
Investigator Number: 094691
Subject Number: 469103
Treatment Number: 0
Case Id: B0816406A
Suspect Drugs: Dolutegravir
Serious Events: Pancreatitis acute

This year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 26 March.

Medical conditions at the time of the event included hypertension aggravated, hypokalemia and systemic inflammatory response syndrome.
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On 30 June a*, 96 days after the start of dolutegravir, the subject developed grade 3 or severe acute pancreatitis. The subject was hospitalised. Treatment with dolutegravir was interrupted on 01 July a* and reintroduced on 06 July a*. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the acute pancreatitis may have been caused by dolutegravir.

Investigator Text:

Subject reports at week 16 visit conducted 16 July a*. Previous hospitalisation on 01 July a* through 04 July a* for acute pancreatitis. Discharge instruction sheet confirms dates. Records requested. More info to follow upon receipt of medical records. Presented to ER with epigastric abdominal pain, abdominal distension, nausea, vomiting, and constipation for past day.

No previous reports of cholelithiasis. Lipase high end of norm since study enrolment. Denies previous pancreatitis.

CT ABD 05Jul a*. increased density of peripancreatic fat, enlargement of pancreas. Inflammatory process extends in anterior left pararenal space and left paracolic space. Impression acute pancreatitis.

US GB 06Jul a*. no evidence of cholelithiasis

Subject admits to moderate daily alcohol use.

Dates of hospitalisation 01 July a* through 09 July a*

Study drug held on 01 July a* to 05 July a*. Rechallenged per patient on 06 July a*

Treatment plan IVF, hydration. Pain control dilaudid. NPO


Follow-up information received on 18 July a*:

The event resolved on 09 July a*.

Follow-up information received on 19 July a*:

Discharge date 04 July a* is an error. Hospital discharge summary and other supporting records indicate discharge was 09 July a*. End of SAE remains open as subject's lipase remains elevated.

Follow-up information received 23 July a*:

a*: The year
The investigator considered the acute pancreatitis to be an important medical event. The event was still resolving at the time of reporting.

Follow-up information received 26 July a*: 

Lipase on 24 July a* was 172 u/l. The event was still resolving at the time of reporting.

Follow-up information received on 03 August a*: 

Lipase re-test performed on 01 August a* showed result of 131 U/L (normal range 7-60).

Follow-up information received 08 August a*: 

IP restart date is 05 July a*. End date of nausea, vomiting and pain are documented resolved in the discharge summary dated 09July a*. On 24 July a*, lipase 172- grade 2, improving. Subject doing well without signs and symptoms of pancreatitis.

Follow up information received on 14 August a*: 

The event resolved on 14 August a*.

Investigator text: 

Lipase collected 08 August a* resulted 164.

Follow-up information received on 07 September a*: 

According to the investigator, the acute pancreatitis was attributed to alcoholism and the continuing elevated lipase to chronic pancreatitis secondary to continued alcoholism.

Protocol Id: ING114915
Investigator Number: 
Subject Number: 475804
Treatment Number: 400007
Case Id: B0828486A
Suspect Drugs: Dolutegravir
Serious Events: Perineal abscess

This 41-year-old male subject was enrolled in an open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects
The subject received dolutegravir from 17 February.

The subject had no relevant medical history or concomitant medications.

On 18 August a*, 183 days after the start of dolutegravir, the subject developed grade 3 or severe perineal abscess. On 24 August a*, the subject presented with groin pain. The subject was hospitalised. Perineal abscess extending up to proximal scrotum was observed. On 26 August a*, the subject underwent incision and drainage procedure in the OR. The perineal abscess tested positive for MRSA. The patient received Zosyn, Bactrim and Augmentin. Treatment with dolutegravir was continued. The event resolved on 27 August a* and the subject was discharged on the same day. There were no complications noted.

The investigator considered that there was no reasonable possibility that the perineal abscess may have been caused by dolutegravir.

Protocol Id: ING114915
Investigator Number: 424783
Subject Number: 476006
Treatment Number: 
Case Id: B0826517A
Suspect Drugs: Dolutegravir
Serious Events: Cholelithiasis

This 21-year-old male subject was enrolled in an open-label ViiV-sponsored, open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 14 December.

Relevant medical conditions and concurrent concomitant medications were unspecified at the time of reporting.

On 21 June b*, 190 days after the start of dolutegravir, the subject developed grade 2 or moderate gallstone. The subject was hospitalised. Treatment with dolutegravir was continued. The event resolved on 02 July b*. The investigator considered that there was no reasonable possibility that the gallstone may have been caused by dolutegravir.

Protocol Id: ING114915
Investigator Number: 476008
Subject Number: 
Treatment Number: 
Case Id: B0814014A
Suspect Drugs: Darunavir plus Ritonavir

a*: The year
b*: Following year
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Serious Events: Arthropod bite, Staphylococcal abscess

This 42-year-old female subject was enrolled in a ViiV-sponsored, open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral darunavir plus ritonavir (800/100 mg) from 27 December.

The subject had no relevant medical conditions or risk factors and was not receiving any relevant concomitant medications.

On 15 May, 140 days after the start of darunavir plus ritonavir, the subject experienced grade 3 or severe spider bite. The subject was hospitalised. The subject did not receive any relevant diagnostic tests. Treatment with darunavir plus ritonavir was continued. The event resolved on 30 May. The investigator considered that there was no reasonable possibility that the spider bite may have been caused by darunavir plus ritonavir.

Follow-up information received on 11 September:

On 27 April, 122 days after the start of Darunavir plus Ritonavir, the subject developed grade 3 or severe methicillin resistant staphylococcus aureus buttock abscess due to a spider bite. The subject was hospitalised on 07 May. The abscess was incised and drained on 08 May. Treatment with Darunavir plus Ritonavir was continued. The events resolved on 10 May and the subject was discharged. The investigator considered that there was no reasonable possibility that the methicillin resistant staphylococcus aureus buttock abscess due to a spider bite may have been caused by Darunavir plus Ritonavir.

Investigator text:

Subject was admitted to the hospital on 07 May and discharged on 10 May. Final diagnoses of lower buttocks abscess by methicillin-resistant staphylococcus aureus. Lower buttocks abscess, cellulitis, leukocytosis secondary to lower buttock abscess, and hyponatremia. Abscess was incised and drained on 08 May while admitted to the hospital.

Protocol Id: ING114915
Investigator Number: 476016
Subject Number: 476016
Treatment Number: Case Id: B0816410A
Suspect Drugs: Dolutegravir
Serious Events: Haemorrhoids

b*: Following year
This 43-year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 31 January.

On 23 June a*, 144 days after the start of dolutegravir, the subject developed grade 2 or moderate ruptured hemorrhoids. The subject was hospitalised. Treatment with dolutegravir was continued. The event resolved on 26 June a*. The investigator considered that there was no reasonable possibility that the ruptured haemorrhoids may have been caused by dolutegravir.

Investigator Text:

Patient states on 6/23/a* he had a lot more pain and had an extensive amount of blood with his haemorrhoids so his partner called 911. The patient was taken via ambulance. Patient was admitted to [deleted] hospital [deleted] for ruptured haemorrhoid. Patient states while admitted he was treated for the ruptured haemorrhoids and for anaemia (due to loss of blood).

Protocol Id: ING114915
Investigator Number: 476042
Subject Number: 476042
Treatment Number: Case Id: B0841489A
Suspect Drugs: Dolutegravir
Serious Events: Asthma

This subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir from an unspecified date.

At an unknown time after the start of dolutegravir, the subject developed asthma. The subject was hospitalised. Treatment with dolutegravir was continued. Outcome was unknown at time of reporting. The investigator considered that there was no reasonable possibility that the asthma may have been caused by dolutegravir.

Protocol Id: ING114915
Investigator Number: 476201
Subject Number: 476201

a*: The year
This 30-year-old male subject was enrolled in an open-label of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 11 January.

Medical conditions at the time of the event included depression. Concomitant medications included Truvada.

On 03 October, 266 days after the start of dolutegravir, the subject developed grade 3 or severe worsened depression. The subject had his car stolen and was hit over the head during the robbery. He developed depression after the incident and required hospitalisation. Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the worsened depression may have been caused by dolutegravir.

Investigator text:

Family member reports that pt's car was stolen and he was hit in the head during the robbery. He developed depression after the incident and was hospitalized. No additional information at this time. (Pt with depression prior to incident that worsened and required the hospitalization).

Follow-up information received 16 October:

The subject was withdrawn from the study on 12 October due to an adverse event, protocol deviation, and non-compliance with study medication.

Follow-up information received 25 October:

The last dose of dolutegravir was on 25 September. The investigator confirmed that this event was a worsening of a previous diagnosis of depression.
Serious Events: Urinary tract infection

This [ ]-year-old female subject was enrolled in a ViiV-sponsored open-label Phase IIIB, randomized study of the safety and efficacy of GSK1349572 to darunavir/ritonavir in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 07 March [ ].

On 16 August a*, 162 days after the start of dolutegravir, the subject developed grade 3 or severe viral syndrome, following a lumbar puncture. The subject was hospitalised. Treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the viral syndrome may have been caused by dolutegravir.

Investigator Text: Subject presented to office complaining of headache, fatigue, nausea starting more than a week ago. She went to the ER on 8/10/a* with the same complaints. Lumbar puncture was performed at that time. She was released from the ER. She continues to have the same complaints with worsening headaches. Hospitalised 8/16/a* for observation and possible blood patch.

Follow up information received on 29 August a*:

The event term was updated from viral syndrome post LP to possible urinary tract infection. The headache, nausea and fatigue were symptoms of the possible urinary infection. The event onset date was updated from 16 August a* to 10 August a*. The event resolved on 21 August a*.

Follow up information received on 30 August a*:

Concomitant medications included acetaminophen + hydrocodone, ondansetron, hydromorphone hydrochloride, morphine, sumatriptan, ketorolac tromethamine and zolpidem. The subject was treated with amoxicillin/clavulanate potassium, ciprofloxacin and piperacillin-tazobactam.

Follow-up information received on 04 September a*:

The subject was originally hospitalized for possible complications of lumbar puncture, but it was later decided it was worsening symptoms of a possible urinary tract infection. The subject presented to the ER on 10 Aug a* with headache, nausea and vomiting. It was informed that the subject had a lumbar puncture performed due to her past history of meningitis; she was not admitted at this time because there was no growth in the CSF culture. She then presented to the hospital for an epidural blood patch, which somewhat, but not completely, relieved the headache. The subject then checked herself out against medical advice (AMA) on 18 Aug a*. She then again presented back to the office with the same symptoms on 20 Aug a* so she was readmitted for an MRI and observation.

a*: The year

* 新薬承認情報提供時に置き換え
MRI of the brain was unremarkable. Subject also experienced dysuria and suprapubic tenderness which was relieved after 24 hours of IV antibiotic therapy.

Follow up information received on 20 September a*:

Relevant assessments on 21 August a* included white blood cell count which measured 4.2 K/UL (normal range: 4.5-11.0), red blood cell count measured 3.85 M/UL (normal range: 4.00-5.40) and hematocrit measured 35.3 % (normal range: 36.0-47.0). The subject's headache and fatigue resolved. Treatment with Augmentin was completed on 27 August a*.

Follow-up information received on 26 September a*:

Concomitant medications also included dextrose + sodium chloride, paracetamol and sodium chloride.

The event onset has been updated to 03 August a*.

Protocol Id: ING114915
Investigator Number: 476720
Subject Number: 476720
Treatment Number: B0839682A
Case Id: B0839682A
Suspect Drugs: Dolutegravir
Serious Events: Renal failure acute

This —year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects.. The subject received dolutegravir from 01 May.

The subject had no relevant medical conditions or risk factors and was not receiving any relevant concomitant medications.

On 06 October a*, 158 days after the start of dolutegravir, the subject developed grade 3 or severe gastroenteritis. The subject was hospitalised on 10 October a*. The subject experienced back pain, nausea, vomiting, diarrhoea and chills. Treatment with dolutegravir was continued. The event resolved on 15 October a*. The investigator considered that there was no reasonable possibility that the gastroenteritis may have been caused by dolutegravir.

Follow-up information received on 18 October a*:

The SAE term "gastroenteritis" was updated to "acute renal failure".
Verbatim text:

The subject was hospitalised from 10 to 15 October a*. The subject reported that, at admission, he had back pain, nausea, vomiting, diarrhoea and chills. At the time of reporting, records were not available. Today, the site reassessed the event term to acute renal failure and considered that the event of gastroenteritis was a non serious AE. The subject was randomised on 01 May a*.

Follow up information received on 18 October a*;

The investigator reported that the subject had not presented with any elevated creatinine at the study visits including the last visit which occurred on 16 October a* (serum creatinine 88.4 mmol/l). The fact that diarrhoea preceded the renal failure suggested prerenal failure but UTI needed to be ruled out.

Protocol Id: ING114915
Investigator Number: 94769
Subject Number: 476915
Treatment Number: 400019
Case Id: B0837758A
Suspect Drugs: Dolutegravir
Serious Events: Grand mal convulsion

This 20-year-old male subject was enrolled in a ViiV-sponsored Phase IIIB, randomized open-label study of the safety and efficacy of GSK1349572 to darunavir/ritonavir in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 14 March.

Medical conditions at the time of the event included seizure disorder.

On 06 October a*, 206 days after the start of dolutegravir, the subject developed grade 3 or severe seizure. The event was clinically significant (or requiring intervention). The subject's partner witnessed a Grand Mal seizure. The subject was taken to the emergency room and was found to have dislocated the right shoulder and had two deep bites to each side of the tongue. The subject had reduction using traction and was treated with Keppra 1000 mg/100ml, lorazepam 2ml intravenously, hydromorphone 1 mg intravenously and keflex 500 mg orally. Treatment with dolutegravir was continued. The event resolved on 06 October a* and the subject discharged the same day. The investigator considered that there was no reasonable possibility that the seizure may have been caused by dolutegravir and that the event was possibly due to the subject not taking his prescribed anti-seizure medication due to loss of income.

Follow-up information received on 15 October a*:

a*: The year

* 新薬承認情報提供時に置き換え
The SAE term has been updated to 'grand mal seizure'. The subject had no other symptoms other than having the seizure on 06 October a*.

Investigator text:

Pt. has history of seizures and had not taken his anti-seizure medication due to income issues. Pt. treated in the emergency and re-started on Keppra.

Protocol Id: ING114915
Investigator Number: 4773
Subject Number: 477303
Treatment Number: 
Case Id: B0818199A
Suspect Drugs: Darunavir plus Ritonavir
Serious Events: Depression

This 31-year old male subject was enrolled in a ViiV-sponsored, open-label open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral darunavir plus ritonavir per day from 27 December.

Medical conditions at the time of the event included anxiety.

On 17 July b*, the subject developed depression and alcohol abuse. The subject was referred for a psychiatric evaluation on 17 July b* after self-harming following alcohol consumption. At the time of the referral, he was not suicidal or homicidal. The subject was hospitalised on 18 July b*. Per investigator, the event did not meet criteria for possible suicidality. Treatment with Darunavir plus Ritonavir was continued. The subject was discharged on 19 July b*. The events were unresolved at time of reporting. The investigator reported the depression and alcohol abuse as unrelated to treatment with unspecified investigational drug.

Follow-up information received on 20 July b*:

On 17 July b*, 203 days after the start of Darunavir plus Ritonavir, the subject developed grade 3 or severe depression with alcohol abuse. The subject was hospitalised on 18 July b* and treated with oral Lexapro at 20 mg per day (primary indication depression) and oral Restoril at 30 mg PRN (primary indication insomnia). Treatment with Darunavir plus Ritonavir was continued. The events improved on an unspecified date. The investigator considered that there was no reasonable possibility that the depression and alcohol abuse may have been caused by Darunavir plus Ritonavir.

Investigator text:

a*: The year
b*: Following year
Subject referred for psychiatric evaluation after self harming after alcohol intake. He was admitted to psych facility and discharged on 19 Jul b*.

Follow-up information received on 03 August b*:

The SAE term has been updated to "worsening depression" and onset date to 16 July b*.

The subject denied family history of psychiatric conditions, denied suicidal ideation in the past but admitted to the thoughts of self-harm in the past. The subject saw counsellor regularly since June b*. The subject had been prescribed Laxapro and Xanax prior to study start, but was only taking Xanax, due to the dislike of the side effects of Lexapro. The PI confirmed the event did not meet criteria of a possible suicidality related event - this has also been confirmed with the current counsellors.

The subject event resolved on 19 July b* and the subject was discharged on the same day.

Follow up information received on 15 August b*:

The investigator confirmed that the depression and alcohol abuse are two separate events. Only the depression was captured as a serious adverse event. The alcohol abuse was an adverse event. The alcohol abuse however intensified the worsening of depression. There was no known history of alcohol abuse per subject report. There was no previous diagnosis of alcohol abuse and subject continues to deny issues with alcohol use. The investigator stated that the event was possibly involved with psychiatric conditions and social stressors. It was not involved with disease under study or concomitant medications.

Protocol Id: ING114915
Investigator Number: 
Subject Number: 484409
Treatment Number: 
Case Id: B0810294A
Suspect Drugs: Darunavir plus Ritonavir
Serious Events: Pneumonia

This 2-year-old male subject was enrolled in an open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naive adult subjects. The subject received oral ritonavir+darunavir (Darunavir plus Ritonavir) 800 mg/100 mg per day from 29 March .

On 15 June a*, 78 days after the start of Darunavir plus Ritonavir, the subject developed grade 2 or moderate pneumonia. The subject was hospitalised. The subject was...
treated with Augmentin. Treatment with Darunavir plus Ritonavir was continued. On 20 June a*, the event resolved. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by Darunavir plus Ritonavir.

Investigator text:

Patient has been hospitalised on June 15 in a hospital separated from study site. Symptoms were fever and cough.

Follow-up information received 27 June a*:

Concomitant medications included Truvada.

Follow-up information received on 15 August a*:

Hospital discharge summary:

Reason for hospitalisation - Fever upon returning from country X in an HIV+ patient.

History: HIV diagnosed at the beginning of a* in the context of lingering pneumonia. CD4 208/mm3, i.e. 19%, viral load 5,810 copies/mL in March a*.

ARV treatment started in March.

Two recent episodes of pneumonia.

Hepatitis A serology previously positive.

Toxoplasmosis serology positive.

HBV serology suggestive of previous contamination.

Hepatitis C serology negative.

Lifestyle:

Completely independent.

No children.

Active smoker at 10 pack-years.

No chronic alcoholism.

No drug use.

Regular overseas travel:

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Vaccinations up-to-date.

No history of vaccination against pneumococcus.

Short stay in country X from 8 June to 11 June a* (accompanied a member of his family back home). Headaches started on 13 June a*, then onset of a fever of 39°C with chills (self-medicated with Paracetamol), accompanied by shortness of breath, joint pain and vomiting. Admission to the hospital XXX 15 June a*: no failure of vital signs, abdominal pain, cough with sputum and shortness of breath with no auscultatory foci initially evident. Temperature: 38 degrees C. Transfer to the department of infectious diseases for continuation of treatment.

Physical examination on admission:

Maximum temperature was 40.3 degrees C, with no haemodynamic insufficiency, saturation at 97% on room air, patient breathing normally. Bloody sputum, presence of some basal rales that were very localised paravertebrally in the left lung base, left lateral chest pain which increased upon inhalation. No rash. No enlarged liver or spleen.

No enlarged lymph nodes. Abdomen was tender but no guarding.

The rest of the physical exam was unremarkable.

Diagnostic results:

Normal blood electrolyte composition.

Normal liver function test.

Creatinine 99 ~mol/L.

CRP 176 mg/L.

White blood cells 14,280, including PMN 12,280/mm³, lymphocytes 970, platelets 180,000/mm³.

Routine blood cultures sterile.

Urine culture sterile.

CD4 at 330/mm³, i.e. 29%.

Legionella antigen detection negative.

Initial chest x-ray normal.

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The second x-ray with profile revealed interlobular pleurisy of the left lung base, with no clear foci.

Progression in the department:

Empirical antibiotic therapy with Augmentin given suspected pneumonia with a slightly uncertain presentation. Progression was favourable.

The patient was afebrile after 24 hours. Decrease of CRP to 53 mg/L on 20 June a* after reaching a nadir [sic] of 260 mg/L on 17 June a*.

The follow-up x-ray performed on 19 June a* revealed interlobular pleurisy of the left lung base, compatible with the patient's symptoms.

The patient's recent medical history includes diagnosis of HIV at the beginning of a* in the context of lingering pneumonia of the right lung base and signs of rhinosinusitis. He presented with a 2nd episode of pneumonia and a persistent cough, leading to a chest CT scan which revealed mucosal thickening of the sinuses and some bronchial dilatation. He presented with keratitis on 21 May a*, for which he received antibiotic eye drops.

Virology: antiretroviral treatment was introduced a priori in March a*; inclusion in the Flamingo protocol. Viral load was undetectable at Week 4 on 27 April a* with CD4 at 266, i.e. 21 %. It should be noted that patient does not currently know his treatment perfectly. He was unable to list it for us.

Given this 3rd episode of pulmonary infection, patient should probably be vaccinated against pneumococcus, but above all, he should be referred to a pulmonologist.

CONCLUSION

Left basal pneumonia that progressed favourably on Augmentin.

The patient will have a follow-up appointment in the XXX hospital. The patient was given his x-rays and laboratory results. A follow-up laboratory work-up is being scheduled for one week after discharge.

Discharge treatment:

First antiretroviral treatment started on 01/03/a*.

Augmentin 500 mg/62.5 mg tablet [amoxicillin trihydrate, clavulanic acid, K salt]: 2 tablets mornings, 2 midday, 2 evenings, every day for 7 days: until 25/06/a*, inclusive (10 days in total)

If needed: Dafalgan 500 mg gel capsule [paracetamol]: 2 capsules, hard mornings, 2 midday, 2 evenings, every day for 7 days: If needed, if the patient experiences pain
Norvir 100 mg tablet [ritonavir]: 1 tablet mornings, every day for 30 days Prezista 400

a*: The year
mg tablet [darunavir ethanolate]: 2 tablets mornings, every day for 30 days Truvada tablet [emtricitabine, tenofovir disoproxil fumarate]: 1 tablet mornings, every day for 30 days

Blood transfusion: no

Blood derivative products: no

Multi-resistant bacteria carrier: no

Nosocomial infection: no

Hepatitis C: no

Protocol Id: ING114915
Investigator Number: 484802
Subject Number: 484802
Treatment Number: B0832463A
Case Id: B0832463A
Suspect Drugs: Darunavir, Ritonavir
Serious Events: Myocardial infarction

This male subject in his late 50s was enrolled in an open-label ViiV-sponsored randomized study of the safety and efficacy of GSK1349572 to darunavir and ritonavir in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral darunavir and ritonavir day from 26 March.

Medical conditions at the time of the event included diabetes mellitus and human immunodeficiency virus infection. Concomitant medications included Truvada and human insulin.

On 28 August, 155 days after the start of Darunavir and Ritonavir, the subject developed grade 4 myocardial infarction. The subject experienced thoracic discomfort on 28 Aug. The ECG at the family doctor showed a myocardial infarction. The event was life-threatening. The subject went to the hospital by an emergency case. The subject underwent coronary stent placement on 28 August. Treatment with Darunavir and Ritonavir was continued. The event resolved on 28 August. The subject was discharged on 03 September. The investigator considered that there was no reasonable possibility that the myocardial infarction may have been caused by Darunavir and Ritonavir.

Diagnostics:
Medical ultrasonic of heart on 03 Sep a* for control.

Follow-up information received on 10 October a*:

The subject was hospitalized. No findings on chest X-ray performed on 29 August a*. No drug therapy given as part of event treatment. The myocardial infarction resolved on 03 September a*.

**Protocol Id:** ING114915
**Investigator Number:** 94852
**Subject Number:** 485206
**Treatment Number:**
**Case Id:** B0827938A
**Suspect Drugs:** Darunavir, Ritonavir
**Serious Events:** Constipation

This [year]-year-old male subject was enrolled in a ViiV-sponsored, open label, Phase IIIB, randomized study of the safety and efficacy of GSK1349572 to darunavir/ritonavir in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral ritonavir+darunavir (Darunavir plus Ritonavir) from 16 May a*.

On 19 August a*, the subject developed grade 3 or severe constipation. On 28 August a*, the subject presented to the emergency department with abdominal pain, nausea and vomiting. The subject was hospitalised. The subject refers to "bowel closed by 9 days" and he also reported hematuria and dysuria. The subject was treated with Selg (polyethylene glycol) at 17.5 g/day. The subject had voluntarily stopped antiretroviral therapy from 10 August a* and he had been receiving mesalazine for suspected Crohn's disease for a month. Further investigations will be performed in the next few days. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the constipation may have been caused by investigational drug.

Follow-up information received on 06 September a*:

The subject's past medical history included declive oedema, diarrhoea, h pylori infection, prostatitis, urinary tract infection and weight loss. Medical conditions at the time of the event included hiv enteropathy, nausea, raynaud's phenomenon, rectal bleeding and urinary retention. Concomitant medications included mesalazine and Kivexa.

On 19 August a*, 95 days after the start of Darunavir plus Ritonavir, the subject developed grade 3 or severe constipation. The subject was hospitalised. Treatment with Darunavir plus Ritonavir was not changed as a result of the event. The subject's personal documents were stolen while travelling, he was not able to return to the site for a a*: The year
schedule visit and ran out of study drug; Darunavir and Ritonavir as well as concomitant antiretroviral Kivexa were therefore interrupted from 10 August and re-started on 30 August. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the constipation may have been caused by Darunavir plus Ritonavir.

Investigator text:

The patient came to the emergency room attention on 28 August for abdominal pain, nausea and vomiting. The patient refers bowel closed by 9 days, and today hematuria and dysuria. The patient had voluntarily stopped antiretroviral therapy since 10 August and mesalazine, for suspected Crohn's disease, for about a month. Further diagnostic tests will be performed in the next days.

Follow-up information received on 14 September:

Constipation was the final diagnosis. The event remained unresolved at time of reporting.

Investigator text:

Patient discharged himself, against medical advice on 11 September. He still had significant constipation. During the admission, the pt had rash, probably an allergic reaction to ketoprofene. Microbiological analyses of urine and semen showed a urinary tract infection by Escherichia coli. All other investigations performed (ultrasound, abdomen and chest X-ray) were negative.

Follow-up information received on 21 September:

The subject was treated for the event with polyethylene glycol, anhydrous sodium sulphate, sodium bicarbonate, sodium chloride, and potassium chloride. The event was not resolved at the time of reporting.

Protocol Id: ING114915
Investigator Number: 394018
Subject Number: 486008
Treatment Number: 
Case Id: B0811162A
Suspect Drugs: Carbamazepine, Dolutegravir
Serious Events: Epilepsy

This -year-old male subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1
infected antiretroviral naïve adult subjects. The subject received oral dolutegravir at 50 mg per day from 23 May.

During screening and on day 1, the subject complained of headache, anxiety, insomnia and depression in the past. He also had a history of skull injuries.

On 16 June a*, 24 days after the start of dolutegravir, the subject developed grade 4 epilepsy and the subject was hospitalised in the clinic with loss of consciousness. The event resolved with sequelae on 16 June a*. The subject continues to complain about periodical dizziness. On 17 June a* he was discharged from the clinic. The subject was diagnosed with epilepsy at an outpatient examination. The event was life-threatening. Treatment with dolutegravir was discontinued on 22 June a* and the subject was withdrawn from the study. The subject received carbamazepine (200 mg, twice daily) on 23 June a*. The investigator considered that there was no reasonable possibility that the epilepsy may have been caused by dolutegravir.

Investigator text:

On screening and day 1 patient complained on headache, anxiety, insomnia, depression in the past. He had scull injuries in the past. 16Jun he was hospitalised in clinic with short loss of consciousness.

He was in clinic till 17Jun. He had outpatient examination by neurologist. Diagnosis Epilepsy. Patient told about it 22Jun. He is complaining on the periodical dizziness.

Follow-up information received 09 July a*:

Diagnostic information and details of the duration and management of the seizure were unknown. The subject was withdrawn from the study as a neurologist had prescribed a prohibited medication, carbamazepine. The subject had not withdrawn his consent. Planned ARV therapy included Kivexa.

Follow-up information received on 27 July a*:

The cause of the SAE was reported as unknown and was a peculiarity of the subject.

It was confirmed that the subject received treatment with carbamazepine.

Follow-up information received on 22 August a*:

The investigator reported the treatment with carbamazepine as another possible cause of the event.

Protocol Id: ING114915
Investigator Number: 262
Subject Number: 486301
Treatment Number:

*a*: The year

*新薬承認情報提供時に置き換え*
This 30-year-old female subject was enrolled in a ViiV-sponsored open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. The subject received oral ritonavir+darunavir (Darunavir plus Ritonavir) from 04 May.

On 25 June, 52 days after the start of Darunavir plus Ritonavir, the subject developed disseminated pulmonary tuberculosis. The subject was hospitalised. Treatment with Darunavir plus Ritonavir was continued. The subject was treated with rifabutin, isoniazid, pyrazinamide, and ethambutol. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the disseminated pulmonary tuberculosis may have been caused by Darunavir plus Ritonavir.

Investigator Text: From routinely x-ray in a patient diagnosed disseminated pulmonary tuberculosis. Patient was hospitalised and receiving treatment: RB 150 + H0.6 + Z 150 + E 120

Follow up information received on 14 July:

The subject had been vaccinated against tuberculosis with BCG vaccine at birth, then aged 14 years, then 16 years.

At the time of the diagnosis, the sensitivity test was not performed.

Follow-up information received on 19 July:

Diagnostic tests results will become available in August. At the time of reporting, the subject remained hospitalized.

Follow up information received on 08 September:

Treatment with isoniazid and pyrazinamide was stopped on 24 August.

9.6.8. ING116070 SAE and Pregnancy Case Narratives

9.6.8.1. Cases Reported up to 07 August

The narratives included in this section correspond to the SAEs and Pregnancy cases included in the ING116070 Week 2 Synoptic CSR (with a data lock point of...
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07 August for safety data), which is located in m5.3.4.2. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October.

Protocol Id: ING116070
Investigator Number: 96962
Subject Number: 23
Treatment Number: NA
Case Id: B0803360A
Suspect Drugs: Abacavir sulphate + lamivudine, Dolutegravir
Serious Events: Pharyngitis

This year-old male subject was enrolled in a ViiV-sponsored open-label study for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg per day from 14 May and oral abacavir sulfate+lamivudine (Epzicom) from 14 May. The subject was HLA-B*5701 negative as required for enrolment in the protocol.

Per correspondence between the investigator and GSK medical monitor, the subject had ongoing sore throat, fever and malaise during the Screening period in ING116070 and had multiple courses of antibiotics, including azithromycin (initiated on May 08, and ongoing) and clindamycin (May 17 – single IV dose). The fever had been waxing and waning and did not worsen after starting abacavir.

On May 21, the subject was seen by an ENT physician for pharyngeal edema. ENT sent him to the ER to have a head/neck CT. The head/neck CT reportedly noted retropharyngeal phlegmon but no evidence of a retropharyngeal abscess. During the ER evaluation pharyngeal oedema worsened and the subject was admitted to the ICU and intubated for airway protection. All study medications were permanently discontinued on admission. The investigator considered that there was no reasonable possibility that the pharyngitis may have been caused by dolutegravir and Epzicom.

Upon admission, the ID consultant and admitting physician noted that this subject had developed a rash. In light of the constellation of symptoms, the ID consultant was concerned about possible abacavir HSR. Initially the investigator informed the GSK medical monitor that the only new symptom since starting abacavir was the rash. The subject was questioned, prior to intubation, if any of his pre-existing symptoms worsened after taking study medication, including abacavir, and he stated that he did not feel worse and in reviewing the subjects chart, subject had complained of intermittent rash over the past several weeks, prior to starting antiretroviral therapy. Additionally, this subject had a very high HIV-1 RNA (~40 million c/mL) in early April with a corresponding negative OraQuick test, which strongly suggests acute or very recent HIV infection. The symptoms (fever, malaise, sore throat, elevated liver enzymes, and rash) could have been associated with acute HIV but the investigator and GSK medical monitor agreed that the length of time with symptoms seemed a bit too long. In light of all this information it is
unlikely the subject had an abacavir HSR, especially since the symptoms pre-dated abacavir administration.

Of note, the subject also had elevated liver enzymes that were not reported as an SAE. On Day 1 (May 14, a*), this subject was noted to have elevated ALT to 297. The subject returned 3 days later for follow-up labs and to send a liver event kit (for additional workup, not because he reached stopping criteria). The repeat ALT was 182, and the workup was positive for opiates on the drug screen. Hepatitis virus (hepatitis A/B/C/E, CMV and EBV) were negative. Syphilis screening was still pending.

As of May 25, a*, the subject remained in the hospital and was still intubated, although ventilating easily. Liver enzymes in the hospital were improving. The subject was transferred to floor and monitored; pharyngitis essentially was resolved. Subject was extubated later that day and was discharged on May 27, a*. Truvada and raltegravir were initiated. On May 29, a*, investigator reported subject was “doing great”.

Per a discussion between the investigator and GSK medical monitor, the RPR and FTA-ABS sent to Quest on 31 May were both positive (RPR titer of 1:4), indicating syphilis infection. This represented a change from a RPR titer sent during the study on May 17, a*, which was negative. A RPR during the hospitalization was also reportedly positive with a titer of 1:4. Therefore, the rash is believed to be secondary syphilis. In light of the recent HIV infection, it may be that the subject acquired syphilis at a similar time. With his relative immunosuppression, he may not be mounting as high a RPR titer as would be expected. Also it is possible in HIV-infected patients to go straight to symptoms c/w secondary syphilis, rather than the typical history of genital lesions.

9.6.8.2. Cases Reported Between 08 August to 26 October

There were no SAE or pregnancy cases reported for this study from the cut-off date for the ING116070 Week 2 Synoptic CSR up to the final 26 October safety data lock point for the ISS.

9.6.9. ING116529 SAE and Pregnancy Case Narratives

9.6.9.1. Cases Reported up to 24 May

There were no SAE or pregnancy cases for this study reported to the Company at the time of 24 May safety data lock point for the ING116529 study synopsis, which is located in m5.3.5.4.

9.6.9.2. Cases Reported Between 24 May to 26 October

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the safety data lock point for the ING116529 study synopsis, up to the final 26 October safety data lock point for the ISS, and includes all initial reports and follow up information received by the company through 26 October. The data included here are not represented in the study synopsis included in m5.3.5.4, and no SAS

a*: The year
safety outputs were produced for this study for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials database in preparation of these narratives.

Protocol Id: ING116529
Investigator Number: 099387
Subject Number: 000082
Treatment Number: 2012, 2012
Case Id: Z0016742A, Z0016742B
Suspect Drugs: Blinded trial medication-ViiV, Dolutegravir
Serious Events: Coronary artery disease, Diarrhoea

This 38-year-old male subject was enrolled in a ViiV-sponsored, Phase III randomized, double-blind study to demonstrate the antiviral activity of dolutegravir (dtg) 50 mg twice daily versus placebo both co-administered with a failing antiretroviral regimen over seven days, followed by an open label phase with all subjects receiving dtg 50 mg twice daily co-administered with an optimised background regimen (obr) in hiv-1 infected, integrase inhibitor therapy-experienced and resistant, adults. The subject received blinded oral investigational product twice per day from 19 July to 24 July, followed by open-label oral dolutegravir at 50 mg twice per day from 25 July.

The subject's medical history included smoking and "PVD".

As of 19 July, the subject had 165 CD4+ cells/mm³ and 25,713 c/mL plasma HIV-1 RNA.

Concomitant ART included saquinavir/ritonavir from prior to Screening to 25 July. From 25 July the subject received tenofovir and tipranavir/ritonavir.

On 20 July, one day after the start of blinded investigational product and prior to starting treatment with open-label dolutegravir, the subject developed grade 3 or severe coronary artery disease. The subject presented to the Emergency Room on 20 July with right sided chest pain. He was evaluated and found not to have an acute coronary syndrome. The subject was released and referred to the Cardiology clinic. By the 25 July, the subject had 190 CD4+ cells/mm³ and 1261 c/mL plasma HIV-1 RNA.

Subsequently the subject complained of intermittent right chest pain, loosely associated with exertion.

By the 15 August, the subject had 168 CD4+ cells/mm³ and <50 c/mL plasma HIV-1 RNA.

The subject had a stress test on 20-Aug which had positive findings of ischemia. On 22 August the subject underwent cardiac catheterization which revealed 3 vessel disease (blockage or partial blockage of 3 coronary arteries). On 29 August a
coronary artery bypass graft was done. Treatment with dolutegravir was continued. The event resolved on 29 August a* and the subject was discharged from hospital on 05 September a*. The investigator considered that there was no reasonable possibility that the coronary artery disease may have been caused by investigational product and/or dolutegravir.

Diagnostic tests:

Echo stress test, 20-Aug-a* positive for ischemia induced wall motion abnormality.

cardiac Catheterization, 22-Aug-a* positive for 3 vessel disease

Investigator text:

Patient was seen in Emergency Room, 20-Jul-a* for Right side chest pain. He was evaluated, found not to have an acute coronary syndrome, and was released and referred to Cardiology clinic. Subsequently he complained of intermittent R. chest pain, loosely associated with exertion. The subject then had a stress test on 20-Aug-a* which had positive findings of ischemia. 22-Aug-a* he underwent cardiac catheterization which revealed 3 vessel disease.

Coronary Artery Bypass Graft was done on 29-Aug-a*. Discharge to home on 5-Sep-a*

On 05 September a*, 48 days after the start of investigational product and 42 days after the start of open-label dolutegravir, the subject developed grade 3 or severe diarrhea. The subject presented at the ER and was hospitalised for work up to rule out infectious cause. All studies were negative. The subject was treated with loperamide hydrochloride. Treatment with dolutegravir was continued. The diarrhea subsided and the subject was discharged. The event resolved on 10 September a*. The subject continues to have mild intermittent diarrhoea, well controlled with loperamide PRN. The investigator considered that there was no reasonable possibility that the diarrhoea may have been caused by investigational product and dolutegravir.

Investigator text:

Subject had been hospitalized for Coronary Artery Bypass Graft and discharged to home. He developed diarrhoea and returned to ER for evaluation and was admitted for work-up to determine if he had infectious cause for the diarrhoea. All studies done are negative. The diarrhoea subsided, and he was discharged. He continues to have mild intermittent diarrhoea, well controlled with Loperamide prn. -

Protocol Id: ING116529
Investigator Number: 099388
Subject Number: 000121
Treatment Number: 2006

a*: The year
This 21-year-old male subject was enrolled in a Viiv-sponsored, double-blind study to demonstrate the antiviral activity of dolutegravir (DTG) 50 mg twice daily versus placebo both co-administered with a failing antiretroviral regimen over seven days, followed by an open label phase with all subjects receiving DTG 50 mg twice daily co-administered with an optimised background regimen (obr) in HIV-1 infected, integrase inhibitor therapy-experienced and resistant, adults. The subject received blinded oral investigational product twice per day from 19 June to 25 June, followed by open-label oral dolutegravir at 50 mg twice per day from 26 June.

Concomitant ART included darunavir/ritonavir from prior to Screening to 25 June. From 26 June the subject received Truvada and atazanavir/ritonavir through 24 August when all ARTs and IP was stopped. On 19 September, IP and Truvada and atazanavir/ritonavir were re-started.

As of the 19 June, the subject had 80 CD4+ cells/mm³ and 433,430c/mL plasma HIV-1 RNA.

By the 14 August, the subject had 200 CD4+ cells/mm³ and <50c/mL plasma HIV-1 RNA.

On 25 August, 67 days after the start of investigational product and 60 days after the start of open-label dolutegravir, the subject experienced grade 4 motor vehicle accident. The subject was hospitalised and the events were life-threatening. It was reported that the subject suffered brain injury, lung contusions and multiple bone fractures. Treatment with dolutegravir was interrupted on 24 August and re-started on 19 September. The subject was discharged from hospital on 09 October. The subject was reported to be stable. His lung contusions had resolved, fractured bones repaired and his brain injury was improving with short term memory loss.

By the 9 October, the subject had 300 CD4+ cells/mm³ and 510c/mL plasma HIV-1 RNA.

The investigator considered that there was no reasonable possibility that the motor vehicle accident may have been caused by investigational product and dolutegravir.

Follow-up information received via email from the clinical study team on 27 August:

Subject 000121 at week 8 visit (on 14 of August) had a grade 3 bilirubin (atazanavir), grade 3 (low) inorganic phosphorus, and grade 2 creatinine. The subject was on vacation, and not available to return to the clinic sooner than 8/24. He had STAT labs
at Hospital X and based on these labs (creatinine 1.9, inorganic phosphorus WNL, urinalysis 2+ protein, and negative glucose. Dr Y, and the subjects PCP agreed he was most likely having drug (tenofovir) related renal toxicity, but not Fanconi syndrome. The decision was made (with GSK study team approval) to stop the tenofovir and start Abacavir. However, the next day the subject suffered the motorcycle accident, and the switch to Epzicom never was made.

Previous HAART: Atazanavir/ Norvir once daily, Truvada, open label Dolutegravir.

New planned regimen: Atazanavir/ Norvir once daily, Epzicom, open label Dolutegravir.

Subject also had retest labs at quest diagnostics.

Sadly, this subject has had a serious motorcycle accident and has suffered extensive injuries. His HAART is currently on hold.

Follow-up information received via email from the investigator on 03 October a*: The subject is awake with some short term memory deficits. He is currently in physical rehab and doing well. He re-started HAART and is taking meds PO, whole and consistently (including IP). He definitely wants to continue on study, the logistics of getting him here for a visit is a definite challenge. His wife is working on that. The site have been very impressed with the response in this subject so far and hope he can continue to participate in the study.

Follow-up information received via email from the investigator on 09 October a*: The subject was being released from hospital on 09 October a*. Subject's wife was unsure of the re-start date for his HAART but he has been back on it for approximately 3 weeks.

Follow-up information received from investigator via answered query report:

The investigator confirmed the short term memory loss was in relation to the SAE brain injury and not a separate SAE.

Investigator text:

subject suffered a serious motorcycle accident on 8/25/a*. he is located at a trauma unit where I am unable to access medical records. SAEs reported to me VIA phone from the wife and the ID doctor at the hospital. Subject suffered a brain injury, lung contusions, and multiple bone fractures, in relation to the SAE of MVA.

Subject released home from the hospital Oct/09/a*. He is stable. Lung contusions resolved, fractured bones repaired and his brain injury is resolving with residual mild

a*: The year
Short term memory loss, that is improving daily. I have not received any medical records admitting hospital. I will continue to attempt obtain them.

The site confirmed on Nov 8, a* that the subject was placed back on Truvada when IP was restarted in the hospital (and not Epzicom). They will monitor his renal function labs.

Protocol Id: ING116529
Investigator Number: 099397
Subject Number: 000181
Treatment Number: 2008
Case Id: Z0016478A
Suspect Drugs: Blinded trial medication-ViiV, Dolutegravir
Serious Events: Chronic obstructive pulmonary disease

This 42-year-old male subject was enrolled in a ViiV-sponsored, double-blind study to demonstrate the antiviral activity of dolutegravir (dtg) 50 mg twice daily versus placebo both co-administered with a failing antiretroviral regimen over seven days, followed by an open label phase with all subjects receiving DTG 50 mg twice daily co-administered with an optimised background regimen (OBR) in hiv-1 infected, integrase inhibitor therapy-experienced and resistant, adults. The subject received blinded investigational product twice per day from 29 June to 06 July, followed by open-label oral dolutegravir at 50 mg twice per day from 06 July.

Medical conditions at the time of the event included chronic obstructive pulmonary disease and smoking. Concomitant medications included valaciclovir hydrochloride, salbutamol sulphate, tiotropium, fexofenadine hydrochloride.

Concomitant ART included Truvada, darunavir/ritonavir and maraviroc from prior to Screening. Maraviroc was stopped on 5 July. From 5 July the subject continued to receive Truvada and darunavir/ritonavir and started etravirine.

As of the 29 June, the subject had 160 CD4+ cells/mm³ and 26,862 c/mL plasma HIV-1 RNA.

By the 26 July, the subject had 170 CD4+ cells/mm³ and 90 c/mL plasma HIV-1 RNA.

On 25 July, 26 days after the start of investigational product and 19 days after the start of open-label dolutegravir, the subject developed grade 2 or moderate exacerbation of chronic obstructive pulmonary disease. The subject complained of wheezing from 25 July. The subject was hospitalised with difficulty breathing. X-rays did not show any signs of pneumonia. The subject was treated with levosalbutamol, prednisone, labetalol hydrochloride and heparin. Treatment with open-label dolutegravir was continued. The subject was discharged on 30 July. The event resolved on 14 August.

The investigator considered that there was no reasonable possibility that...
the exacerbation of chronic obstructive pulmonary disease may have been caused by investigational product and dolutegravir.

Investigator text:

Subject came in for week 28 visit complaining of wheezing since July 25th, a*. Referred to emergency room and was given respiratory therapy. He is being admitted to [deleted] University Hospital. Subject was admitted to hospital with difficulty breathing. Xrays did not show any signs of pneumonia. Was evaluated by pulmonologists and given breathing treatments and steroids with improvements to symptoms was discharged on Jul 30, a*.

Protocol Id: ING116529
Investigator Number: 099400
Subject Number: 000241
Treatment Number: 2007
Case Id: Z0016574A
Suspect Drugs: Blinded trial medication-ViiV, Dolutegravir
Serious Events: Cardiac death

This ■-year-old male subject was enrolled in a ViiV-sponsored, double-blind study to demonstrate the antiviral activity of dolutegravir (DTG) 50 mg twice daily versus placebo both co-administered with a failing antiretroviral regimen over seven days, followed by an open label phase with all subjects receiving DTG 50 mg twice daily co-administered with an optimised background regimen (OBR) in HIV-1 infected, integrase inhibitor therapy-experienced and resistant, adults. The subject received blinded oral investigational product at 1 tablet twice per day from 28 June ■, followed by open-label oral dolutegravir at 50 mg twice per day from 05 July a* to 31 July a*.

The subject's past medical history included stroke. Medical conditions at the time of the event included hypertension and left ventricular hypertrophy

Concomitant ART included enfuvirtide and atazanavir/ritonavir from prior to Screening to 5 July a*. From 5 July a* the subject received etravirine and darunavir/ritonavir.

As of the 28 June a*, the subject had 230 CD4+ cells/mm³ and 3,823c/mL plasma HIV-1 RNA.

By the 25 July a*, the subject had 335 CD4+ cells/mm³ and <50c/mL plasma HIV-1 RNA.

On 01 August a*, 34 days after the start of investigational product and 27 days after the start of open-label dolutegravir, the subject died at home due to (grade 4) suspected

a*: The year

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cardiovascular death. Exact cause of death was unknown. The subject was withdrawn from the study. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the suspected cardiovascular death may have been caused by investigational product and dolutegravir.

Investigator text:

Subject died at home. No details of the death are known. Subject was seen the day prior for a routine visit with Podiatry and was said to have no complaints. Cause of death is currently presumed vascular in nature as the subject had long history of stroke. To date PI has not been able to contact family for details. we have been unable to get the death certificate, it is unknown if an autopsy was done. Exact cause of death, unknown.

9.6.10. ING114916 SAE and Pregnancy Case Narratives

9.6.10.1. Cases Reported up to 18 May

There were no SAE or pregnancy cases for this study reported to the Company at the time of 18 May safety data lock point for the ING114916 study synopsis, which is located in m5.3.5.4.

9.6.10.2. Cases Reported Between 19 May to 26 October

Protocol Id: ING114916
Investigator Number: 101592
Subject Number: 010201
Treatment Number:
Case Id: B0837070A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia fungal

This clinical trial case received on 01Oct involved a year old male subject who was enrolled in study protocol ING114916 entitled "A GSK1349572 Open Label Protocol for HIV-infected, Adult Patients with Integrase Resistance".The subject's medical history included the following: AIDS (w to present), Diabetes Mellitus, tobacco abuse, and alcohol intake. Concomitant medications included Celexa (citalopram hydrobromide), Advair (fluticasone propionate, salmeterol xinafoate), Toprol (metoprolol succinate), minocycline, Multivitamins (ascorbic acid, ergocalciferol, folic acid, nicotinamide, panthenol, retinol, riboflavin, thiamine hydrochloride), Protonix (pantoprazole sodium sesquihydrate), Solu Medrol (methylprednisolone sodium succinate), atovaquone, Pravachol (pravastatin sodium), Albuterol (salbutamol), Spiriva (tiotropium bromide), isosorbide, loperamide, and Alavert (loratadine). The subject received the first dose of DTG on 13Jul via oral route at a dose of 50 mg BID. On
24Aug a*, 43 days after the start of DTG, the subject experienced severe Paecilomyces pneumonia. The subject was hospitalized with shortness of breath, coughing spells and chest pain. On admission, he was worked up for COPD but further investigations revealed a mass like pulmonary infiltrate with positive fungal culture of the lung sample. The dose of DTG was not changed due to this event. Rechallenge was not applicable. Treatment medications included Tylenol, Coreg, Colace, Procrit, Fentanyl Patch, Ferrous Sulfate, Neupogen, Vfend, Tessalon Perles, Guiafenesin with codeine, Dilaudid, Lactulose, Zofran, Ultram, Ambien, and Levaquin. The outcome of the event Paecilomyces Pneumonia was not recovered/not resolved. The seriousness criterion for this event was required hospitalization. The Physician assessed the relationship between Paecilomyces pneumonia and DTG as not related, and the Physician assessed the relationship between pneumonia and study procedure as not related. The event was considered not related to any concomitant medication.

This clinical trial case received on 17Sep involved a year old female subject who was enrolled in study protocol ING114916 entitled "A GSK1349572 Open Label Protocol for HIV-infected, Adult Patients with Integrase Resistance". The subject's medical history included the following: AIDS (01Jan w* to present), asthma (01Sep q* to present), HIV Wasting (16Mar e* to present), and anemia (06Mar i* to present). The subject's concomitant medications included Truvada (emtricitabine, tenofovir disoproxil fumarate), Integra (ascorbic acid, ferrous fumarate, nicotinamide, polysaccharide-iron complex), Advair (fluticasone propionate, salmeterol xinafoate), Albuterol (salbutamol), Prezista (saibutamol sulfate), and Glucerna (amino acids NOS, carthamus tinctorius oil, fructose, glycine max seed oil, minerals NOS, vitamins NOS).The subject received the first dose of DTG beginning on 29Aug a* for HIV infection. On 16Sep a*, 19 days after the start of DTG, the subject experienced severe Pneumonia. On 17Sep a*, the subject called to notify the research department that she was in the hospital. She had chest discomfort on 16Sep a*, went to the emergency room (ER), and was admitted with pneumonia. The subject's laboratory test results were not available. Treatment included Levaquin, Prezista and Norvir. On 20Sep a*, the subject called at 1550 hours and stated that she had been released from the hospital on 19Sep a* at 2030 hours. She was to see the sub-investigator on 21Sep a*. No action was taken with study product. Rechallenge was not applicable. The outcome of the event Pneumonia was recovering / resolving. The seriousness criterion for this event was required hospitalization. The Physician assessed the relationship between Pneumonia and DTG as not related, and the physician assessed the relationship between pneumonia and study procedure as not related. The event was considered not related to any concomitant medication.

Protocol Id: ING114916
Investigator Number: 102936
Subject Number: 010404
Treatment Number:
Case Id: B0834038A
Suspect Drugs: Dolutegravir
Serious Events: Pneumonia
and study procedure as not related. The Physician did not feel that the event Pneumonia was associated with any medication that the subject was taking. Follow-up information received on 25Sep a* included additional medical history: Hypokalaemia (16Sep a* to present). The subject's laboratory test results included the following: Chest x-ray (16Sep a*: abnormal - artifact), CT-angio chest (16Sep a*: pneumonia left base, Hgb (16Sep a*: 7.5 g/dL), potassium (16Sep a*: 2.3 mmol/L), and ECG (16Sep a*: sinus tachycardia normal). Treatment medications were updated to include: potassium, Azithromycin, levofloxacin, and ceftriaxan. Prezista and Norvir were no longer reported as treatment medications. Follow-up information received on 08Oct a*. The medical history of hypokalemia was deleted. The normal range of potassium was 3.5 mmol/L - 5.2 mmol/L and that of Hgb was 12.0 g/dl - 16.0 g/dl. The site verified that the dose of the treatment medication Levofloxacin was 150 mg IV q 12 hours. The subject completed Levaquin on 02-OCT-a*. The outcome of the event Pneumonia was recovered / resolved.

Protocol Id: ING114916
Investigator Number: 103851
Subject Number: 020103
Treatment Number: 
Case Id: B0830697A
Suspect Drugs: Dolutegravir
Serious Events: Pyrexia

This clinical trial case received on 13Sep a involved a year old male subject who was enrolled in study protocol ING114916 entitled "A GSK1349572 Open Label Protocol for HIV-infected, Adult Patients with Integrase Resistance". The subject's medical history was not available. The subject's concomitant medications included: Combivir (lamivudine, zidovudine) 150/300 mg BID, Intelence (etravirine) 200 mg BID, Norvir (ritonavir) 100 mg BID, Prezista (darunavir ethanolate) 600 mg BID, Viread (tenofovir disoproxil fumarate) ) 300 mg once daily, and Celsentri (maraviroc) 150 mg BID.

The subject received the first dose of DTG beginning on 01Aug a*, administered at a dose of 50 mg BID. On 11Sep a*, 42 days after the start of study product, the subject experienced Grade 4 high fever. The site was contacted by the subject on 12Sep a* to report that he had been hospitalized since 11Sep a* because of high fever symptoms. The subject was still in the hospital under observation. The subject's laboratory test results and the treatment received were not available. The site was awaiting receipt of hospital records for more information. The dose of Dolutegravir was not changed. Rechallenge was not applicable. The outcome of the event high fever was not recovered / not resolved. The seriousness criteria for this event were required hospitalization, disability, and medically significant. The Physician assessed the relationship between high fever and DTG as not related, and the Physician assessed the relationship between high fever and study procedure as not related. Follow-up information received on a*: The year
05Oct a* reported that the event high fever was not related to any concomitant medication.

9.6.11. ING115502 SAE and Pregnancy Case Narratives

9.6.11.1. Cases Reported up to 18 May

The narratives included in this section correspond to the SAEs and Pregnancy cases reported up to the 18 May safety data lock point for the ING115502 study synopsis which is located in m5.3.5.4. The narratives presented here include any follow up information for the concerned cases received by the company through to 26 October. No SAS safety outputs were produced for this study for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials database in preparation of these narratives.

Protocol Id: ING115502
Investigator Number: BRA-001
Subject Number: BRA-001-001
Treatment Number: 
Case Id: B0783197A
Suspect Drugs: Combivir, Darunavir, Dolutegravir, Etravirine, Ganciclovir, Maraviroc, Paclitaxel, Ritonavir
Serious Events: Cytomegalovirus chorioretinitis, Pulmonary haemorrhage

This 50-year-old male subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received dolutegravir at 50 mg twice daily from 02Feb.

Medical conditions at the time of the event included kaposi’s sarcoma. Concomitant medications included paclitaxel.

On 14Feb a*, the subject developed Grade 1 or mild cytomegalovirus (CMV) retinitis. The subject was hospitalised. Ophthalmic examination and retinography confirmed CMV retinitis. The subject was treated with ganciclovir and treatment with dolutegravir was continued. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the cytomegalovirus retinitis may have been caused by dolutegravir and that the event was possibly due to medical condition CD4 counts, disease under study and immune reconstitution inflammatory syndrome (IRIS).

The subject experienced an another SAE of Grade 4 pulmonary bleeding on 08Mar a* and received an IV infusion of 90 mg of Taxol after 4 weeks of interruption of this drug. The subject complained of chest pain during the first hours and went to a hospital. 
nearby hospital. In the emergency room the subject presented with massive pulmonary bleeding. Attempts to reanimate failed. One hypothesis was a bleeding of the Kaposi sarcoma in the lungs after the chemotherapy section. In the past, the subject has presented with many episodes of necrosis of Kaposi sarcoma in the left leg after receiving chemotherapy. The subject also had anaemia and leucopenia during ganciclovir treatment and the subject's last platelet count was 150,000 μL. The subject died on 08Mar a*. The investigator considered that there was no reasonable possibility that the pulmonary bleeding or the CMV may have been caused by dolutegravir and the event was possibly related to HIV disease, kaposi sarcoma and CMV retinitis. The event was also due to the concomitant medications taxol, ganciclovir, darunavir, ritonavir, etravirine, maraviroc, zidovudine and lamivudine.

On 02 May a* the subject was withdrawn from the study.  

Protocol Id: ING115502  
Investigator Number: GBR-002  
Subject Number: GBR-002-001  
Treatment Number:  
Case Id: B0748459A, B0748459B  
Suspect Drugs: Dolutegravir, Lersivirine  
Serious Events: Lung infection pseudomonal

This 49-year-old male subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received dolutegravir 50 mg twice per day beginning 20Apr and lersivirine 1000 mg since 04Oct e* (the subject was also participating in a lersivirine named patient program).

The subject's past medical history included ex smoker and ex intravenous drug user. The subject had advanced HIV since 17May a*. Medical conditions at the time of the event included pseudomonas chest infection. Concomitant medications included sertraline hydrochloride, acyclovir, Truvada, ritonavir, tipranavir, diclofenac, lersivirine, itraconazole and azithromycin.

On 16Aug b*, the subject developed pseudomonas lower respiratory tract infection. The subject was hospitalised with a dry cough and associated shortness of breath, fever and night sweats. There was no haemoptysis. The subject was treated with salbutamol nebuliser, ipatropiumm nebuliser, IV meropenem, Seprtin, and cough linctus. No action was taken with dolutegravir or lersivirine as a result of this event. The event improved on 23Aug b* and the subject was discharged home well. Investigator causality was unknown at the time of reporting but the investigator considered that the event was possibly due to the disease under study and lack of efficacy (virological failure).

The investigator considered that there was no reasonable possibility that the event was related to treatment with dolutegravir or lersivirine.
On 28 Mar c*, 708 days after the start of dolutegravir, the subject developed Grade 1 or mild chest infection. The subject was hospitalised. Sputum cultures were positive for pseudomonas and the chest x-ray showed nil focal. The event improved on 04 Apr c*. The subject was treated with intravenous Tazocin for 7 days and discharged on oral ciprofloxacin. Medical conditions at the time of the event also included low CD4 count. Concomitant medications also included Co-trimoxazole, Symbicort, ADCAL-D3, salbutamol sulphate, Ensure plus, cyclizine, lactulose and dultograve. The investigator confirmed the final diagnosis of the chest infection to be pseudomonal lower respiratory tract infection. The investigator considered that there was no reasonable possibility that the chest infection may have been caused by dolutegravir and that the event was possibly due to recurrent chest infections.

On 10 Apr c*, the subject was admitted to hospital with a Grade 2 or moderate pseudomonas chest infection. It was reported that the subject was admitted with persistent cough after recent admission for pseudomonas chest infection. The subject was initially treated per post infective cough without antibiotics, however, the sputum cultures grew pseudomonas and the subject was therefore treated with intravenous antibiotics (pipercillin/tazobactam and gentamycin). Other relevant diagnostic data included: Increased CRP to 20 (units and dates not provided). The events improved on an unspecified date. It was reported that the subject is improving and currently off antibiotics. The investigator confirmed the final diagnosis of the chest infection with onset date of 28 March c* to be pseudomonal lower respiratory tract infection. The investigator explained that the bronchiectatic changes are often colonised with Pseudomonas. With the addition of severe immunosuppression in this subject's case, he is unlikely to clear the bacteria. Short courses of appropriate antibiotic therapy are required when he presents with symptoms and is clinically unwell (i.e. pyrexial, productive cough, raised inflammatory markers). The subject was clinically improved from respiratory point of view and was discharged 27 April c* recovered from this event. The event term of pseudomonal chest infection was updated to worsening of pseudomonal lower respiratory tract infection. The investigator stated that "the subject was considered as recovering rather than fully recovered during the first event at discharge, however as the sensitivities for the pseudomonas came back as resistance to ciprofloxacin, one can consider the second admission to represent a worsening of the pseudomonal lower respiratory tract infection". The investigator considered that there was no reasonable possibility that the pseudomonas chest infection may have been caused by dolutegravir and that the events were possibly due to disease under study and pseudomonas colonisation of respiratory tract. The event of worsening pseudomonal lower respiratory tract infection was improved on 27 Apr c*.

The start date of investigational product was confirmed as 21 April b*.

b*: Following year
c*: 2 years later
This 22-year-old male subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day from 08Jul.

The subject's past medical history included HIV infection since v*, candidiasis, cystitis, diarrhea, duodenal ulcer, endocarditis rheumatic, herpes zoster, incomplete bundle branch block, interstitial pneumonia, irritability, leukoplasia, parotid cyst, resection of basalioma, rheumatic disease, salmonella infection, skin lesion, spinocellular skin cancer excised and abdominal lipoblastoma. Medical conditions at the time of the event included hypertriglyceridemia, lipodystrophy, petechiae on legs, pulmonary fibrosis (being treated with steroids), thrombocytopenia and Type 2 Diabetes Mellitus. Concomitant medications included amlodipine, lansoprazole, aspirin, bisoprolol fumarate, prednisone, Bactrim F, azithromycin, lamivudine-hiv, tipranavir, ritonavir, maraviroc, intermediate/long-acting insulin, human short-acting insulin, epoetin beta and base.

On 12September a*, 66 days after the start of dolutegravir, the subject developed Grade 3 severe angina pectoris and was subsequently hospitalised. A negative troponin test indicated that it was not an acute myocardial infarction. Treatment with dolutegravir was continued. On 13September a* the subject underwent a coronary angiography which revealed trivascular coronary artery disease. The subject underwent coronary artery bypass surgery on 23Sep a*. The subject’s health conditions are now stationary and he is able to begin this post-operative cardiac rehabilitation. The subject was admitted to the post-operative ICU on the 5th post-operative day following double coronary artery bypass surgery in the cardiac surgery department (anterior circumflex and right coronary a.). In the immediate post-operative period he had fever, despite second generation cephalosporin and vancomycin as surgical prophylaxis, with piperacillin-tazobactam introduced subsequently. After removal of the CVC and urinary catheter, the fever abated rapidly. An echocardiogram performed on 28Sep a* ruled out pericardial effusion and revealed moderate aortic stenosis. With a physician's agreement, post-operative antiplatelet therapy was instituted with Ibustrin, despite the severe thrombocytopenia.

On 29Sep a* the subject was transferred to infectious diseases. On admission, the subject was afebrile, had dyspnea and was co-operative and oriented. Laboratory tests revealed severe thrombocytopenia (10,000 plt/mL), mild neutropenia, elevated inflammatory index, loss of glycaemic control, dyslipidaemia and hypokalaemia. The CT
scan performed during his stay in post-operative ICU revealed the onset of extensive
geographic areas of parenchyma with increased basal density, of ground-glass opacity,
with no signs of frank consolidation, mainly occupying the left upper lobe and the central
parenchymal region of the right upper lobe. The viro-immunological results indicates
that the current antiretroviral treatment is effective: CD4 count was 95 cells/mL (5.34 %)
and the HIV-1 RNA was 548 copies/mL.

The antibiotic therapy initiated in the post-operative ICU was therefore confirmed, and
diuretic treatment and oxygen therapy were added because of mild pulmonary oedema of
cardiogenic origin. Rehydration therapy with added potassium was instituted.

During the admission the subject's clinical condition gradually improved and in particular
he reported an improved mini dyspnoea at the same time as losing weight (around 1 kg
per day); his exercise endurance also gradually increased up to an acceptable level (the
subject reported managing to walk for about 30 metres). It was therefore possible to
reduce the diuretic treatment.

When anaemia started developing, transfusion of irradiated packed red cells were given
on 01Oct a* and 03Oct a*. Subsequently, no further transfusions were necessary. The
loss of glycaemic control, which was partly due to steroid treatment, has been controlled
by increasing the dosage of fast-acting insulin to the current level. It was necessary to
continue monitoring blood sugar levels before meals. On 04Oct a* the dosage of
Ibustrian was reduced to one tablet daily, as recommended by the cardiologist.

On 08Oct a*, the subject was discharged from the infectious diseases ward with a
diagnosis of "acute coronary artery disease and heart failure in a patient recently operated
double coronary bypass - basal pneumonia, decompensated diabetes mellitus type II -
dyslipidaemia". At the time of discharge the subject had good haemodynamic and
glycaemic control. Follow-up laboratory tests showed that the inflammatory index had
reversed; the thrombocytopenia was still severe, the electrolyte level was normal.

The investigator considered that there was no reasonable possibility that the angina
pectoris may have been caused by dolutegravir and that the event was possibly due to the
subject's medical history. The investigator confirmed the acute coronary artery disease
and heart failure did not meet SAE criteria. The concomitant medications amlodipine,
lansoprazole, aspirin and bisoprolol fumarate were changed to treatment medications.

Protocol Id: ING115502
Investigator Number: FRA-001
Subject Number: FRA-001-002
Treatment Number: B0804048A
Suspect Drugs: Dolutegravir, Methandienone
Serious Events: Transaminases increased

a*: The year 730
This 68-year-old male subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir at 50 mg twice per day beginning 10 Jan.

The subject had no relevant medical history or risk factors. Concomitant medications included darunavir, ritonavir, etravirine, maraviroc and lamivudine-hiv.

On 15 May, 126 days after the start of dolutegravir, the subject developed Grade 4 ALT/AST increase. The event was considered clinically significant (or requiring intervention). Relevant laboratory assessments on 18 May included ALT 438 U/L (normal range: 16-35) and AST of 122 U/L (normal range: 20-32). On 22 May, the subject had an ALT of 1125 U/L and AST of 344 U/L. Treatment with dolutegravir and all ARVs was interrupted on 24 May.

On 23 May, relevant diagnostics included serology results for hepatitis C and B which were both negative. It was reported that the subject was not hospitalised, felt good with no particular clinical signs or symptoms.

Previous relevant laboratory results (21 Feb) included AST 31 U/L, ALT 31 U/L, and total bilirubin 9 \( \mu \text{mol/L} \) (normal ranges not provided). Tests for hepatitis A, B, C, and E were negative. CMV and EBV were also negative. The subject had been taking methandienone (Dianabol) for three weeks prior to the event. The event improved on 01 Jun (AST 91 U/L and ALT 476 U/L). Treatment with dolutegravir and other ARVs was re-started on 01 Jun. The treating physician indicated that it had been suspected that the event was caused by the anabolic steroids that the patient had been taking (boosted by ritonavir) in the three weeks prior to the event. The investigator considered that there was no reasonable possibility that the ALT/AST increase may have been caused by dolutegravir. The final diagnosis (04 Jun) was reported as liver transaminases increased.

Protocol Id: ING115502
Investigator Number: NDL-001
Subject Number: NDL-001-002
Treatment Number: 
Case Id: B0806332A
Suspect Drugs: Dolutegravir
Serious Events: Intervertebral disc compression

This 68-year-old male subject was enrolled in ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received dolutegravir 50 mg twice daily from 30 January.

Medical conditions at the time of the event included malnutrition and osteoporosis. Concomitant medications included ritonavir, maraviroc, etravirine, zidovudine, tenofovir, darunavir, pentamidine, caspofungin, temazepam, pantoprazole and nicoumalone.
On 07 May a*, 98 days after the start of dolutegravir, the subject developed Grade 3 severe compression of L1 after working in the garden. The event was disabling and clinically significant (or requiring intervention). After working in the garden patient developed back pain, initially worsening, later becoming less prominent. GP prescribed the pain medication. At the out-patient visit x-lumbar spine: compression of L1. The subject was bedridden most part of the day. Treatment with dolutegravir was continued. Dexa scan on 31 May a* of lumbar spine showed T score of 4.5; Z score of 3.6.

The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the compression of L1 may have been caused by dolutegravir and that the event was possibly due to the disease under study and osteoporosis.

9.6.11.2. Cases Reported Between 19 May to 26 October

The narratives included in this section correspond to the SAEs and Pregnancy cases reported from the safety data lock point for the ING115502 study synopsis up to the final 26 October safety data lock point for the ISS, and includes all initial reports and follow up information received by the company through 26 October. The data included here are not represented in the study synopsis included in m5.3.5.4, and no SAS safety outputs were produced for this study for the ISS. It is important to note that no reconciliation was performed between OCEANS and the clinical trials database in preparation of these narratives.

Protocol Id: ING115502
Investigator Number: AUS-003
Subject Number: AUS-003-001
Treatment Number:
Case Id: B0839516A
Suspect Drugs: Dolutegravir
Serious Events: Coronary artery occlusion

This 40-year-old male subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir (DTG) at 50 mg BID from 02 Sep.

Medical conditions at the time of the event included hyperlipidemia. Smoking was considered a relevant risk factor. Concomitant medications included ritonavir. Relevant medical history included coronary atherosclerosis.

On 03 Oct b*, at an unknown time after the start of DTG, the subject developed Grade 3 or severe coronary artery occlusion. The subject was hospitalised. The subject experienced anterior chest pain intermittently from 03 Oct b* and the subject presented to hospital on 06 Oct b* with chest pain. A stent was applied to LAD with excellent angiographic result. Treatment with DTG was continued. The event resolved on
10Oct b*. The investigator considered that there was no reasonable possibility that the coronary artery occlusion may have been caused by DTG and that the event was possibly due to coronary atherosclerosis.

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<td>Co-trimoxazole, Dolutegravir</td>
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<tr>
<td>Serious Events:</td>
<td>Toxoplasmosis</td>
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This 27-year-old male patient was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received dolutegravir (DTG) 50 mg BID from 22 May 2022.

Medical conditions at the time of the event included low CD4 count.

On 09Aug 2022, 78 days after receiving DTG, the patient developed cerebral toxoplasmosis. The patient was hospitalised on August 8th with neurologic symptoms interpreted as being compatible with neurotoxoplasmosis. The subject had a severe immunodeficiency and opportunistic infection was expected. The subject had no history of neurotoxoplasmosis. The RMN cerebral, in August 9th, showed multiple ring-enhancing lesions with perifocal oedema and mass effect compressing the subjacent structures. The subject started treatment from 09Aug 2022 to 20Sep 2022 with sulfadoxine and pyrimethamine. Concomitant medications included sulfametoxazol/trimetroprim for prophylaxis. Treatment with DTG was continued. On 04 September 2022 the event term was updated to Grade 2 neurotoxoplasmosis with an onset date of 08Aug 2022. The subject is asymptomatic now. He is already at home. He will take the medicines for six weeks and then he will start secondary prophylaxis. He is taking DTG every day with no interruption even during the hospitalisation. On 11Sep 2022, the CD4 count was 8cells/mm3 and viral load exams are pending.

The event resolved on 20 September 2022.

The subject was reported to be better now and at home. Treatment with dolutegravir was not interrupted. The investigator considered that there was no reasonable possibility that the cerebral toxoplasmosis may have been caused by DTG and that the event was possibly due to the patient's low CD4 count.

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<td>Case Id:</td>
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a*: The year
b*: Following year
Module 2.7.4 Summary of Clinical Safety

Suspect Drugs: Dolutegravir
Serious Events: Abdominal pain, Pancytopenia

This 9-year-old male patient was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir (DTG) at 50 mg BID from 04 April.

Medical history included HIV infection diagnosed 15Jun w* and a history of allergy to penicillin. 13Feb a* subject had a persistent fever. ART Treatment history: included 15Jun s* to 15Sep x* Hivid/ Norvir(discontinued for treatment simplification), 15Sep s* to 15Jun r* Crixivan/ Epivir/ Zerit (discontinued because of immunological failure), 02Jan q* to 15Apr q* Epivir/Invirase/Videx/Zerit (discontinued because of cutaneous adverse effects),

15Dec p* to 15Feb o* Crixivan/ Norvir/ Sustiva/ Ziagen (discontinued because of hypersensitivity syndrome), 15Jun m* to 15Jun l* Agenerase/ Norvir/ Viread (discontinued because of virological failure), 15Jun l* to 15Jun k* Fuzeon/ Norvir/ Telzir/ Viread (discontinued because of virological failure), 15Jun k* to 15Jun j* Aptivus/ Fuzeon/ Norvir (discontinued because of virological failure), 20Jun j* to 15Jun i* Kaletra/ Truvada/ Videx (discontinued because of virological failure), 15Jun i* to 15Jun h* Norvir/ Prezista/ Videx (discontinued because of virological failure) 15Jun h* to 15Jun g* Intolerance/ Isentress/ Viread (discontinued because of virological failure), and 12May f* to 04Apr a* Celsentri/ Isentress/ Truvada (discontinued because of virological failure).

Since 04Apr a* Aptivus/ Celsentri/ Norvir/ Truvada/ DTG.

Concomitant medications included Truvada, tipranavir, maraviroc and ritonavir.

On 15 June a*, 72 days after the start of DTG, the subject developed pancytopenia. The event was clinically significant (or requiring intervention). The subject was treated with a transfusion. Treatment with dolutegravir was continued. On 26Jul a*, 113 days after the start of DTG, The subject was hospitalised and underwent a splenectomy. Prior to the subject's hospitalisation, the subject had a decrease in red blood cells, white blood cells and platelets. The subject had pallor and fatigue. The subject was not initially hospitalised for pancytopenia. The subject was not diagnosed with splenomegaly. The event term was updated from splenectomy to voluminous and painful spleen. On 20Jul a*, the subject had a fever of 39 degrees C, secondary thrombocytopenia and Herpes simplex of the lip. The subject also had severe pancytopenia. Relevant assessments showed less than 50000 platelets and received EPO infusion. It was reported that the severe pancytopenia was associated with a high decrease of platelets count, white blood cells and red blood cells. Platelet count <50000. The subject received Granocyte 13 Mui/ml, 1 injection (3 times per week) for 30 days. On the 16 August white blood cells 7.73 and haemaglobin 9.8 g/l.

a*: The year m*: 9 years ago
f*: 2 years ago o*: 12 years ago
g*: 3 years ago p*: 13 years ago
h*: 4 years ago q*: 14 years ago
l*: 5 years ago r*: 15 years ago
j*: 6 years ago s*: 16 years ago
k*: 7 years ago w*: 23 years ago
l*: 8 years ago x*: 26 years ago
The patient is well, nocturnal frequency (2 to 3 times a night). Sterile urine culture, urologist consultation with PSA assay. Elevation of WBC (7.73) and Hb (9.8 g/l). The investigator considered that there was no reasonable possibility that the splenectomy may have been caused by DTG. The investigator considered that there was no reasonable possibility that the pancytopenia may have been caused by DTG. The event had resolved without sequelae.

Protocol Id: ING115502
Investigator Number: FRA-022
Subject Number: FRA-022-001
Suspect Drugs: Dolutegravir
Serious Events: Sepsis, Septic shock

Medical conditions at the time of the event included encephalitis, kaposi, meningioma and pancytopenia. Concomitant medications included darunavir, ritonavir, Truvada and maraviroc.

On 25 August the subject developed septicemia and septic shock associated with myocardial infarction and cardiorespiratory arrest. The subject died on 31 August due to septic shock and septicemia. The investigator considered that there was no reasonable possibility that the septicemia and septic shock may have been caused by dolutegravir.

Protocol Id: ING115502
Investigator Number: GBR-002
Subject Number: GBR-002-001
Case Id: B0748459C, B0748459D
Suspect Drugs: Dolutegravir
Serious Events: Lower respiratory tract infection

The subject's past medical history included intravenous drug user and smoker. Medical conditions at the time of the event included advanced hiv infection and pseudomonas chest infection. Concomitant medications included azithromycin, Symbicort, Adecal d3, itraconazole, acyclovir, Truvada, ritonavir, tipranavir, lersivirine, Ensure plus, Simple

a*: The year
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Module 2.7.4 Summary of Clinical Safety

lincutus, ketoconazole, atovaquone, domperidone, ondansetron hydrochloride, chlorpheniramine maleate, and loperamide hydrochloride.

On 12 June b*, 418 days after the start of DTG, the subject developed Grade 2 or moderate lower respiratory tract infection. Patient presented with clinical signs and symptoms of chest infection. Blood tests show raised inflammatory markers (CRP 120). On 23 Jun b* sputum cultures showed normal respiratory flora. The subject was hospitalised 22 Jun b* with 10 day history of worsening cough, 2 months after previous admission for Pseudomonal chest infection. Treatment with DTG was discontinued. The subject was treated for chest infection which was diagnosed based on clinical findings and blood tests. Treatment included piperacillin/tazobactam, nebulisers and fluids. Responded well to treatment clinically. Inflammatory markers now falling. Also treated for oral candida with itraconazole. Given atovaquone to cover for potential PCP.

Action taken with dolutegravir was interrupted. Treatment with dolutegravir was restarted on 09 July b*. The event resolved on 29 June b*. The investigator considered that there was no reasonable possibility that the lower respiratory tract infection may have been caused by DTG.

On 14 Aug b*, 482 days after the start of DTG, the subject developed Grade 1 or mild chest infection. Admitted 23/8/b* with 2 week history of dry cough and fevers. Chest radiograph reveals triangular patch of consolidation right lower lobe. Blood tests show raised C-reactive protein of 107 (normal range less than 5). Started on intravenous antibiotics (tazocin). Treatment with DTG was continued. The event improved on an unspecified date. The investigator considered that there was no reasonable possibility that the chest infection may have been caused by dolutegravir and that the event was possibly due to the subject's medical condition of recurrent chest infections.

Protocol Id: ING115502
Investigator Number: GBR-002
Subject Number: GBR-002-002
Treatment Number: B0835660A
Suspect Drugs: Dolutegravir
Serious Events: Escherichia bacteraemia, Urinary tract infection

This 32-year-old male subject was enrolled in ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received DTG from an unspecified date.

Concomitant medications included Kaletra, Co-trimoxazole and frusemide.

On 19 Sep b*, the subject developed Grade 1 or mild E.coli bacteremia secondary to Grade 1 or mild urinary tract infection. The subject was hospitalised with diarrhoea and nausea and found to have E. coli bacteraemia and E. coli in urine culture (resistant to co-

b*: Following year
amoxiclav, sensitive to ciprofloxacin). Treated with intra-venous ciprofloxacin. Treatment with DTG was continued. The events are clinically improved on an unspecified date. The investigator considered that there was no reasonable possibility that the E.coli bacteraemia and urinary tract infection may have been caused by DTG and that the events were possibly due to the disease under study.

Protocol Id: ING115502
Investigator Number: NDL-001
Subject Number: NDL-001-002
Treatment Number: 
Case Id: B0831698A
Suspect Drugs: Dolutegravir
Serious Events: Foot fracture, Tibia fracture

This 37-year-old male subject was enrolled in ViiV-supported compassionate use programme for the treatment of human immunodeficiency virus infection. The subject received oral dolutegravir (DTG) at 50 mg BID from an 30Jan 

The subject's past medical history included vertebral compression fracture (07May a*). Medical conditions at the time of the event included osteoporosis. Concomitant medications included pentamidine, caspofungin, temazepam, pantoprazole, nicoumalone, ritonavir, maraviroc, etravirine, zidovudine, tenofovir, darunavir, t-20, alendronate sodium and Paracetamol + codeine.

In August a*, the subject experienced pain in his feet and ankles. An x-ray was performed but did not provide any explanation to the subject's symptoms. On 07Sep a*, after the start of DTG, the subject experienced Grade 2 or moderate insufficiency fractures of the right tibia and left calcaneus. The MRI scan showed insufficiency fracture of the right tibia without dislocation and no erosions. The subject did not undergo any surgery, treatment was conservative, and no other specific therapy was given. Treatment with DTG was continued. Outcome was unknown at time of reporting. The investigator considered that there was no reasonable possibility that the tibia fracture and calcaneus fracture may have been caused by dolutegravir and that the events were possibly due to the subject's disease under study and underlying medical condition of osteoporosis.

Protocol Id: ING115502
Investigator Number: NDL-001
Subject Number: NLD-001-001
Treatment Number: 
Case Id: B0806330A, B0806330B
Suspect Drugs: Dolutegravir
Serious Events: Respiratory tract infection, Depression

a*: The year
This 39-year-old female subject was enrolled in a ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received DTG 50 mg BID from 07 March.

Medical conditions at the time of the event included recurrent depression. Concomitant medications included pantoprazole, valaciclovir hydrochloride, ritonavir, darunavir, Abacavir sulfate + lamivudine, maraviroc, Diclofenac + misoprostol and fluoxetine.

On 20 May, the subject developed respiratory tract infection. The subject was hospitalised 28 May with pulmo auscult: diminished breathing sounds R. (One to two weeks before admission productive cough getting worse, fever 39 degrees C every evening. Feeling sicker. Pain in the ear, headache, sore throat, chest pain due to cough.) A chest x-ray on 28 May showed accentuated lung interstitium bilaterally. Started with AB. Treatment with DTG was continued.

The signs and symptoms of RTI resolved. Discharged from the hospital on May 31st. The investigator considered that there was no reasonable possibility that the respiratory tract infection may have been caused by dolutegravir.

On 18 Sep, the subject developed depression and was hospitalised. Dolutegravir was continued and she started fluoxetine 18 Sep. Outcome was unknown at time of reporting. Medical history included autoimmune, iron deficiency, psychosocial problems, psychotherapy, and avascular necrosis of the femoral head. The patient was first diagnosed with depression in 0*.

The investigator considered that there was no reasonable possibility that the may have been caused by DTG and that the event was possibly due to her underlying depression.

Treatment with dolutegravir 50 mg twice daily started on 11 January.

Protocol Id: ING115502
Investigator Number: USA-005
Subject Number: USA-005-001
Case Id: B0807217A
Suspect Drugs: Dolutegravir
Serious Events: Adrenal insufficiency, Hypotension, Non-Hodgkin's lymphoma

This 39-year-old male subject was enrolled in an ViiV-supported Named Patient Program for the treatment of human immunodeficiency virus infection. The subject received dolutegravir (DTG) 50 mg BID from 19 January to 21 June.

Medical conditions at the time of the event included HIV infection. Concomitant medications included amoxicillin clavulanate (Augmentin), levofloxacin (Levaquin),
piperacillin (Zosyn), fluconazole, ceftriaxone, ampicillin+subactam, meropenem, valacyclovir and tenofovir.

On 01 Jun a*, 134 days after starting DTG and ibalizumab, the subject developed fever (103 degrees Celsius) and heart rate high (125 bpm). The subject was hospitalised. The subject had no recorded relevant risk factors. He had been seen in clinic on 31 May a* with fevers and headache attributed to a sinus infection, but it was clear even then this might be something other than a sinus infection. Two weeks later the work-up revealed the 'sinus infection' was actually lymphoma with brain masses. Test results and examinations were normal, apart from aspartate aminotransferase 79 (normal range 5 – 37 U/L). The subject was diagnosed with Grade 2 or moderate fever and headache of unknown etiology. Treatment with DTG and ibalizumab was continued. Adrenal insufficiency also diagnosed on 21 Jun a*. Hypotension on 03 Jul a*. The hypotension due to adrenal insufficiency was of a seriousness that required hospitalisation with ICU care (dopamine drip). Separate SAE form was pending for this event. The hypotension was not related to study medications but was due to NHL. The NHL was never treated despite the placement of a Hickman catheter, because it became clear the subject was too sick to tolerate systemic chemotherapy or brain irradiation. His adrenal insufficiency was initially treated from June 19th, with hydrocortisone and fludrocortisone. When subject was readmitted week of June 25, he was treated with dexamethasone. Despite appropriate corticosteroid therapy, the hypotension did not improve, required life support (dopamine) and eventually it was decided to stop all treatment and change to hospice/comfort care. Pt put on comfort care on around 01 Jul a*. On 04 Jul a* the subject was diagnosed non Hodgkin's lymphoma. The headache was an aspect of the non-hodgkin's lymphoma NHL (and not an sAE) which invaded liver and pituitary. The adrenal failure was secondary to cancer invading the brain.

The subject received oral dolutegravir 50 mg twice daily from 19 January a* to 21 June a*. Concomitant medications included ibalizumab. The subject was diagnosed with Non-Hodgkin's lymphoma on 04 June a*. The subject died due to this event on 07 July a*.

The investigator considered that there was no reasonable possibility that the fever and heart rate high may have been caused by DTG and ibalizumab and that the events were possibly due to AIDS-related malignancy and suspected sinus infections.

Follow-up information received 31 July a*:

The additional SAEs were hypotension and adrenal insufficiency, both remained unresolved and were not related to investigational products. Stop date of investigational product was updated and reported as 04 Jul a*.
This [redacted]-year-old male subject was enrolled in a blinded study to evaluate the safety, tolerability, and pharmacokinetics of a supratherapeutic dose of GSK1349572. The subject received oral investigational product from [redacted].

The subject was randomised to cohort 2 sequence 1 of the study design. In period 1 he received one dose of GSK1349572 50 mg (within 30 min after the start of a high-fat meal), followed by a 7-day washout period, and in period 2 he received one dose of GSK1349572 50 mg (fasted).

Medical conditions at the time of the event included anxiety, bipolar disorder, depression and post-traumatic stress disorder. The subject was reported as having a history of cocaine use, cognitive delay, childhood physical and sexual abuse, and a family history of depression (mother) and mental illness (aunt).

On [redacted], four days after the start of investigational product, the subject developed grade 2 or moderate manic episode. The subject was hospitalised. Treatment with investigational product was discontinued, with the last dose taken on [redacted] and the subject was withdrawn from the study. The event resolved on [redacted]. The investigator considered that there was no reasonable possibility that the manic episode may have been caused by investigational product.

Follow-up information received on [redacted]:

The subject did not meet criteria for involuntary confinement as per psychiatric evaluation. He was recommended for psychiatric follow-up by the consulting psychiatrist. The subject did not receive any medication upon discharge. The investigator commented that although the subject had taken investigational product on [redacted], after the event had resolved, the study staff were not made aware of the event until it had been resolved and dosing had resumed. As soon as the staff had been notified of
the event, the investigational product was discontinued and the subject was withdrawn from the study.

9.6.12.2. **ING113099 - An open-label study to investigate the effect of rifampin and rifabutin on DTG PK**

Protocol Id: ING113099  
Investigator Number: 84493  
Subject Number: 992012  
Treatment Number: 2012  
Case Id: B0755074A  
Suspect Drugs: Dolutegravir, Rifabutin  
Serious Events: Adverse drug reaction

This 21-year-old female subject was enrolled in an open-label ViiV-sponsored study to investigate the effect of rifampin and rifabutin on GSK1345972 pharmacokinetics in healthy volunteers. The subject received oral dolutegravir at 50 mg per day from 27 September and oral rifabutin at 300 mg per day from 04 October a*.

Medical conditions at the time of the event included sulfa allergy.

On 04 October a*, seven days after the start of dolutegravir and the same day as the start of rifabutin, the subject developed grade 3 or severe vertigo, grade 4 agitation, mental confusion, grade 3 or severe back pain, grade 3 or severe pain in hip, grade 3 or severe pain - proximal thigh, feels pins and needles and grade 3 or severe hypertension. On 05 October a*, the subject developed grade 1 or mild nausea, grade 3 or severe fever and grade 3 or severe hypotension. The investigator reported that these signs and symptoms were most consistent with a hypersensitivity syndrome. The subject was hospitalised and the events were life-threatening. The investigator reported that the subject was hemodynamically unstable in the emergency room with a blood pressure of 83/33 and required fluid resuscitation. The subject was treated with paracetamol, ondansetron hydrochloride, lorazepam, sodium chloride and K-Phos Neutral. Treatment with dolutegravir and rifabutin was discontinued on 04 October a*. The hypertension was resolved and the other events improved on an unspecified date. The investigator considered that there was a reasonable possibility that the vertigo, agitation, mental confusion, back pain, pain in hip, pain - proximal thigh, feels pins and needles, hypertension, nausea, fever and hypotension may have been caused by rifabutin only or the combination of rifabutin and dolutegravir.

Follow up information received via deletion report and follow up on 14 October a*:

The investigator reported the final diagnosis as severe drug reaction.

The investigator deleted the following events severe vertigo, agitation, mental confusion, back pain, severe pain in hip, severe pain - proximal thigh, feels pins and needles, severe
hypertension, mild nausea, severe fever and severe hypotension as they were symptoms of the drug reaction.

The subject was discharged on the 05 October a* when vital signs had stabilised. The event resolved on 13 October a*. The subject was withdrawn from the study.

The investigator considered that there was a reasonable possibility that the drug reaction may have been caused by dolutegravir and rifabutin and that the event was possibly due to study participation.

Investigator Text:

992012 was inpatient for PK #1 10/2 to 10/4. Prior to discharge she had received her first study dose of rifabutin together with dolutegravir, and she looked well and had no complaints. She was discharged in good health. Per the ER doctor, she developed agitation, a feeling of pins and needles, and diffuse muscle and joint pain together with confusion. She came to the ER where she was found to be tachycardic with a blood pressure in the 170s/100s. She received a dose of benzodiazepines for agitation. Over the course of the next hour or two, she developed a fever to 39.9 and BP dropped to 90s/40s. Laboratory analysis shows a platelet count of 147K and lymphocyte count of 790 (down from 1970 on 10/3). LFTs are WNL, and she has no rash. Because of the fever and hypotension she was admitted to [deleted]. This sounds very much like rifamycin hypersensitivity syndrome.

Update: At the time of hospital discharge on 10/5/a* the participant's vital signs had stabilized.

Hospital Note:

Subject [deleted] is [redacted]-year-old woman who is participating as a healthy volunteer in the above-referenced trial. She started GSK1349572, 50 mg q day on 9/27(Day 1), which she was tolerating well. She was admitted from 10/2-10/4/a* for pharmacokinetic sampling. She was given the first study dose of rifabutin 300 mg plus dolutegravir 50 mg on the morning of 10/4 (Study Day 8) and was discharged home in good condition. Her husband reports that he talked to her at 4 pm, at which time she was fine and at work. Around 2200 hours on 10/04, she called him in a panic. She complained of pain in her back and hips and nausea. She appeared to have a high fever and was incoherent. He brought her directly to the Emergency Department at [deleted].

Upon presentation to the ED, the patient appeared agitated and was mumbling. She complained of lower back, hip, and proximal thigh pain, and impairment of cognition. Initial vital signs revealed a temperature of 37.4, heart rate 138, blood pressure 177/111, respirations 26, O2 saturation 98% on room air. Physical examination in the ED revealed an agitated patient, who was writhing and talking to herself while lying on the stretcher. Her physical exam was remarkable for tachycardia, and mild diffuse tenderness over the hips. Otherwise, she was alert and oriented to person, place and time, and her respiratory,
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skin, GI and neuro exams were unremarkable. Her psych exam revealed very agitated mentation, easily distracted, repetitively saying "just stop, just stop". She did not appear to be experiencing hallucinations, suicidal or psychotic thoughts.

Her laboratory evaluation was notable for a slightly low platelet count of 147K and an absolute lymphocyte count of 790/mm3. WBC was normal at 5,460/mm3 and hematocrit of 36.7%. Urine tox and urine Hcg were negative, and she had a normal urinalysis. Her metabolic panel was unremarkable with AST/ALT values of 21/17 IU, and total bilirubin of 0.5 mg/dl. Her initial serum lactate drawn at 01:11 hours on 10/05/a* was just above normal range at 2.3, but following vigorous hydration, the lactate level at 03:38 hours on 10/05/a* improved to 0.9 mmol/L. Her lab results were also remarkable for a low magnesium and phosphate at 1.2 mEq/L and 1.9 mg/dl, respectively. Blood cultures were also obtained.

At 00:14 hours on 10/05/a*, her temp was measured at 39.9, she remained tachycardic at 138 beats per minute and her blood pressure measured 91/55 mm Hg. She was given acetaminophen 975 mg PO x one. In consultation with the Study PI, [deleted], it was felt that the clinical picture was most consistent with a hypersensitivity reaction. At approximately 00:45 hours on 10/05, the subject reported nausea and was given odensatron 4 mg IV push. She was also given lorazepam 2 mg IV injection and vigorously hydrated with 3 liters of normal saline over the next five hours. Her blood pressure reached a nadir of 83/33 mm Hg at 01:15 hours but had improved to 110/52 at 02:59, and her temperature dropped to 36.7 by 04:53 hours, following a repeat dose of PO Tylenol. She was also given a single oral dose of sodium phosphate. Her symptoms were much improved after she received aggressive fluid resuscitation and Tylenol in the ED. She was transferred to an inpatient bed for close clinical and laboratory monitoring, and continued normal saline hydration at 150 cc/hr given she still had mild tachycardia and fever.

This morning she was seen by the clinical pharmacology study team. The subject appears tired but is resting comfortably in bed. Additional history included the fact that the subject reported sleeping very poorly during her hospitalization from October 2-4, with perhaps only 2-3 hours total sleep during that time. She believes her myalgias and back pain began around 18:00 on 10/4, but did not become severe until around 22:00. She also remembers being tachypneic during this episode, which she attributed to anxiety. The subject reports taking chondroitin sulfate and several herbal products up until two weeks before beginning the study on September 27, but she denies any other medications or prior exposure to rifabutin or rifampin. Her physical examination is unremarkable at this time. Her temperature at 09:44 hours is 37.4, heart rate 82, blood pressure 86/52, respirations 16 and O2 saturation is 97% on room air. All study medication has been discontinued. The assessment of the study team is that this most likely represents a rifamycin hypersensitivity reaction. The subject feels much improved and the plan is for her to be discharged today, with outpatient follow-up and safety labs in 1-2 days. She will be instructed to contact us via the Drug Development Unit emergency pager if she has any problems in the interim.

a*: The year
9.6.12.3. ING115697 – An open-label, randomized, two Cohort, two period, one-way study to evaluate the effect of bocervir and telaprevir on DTG PK

Protocol Id: ING115697
Investigator Number: 99237
Subject Number: 672010
Treatment Number: 2010
Case Id: B0800519A
Suspect Drugs: Dolutegravir, Telaprevir

This female subject was enrolled in a Phase 1, Open-Label, Randomized, Two Cohort, Two Period, One-Way Study to Evaluate the Effect of Bocervir and Telaprevir on Dolutegravir Pharmacokinetics in Healthy Adult Subjects.

The subject received oral dolutegravir at 50 mg from 12 April \( a^* \) to 20 April \( a^* \) and oral telaprevir at 2250 mg from 17 April \( a^* \) to 20 April \( a^* \).

The subject's past medical history included spontaneous abortion.

On 21 March \( a^* \), the subject had her last menstrual period. Twenty-two days later, on 12 April \( a^* \), she received dolutegravir (50 mg/day). On 17 April \( a^* \), she also received telprevir (2250 mg). On 20 April \( a^* \), both dolutegravir and telprevir were stopped. Outcome was unknown at time of reporting.

Follow-up information received 27 September \( a^* \):

The subject was approximately six months into her pregnancy and there were no reported complications. The estimated date of delivery is 31 December \( a^* \).
## 9.7. APPENDIX 7: Tabular Listings of Pregnancies

### Appendix Table 8  Listing of Pregnancies Reported from Studies in ART-Naïve Subjects

<table>
<thead>
<tr>
<th>Trial/Source</th>
<th>Centre</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP</th>
<th>TTO Positive Pregnancy Test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING112276</td>
<td>65771</td>
<td>83</td>
<td></td>
<td>DTG TDF/FTC</td>
<td>10 Q24 300/200 Q24</td>
<td>12 May 15 Feb b*</td>
<td>Not specified</td>
<td>Normal infant</td>
<td>37 to 42</td>
<td>One prior spontaneous abortion and one prior normal birth</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING112276</td>
<td>6675</td>
<td>641</td>
<td></td>
<td>DTG TDF/FTC</td>
<td>10 Q24 then 50 Q24 300/200 Q24</td>
<td>28 Jul 03 May b*</td>
<td>98 weeks</td>
<td>Normal infant</td>
<td>39</td>
<td>Not specified</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>83400</td>
<td>3964</td>
<td></td>
<td>DTG TDF/FTC</td>
<td>50 Q24 300/200 Q24</td>
<td>11 Mar UNK</td>
<td>Not specified</td>
<td>Elective termination</td>
<td>9</td>
<td>One prior spontaneous abortion, one prior elective termination and one prior full term normal birth</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>83505</td>
<td>4311</td>
<td></td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>29 Apr UNK</td>
<td>16 weeks</td>
<td>Elective termination</td>
<td>&lt;4</td>
<td>Three prior elective terminations and one prior normal birth. HIV positive partner</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>83517</td>
<td>4355</td>
<td></td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>26 Oct 02 Aug a*</td>
<td>42 weeks</td>
<td>Normal infant</td>
<td>39</td>
<td>Not specified</td>
<td>Prior to conception and during first trimester</td>
</tr>
</tbody>
</table>

*a*: The year  
*b*: Following year  

* 新薬承認情報提供時に置き換え
<table>
<thead>
<tr>
<th>Trial/Source</th>
<th>Centre ID</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP</th>
<th>TTO Positive Pregnancy Test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING113086</td>
<td>83517</td>
<td>4358</td>
<td>43</td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>20 Aug 25 May a*</td>
<td>32 weeks</td>
<td>Normal infant</td>
<td>Not specified</td>
<td>One prior missed abortion and one prior premature birth</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>83517</td>
<td>4411</td>
<td>44</td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>20 Sep 26 Jun b*</td>
<td>32 weeks</td>
<td>Normal infant</td>
<td>40</td>
<td>Two prior elective terminations and one normal pregnancy. HIV negative partner</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>82945</td>
<td>3810</td>
<td>38</td>
<td>RAL TDF/FTC</td>
<td>400 Q12 300/200 Q24</td>
<td>25 May 15 Feb b*</td>
<td>Not specified (&lt;27 weeks)</td>
<td>Elective termination</td>
<td>14 weeks per investigator</td>
<td>Prior elective abortion</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>83509</td>
<td>4381</td>
<td>43</td>
<td>RAL ABC/3TC</td>
<td>400 Q12 600/300 Q24</td>
<td>28 Feb 20 Nov a*</td>
<td>Not specified (&lt;4 weeks)</td>
<td>Elective termination</td>
<td>&lt;4</td>
<td>Five prior elective terminations, one prior full term normal birth. HIV positive partner</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>84346</td>
<td>4776</td>
<td>47</td>
<td>RAL TDF/FTC</td>
<td>400 Q12 300/200 Q24</td>
<td>25 Dec 20 Sep b*</td>
<td>4 weeks</td>
<td>Spontaneous abortion</td>
<td>Approximately 5 to 12 weeks</td>
<td>Two prior spontaneous abortions and two prior elective terminations</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>84343</td>
<td>4125</td>
<td>41</td>
<td>RAL TDF/FTC</td>
<td>400 Q12 300/200 Q24</td>
<td>14 Apr 20 Jan b*</td>
<td>67 weeks</td>
<td>Ongoing pregnancy</td>
<td>Not applicable</td>
<td>Not specified</td>
<td>Prior to conception and during first trimester</td>
</tr>
</tbody>
</table>

*a*: The year  
*b*: Following year

* 新薬承認情報提供時に置き換え
<table>
<thead>
<tr>
<th>Trial/Source</th>
<th>Centre ID</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP</th>
<th>TTO Positive Pregnancy Test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
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<tr>
<td>ING113086</td>
<td>82873</td>
<td>3405</td>
<td></td>
<td>DTG TDF/FTC</td>
<td>50 Q24 300/200 Q24</td>
<td>May Feb b*</td>
<td>73 weeks</td>
<td>Elective termination</td>
<td>7 weeks</td>
<td>Subjects partner HIV positive receiving Atripla</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>83503</td>
<td>4420</td>
<td></td>
<td>RAL* ABC/3TC</td>
<td>Unk 600/300 Q24</td>
<td>03 Jun March a*</td>
<td>72 weeks</td>
<td>Ongoing pregnancy</td>
<td>Not applicable</td>
<td>Not specified</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING113086</td>
<td>83268</td>
<td>3512</td>
<td></td>
<td>RAL*</td>
<td>400 Q12</td>
<td>29 Jun</td>
<td>Not specified</td>
<td>Abortion</td>
<td>Not specified</td>
<td>Two abortions</td>
<td>Prior to conception and during first trimester</td>
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<tr>
<td>ING113086</td>
<td>83765</td>
<td>3514</td>
<td></td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>17 Sep 01 July b*</td>
<td>Not specified</td>
<td>Ongoing pregnancy</td>
<td>Not applicable</td>
<td>One previous elective abortion</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING114467</td>
<td>86916</td>
<td>6046</td>
<td></td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>15 Oct UNK</td>
<td>30 Weeks</td>
<td>Elective termination</td>
<td>Not specified</td>
<td>Three elective abortions, 1 normal birth</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING114467</td>
<td>86924</td>
<td>6030</td>
<td></td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>Dec Sep b*</td>
<td>49 weeks</td>
<td>Normal infant</td>
<td>39</td>
<td>Two elective abortions; two normal births</td>
<td>Prior to conception and during first trimester</td>
</tr>
</tbody>
</table>

a*: The year
b*: Following year

* 新薬承認情報提供時に置き換え
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<table>
<thead>
<tr>
<th>Trial/Source</th>
<th>Centre ID</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP/EDD</th>
<th>TTO Positive Pregnancy Test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
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<tr>
<td>ING114467</td>
<td>84229</td>
<td>5792</td>
<td></td>
<td>EFV/FTC/TDF</td>
<td>600/200/300 Q24</td>
<td>02 Feb 10 Nov a*</td>
<td>Not specified</td>
<td>Unknown</td>
<td>Not applicable</td>
<td>One elective abortion</td>
<td>Prior to conception and during first trimester</td>
</tr>
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<td>ING114467</td>
<td>86924</td>
<td>6026</td>
<td></td>
<td>EFV/FTC/TDF</td>
<td>600/200/300 Q24</td>
<td>11 Feb Nov a*</td>
<td>Not specified</td>
<td>Unknown</td>
<td>Not applicable</td>
<td>One previous normal birth</td>
<td>Prior to conception and during first trimester</td>
</tr>
<tr>
<td>ING114467</td>
<td>81267</td>
<td>5293</td>
<td></td>
<td>EFV/FTC/TDF</td>
<td>600/200/300 Q24</td>
<td>22 Feb 29 Nov a*</td>
<td>Not specified</td>
<td>Spontaneous abortion</td>
<td>9</td>
<td>No previous pregnancies</td>
<td>Prior to conception and during first trimester</td>
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<td>ING114467</td>
<td>86971</td>
<td>7817</td>
<td></td>
<td>EFV/FTC/TDF</td>
<td>600/200/300 Q24</td>
<td>10 Feb UNK</td>
<td>Not specified</td>
<td>Ectopic pregnancy</td>
<td>Not specified</td>
<td>No previous pregnancies</td>
<td>Prior to conception and during first trimester</td>
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<tr>
<td>ING114467</td>
<td>81284</td>
<td>5473</td>
<td></td>
<td>EFV/FTC/TDF</td>
<td>600/200/300 Q24</td>
<td>04 Jun UNK</td>
<td>67 weeks</td>
<td>Abortion induced</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Prior to conception and during first trimester</td>
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<tr>
<td>ING114467</td>
<td>084011</td>
<td>5940</td>
<td></td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>29 Jun Mar b*</td>
<td>Not specified</td>
<td>Spontaneous abortion</td>
<td>10</td>
<td>Not specified</td>
<td>Prior to conception and during first trimester</td>
</tr>
</tbody>
</table>

a*: The year  
b*: Following year  

* 新薬承認情報提供時に置き換え
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<table>
<thead>
<tr>
<th>Trial/ Source</th>
<th>Centre ID</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP EDD</th>
<th>TTO Positive Pregnancy Test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
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<tr>
<td>ING114467</td>
<td>86919</td>
<td>6104</td>
<td></td>
<td>DTG ABC/3TC</td>
<td>50 Q24 600/300 Q24</td>
<td>08 Sep 15 Jun b*</td>
<td>Not specified</td>
<td>Pregnancy ongoing</td>
<td>Not applicable</td>
<td>One previous pregnancy with normal birth. Partner has medical history of necrosis of the femoral head</td>
<td>Prior to conception and during first trimester</td>
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</tbody>
</table>

**Source Data:** Safety database (OCEANS), which is maintained separately from the clinical trials database. There may, therefore, be descriptive differences of little or no clinical significance between the data presented in this table and the tables and appendices which are produced from the clinical trials database. The OCEANS and clinical trials’ databases are cross-checked to ensure compatibility of subject identifiers, study treatment at the time of event, outcome, causality, and the clinical nature of SAEs experienced. Discrepancies may arise between subject age presented elsewhere in this summary and in this table since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

a. Pregnancy reported between the ISS database cut-off for study ING113086 (24 May) and the submission data-cut-off date (26 October)

### Appendix Table 9  Listing of Pregnancies Reported from Studies in ART-Experienced (INI-Naïve) Subjects

<table>
<thead>
<tr>
<th>Trial/ Source</th>
<th>Centre ID</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP EDD</th>
<th>TTO Positive Pregnancy Test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
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<tbody>
<tr>
<td>ING111762</td>
<td>85074</td>
<td>2214</td>
<td></td>
<td>RAL</td>
<td>400 Q12</td>
<td>22 Jul 10-18 28 Apr b*</td>
<td>Not specified</td>
<td>Unknown</td>
<td>Not applicable</td>
<td>Previous pre-term pregnancy resulting in spontaneous abortion</td>
<td>Prior to conception and during first trimester</td>
</tr>
</tbody>
</table>

**Data Source:** Safety database (OCEANS), which is maintained separately from the clinical trials database. There may, therefore, be descriptive differences of little or no clinical significance between the data presented in this table and the tables and appendices which are produced from the clinical trials database. The OCEANS and clinical trials’ databases are cross-checked to ensure compatibility of subject identifiers, study treatment at the time of event, outcome, causality, and the clinical nature of SAEs experienced. Discrepancies may arise between subject age presented elsewhere in this summary and in this table since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

EDD = estimated delivery date, LMP = last menstrual period, Q12 = twice daily, RAL= raltegravir, TTO = time to observed

b*: Following year

*新薬承認情報提供時に置き換え*
### Appendix Table 10  Listing of Pregnancies Reported from Completed Clinical Pharmacology Studies in Adults

<table>
<thead>
<tr>
<th>Trial/ Source</th>
<th>Centre</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP</th>
<th>EDD</th>
<th>TTO Positive Pregnancy Test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING115697</td>
<td>99237</td>
<td>672010</td>
<td></td>
<td>DTG</td>
<td>50 Q24</td>
<td>21 Mar</td>
<td></td>
<td>Not specified</td>
<td>Unknown</td>
<td>Not applicable</td>
<td>History of spontaneous abortion</td>
<td>Prior to conception and during first trimester</td>
</tr>
</tbody>
</table>

Data Source: Safety database (OCEANS), which is maintained separately from the clinical trials database. There may, therefore, be descriptive differences of little or no clinical significance between the data presented in this table and the tables and appendices which are produced from the clinical trials database. The OCEANS and clinical trials’ databases are cross-checked to ensure compatibility of subject identifiers, study treatment at the time of event, outcome, causality, and the clinical nature of SAEs experienced. Discrepancies may arise between subject age presented elsewhere in this summary and in this table since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

DTG = dolutegravir, EDD = estimated delivery date, LMP = last menstrual period, Q24 = once daily, TTO = time to observed.

### Appendix Table 11  Listing of Pregnancies Reported from Other Ongoing Studies in Adults

<table>
<thead>
<tr>
<th>Trial/ Source</th>
<th>Centre</th>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Treatment</th>
<th>Dose (mg)</th>
<th>Date LMP EDD</th>
<th>TTO Positive Pregnancy test</th>
<th>Outcome</th>
<th>Week of Gestation</th>
<th>Other Medical Conditions</th>
<th>Duration of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING114915</td>
<td>94847</td>
<td>484704</td>
<td></td>
<td>DTG</td>
<td>50Q24</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Unknown</td>
<td>Not applicable</td>
<td>Not specified</td>
<td>Prior to conception and during first trimester</td>
</tr>
</tbody>
</table>

Data Source: Safety database (OCEANS), which is maintained separately from the clinical trials database. There may, therefore, be descriptive differences of little or no clinical significance between the data presented in this table and the tables and appendices which are produced from the clinical trials database. The OCEANS and clinical trials’ databases are cross-checked to ensure compatibility of subject identifiers, study treatment at the time of event, outcome, causality, and the clinical nature of SAEs experienced. Discrepancies may arise between subject age presented elsewhere in this summary and in this table since OCEANS reports the age of the subject at SAE onset whereas the clinical trial database records age of subject at screening.

DTG = dolutegravir, EDD = estimated delivery date, LMP = last menstrual period, Q24 = once daily, TTO = time to observed.
2.7.5 REFERENCES

*denotes references available in m5.4


De Houwer S, Demeulemeester J, Thys W, Taltynov O, Christ F, Debyser Z. Identification of residues in the C-terminal domain of HIV-1 integrase that mediate binding to TRN-SR2. JBC Papers in Press. Published on August 7, 2012 as Manuscript M112.387944


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Module 2.7.5 References


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Multistix Reagent Strips Product Information. April 1999.


*Song I, Chen S, Piscitelli S. Meta-analysis of the pharmacokinetic-pharmacodynamic relationship of integrase inhibitors. 11th International Workshop on Clinical Pharmacology of HIV Therapy; 1-9 April 2010; Sorrento, Italy. Abstract 50.


## 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Type of Study</th>
<th>Study Objective(s)</th>
<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
</table>
| ING113674    | Bioavailability | To evaluate relative the bioavailability of three different tablet formulations of dolutegravir (DTG) 50 mg and effect of food on the selected formulation | Randomized, open-label, single dose, two part, three-period crossover | Part A: 18-65yrs, Healthy subjects, male / female  
Part B: 18 subjects  
9 M/9 F  
41.8yrs (20-61) | Part A: DTG 50 mg using current formulation; 25 mg; tablet; oral; single dose; fasting  
Part B: DTG 50 mg using 25 mg/150 mg compression; 25 mg; tablet; oral; single dose; fasting  
DTG 50 mg using 25 mg/200 mg compression; 25 mg; tablet; oral; single dose; fasting | Completed; Clinical Pharmacology Study Report (CPSR) | 5.3.1.2 |
### 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Type of Study</th>
<th>Study Objective(s)</th>
<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
</table>
| ING114556    | Bioavailability and safety        | To evaluate the relative bioavailability and safety of a DTG granule formulation in healthy subjects | Randomized, open label, single dose, five-period crossover                    | 18-65yrs, Healthy subjects, male / female | 20 subjects 10M/10F 41.9yrs (21-61) | DTG 50 mg; tablet; oral; single dose  
DTG 50 mg; granule; direct to mouth; single dose  
DTG 50 mg; granule with purified water; oral; single dose  
DTG 50 mg; granule with mineral water; oral; single dose  
DTG 50 mg; granule with baby formula; oral; single dose | Completed; CPSR                   | 5.3.1.2                  |
| ING114581    | Bioavailability                   | To evaluate relative bioavailability of DTG, abacavir (ABC) and lamivudine (3TC) of single dose administration of two experimental FDC tablet formulations | Open-label, single dose, randomized, 3-period, crossover study                | 18-65yrs, Healthy subjects, male / female | 18 subjects 10M/8F 29.8yrs (19-45) | Treatment A: DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 1; tablet; oral; single dose  
Treatment B: DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 2; tablet; oral; single dose  
Treatment C: DTG 50 mg; (formulation code BC) plus EPZICOM; tablet; oral; single dose | Completed; CPSR                   | 5.3.1.2                  |
## 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Type of Study</th>
<th>Study Objective(s)</th>
<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
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<tbody>
<tr>
<td>ING111207</td>
<td>PK</td>
<td>To assess safety, tolerability and PK of single doses of DTG</td>
<td>Double-Blind, Randomized, Placebo-Controlled</td>
<td>18-55yrs, Healthy subjects, male/female</td>
<td>25 subjects 20M/5F 31.8yrs (19-54)</td>
<td>DTG 2 to 100 mg; oral suspension; single dose; fasted</td>
<td>Completed; CPSR</td>
<td>5.3.3.1</td>
</tr>
</tbody>
</table>
| ING111322    | PK           | Part 1: To assess safety, tolerability and Pharmacokinetics (PK) of repeat doses of DTG
Part 2: To assess safety, tolerability and PK of single doses of DTG suspension and single doses of DTG tablets with or without food
| Part 1: Double-Blind, Randomized, Placebo-Controlled
Part 2: Randomized, 3-Period, Balanced, Crossover | 18-50yrs, Healthy subjects, male/female | Part 1: 32 subjects 27M/5F 31.7yrs (18-50) Part 2: 12 subjects 12M/0F 30.8yrs (18-50) | Part 1: DTG 10 to 50 mg; oral suspension; once daily; 10 days; fasted
Part 2: DTG 10 mg x2 (20 mg); tablet; oral; single dose; fasted
DTG 10 mg x2 (20 mg); tablet; oral; single dose; fed | | | Completed; CPSR | 5.3.3.1 |
| ING111853    | PK           | To investigate the recovery, excretion, and PK of 14C-DTG                        | Open-label, single dose study          | 30-55yrs, Healthy subjects, male   | 6 subjects 6M/0F 37.5yrs (32-46)              | DTG 20 mg; oral suspension; single dose; fasted            | Completed; CPSR             | 5.3.3.1                 |
| ING115465    | PK           | To describe DTG exposure in cervicovaginal fluid, cervical and vaginal tissue    | Open-label, repeat dose study          | 18-35yrs, Healthy subjects, female | 8 subjects 0M/8F 21yrs (18-27) *Median age    | DTG 50 mg; tablet; oral; once daily; 5-7 days              | Completed; CPSR             | 5.3.3.1                 |
## 2.7.6 Synopses of Individual Studies

<table>
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<tr>
<th>Protocol No.</th>
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<th>Study Design</th>
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<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
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<tbody>
<tr>
<td>ING116195</td>
<td>PK</td>
<td>To describe DTG exposure in semen and rectal tissue</td>
<td>Open-label, repeat dose study</td>
<td>18-49yrs, Healthy subjects, male</td>
<td>12 subjects 12M/0F *25.5yrs (21-44) *Median age</td>
<td>DTG 50 mg; tablet; oral; once daily; 8 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.1</td>
</tr>
<tr>
<td>ING113125</td>
<td>PK</td>
<td>To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with severe renal impairment</td>
<td>Single dose, open-label, parallel group, two-part study</td>
<td>18-70yrs, Severe renal impairment subjects and matched, healthy control subjects with normal renal function, male / female</td>
<td>Renal impaired: 8 subjects 5M/3F 56.8yrs (47-65)</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>Completed; CPSR</td>
<td>5.3.3.3</td>
</tr>
<tr>
<td>ING113097</td>
<td>PK</td>
<td>To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with mild or moderate hepatic impairment based on Child-Pugh category</td>
<td>Single dose, open-label, parallel group, two-part, adaptive study</td>
<td>18-70yrs, Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function, male / female</td>
<td>Hepatic impaired: 8 subjects 5M/3F 55.5yrs (50-61)</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>Completed; CPSR</td>
<td>5.3.3.3</td>
</tr>
</tbody>
</table>
### 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Type of Study</th>
<th>Study Objective(s)</th>
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<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING115381</td>
<td>PK</td>
<td>To assess safety, tolerability and PK of single doses of DTG in healthy Japanese subjects</td>
<td>Open label, single dose study</td>
<td>20-55yrs, Healthy Japanese subjects, male / female</td>
<td>10 subjects 6M/4F 33.4yrs (22-52)</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>Completed; CPSR</td>
<td>5.3.3.3</td>
</tr>
<tr>
<td>ING113099</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and rifampin (RIF) and between DTG and rifabutin (RIFABUT)</td>
<td>Randomized, open-label, two-period, single-sequence, two cohort study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>ITT-E: 26 subjects 19M/7F 44.7yrs (26-59)</td>
<td>DTG 50 mg; tablet; oral; once daily; 7 days. DTG 50 mg; tablet; oral; BID; 7 days then DTG 50 mg; tablet; oral; BID + RIF 600 mg; capsule; oral; once daily; 14 days DTG 50 mg; tablet; oral; once daily for 7 days then DTG 50 mg; tablet; oral BID+ RIFABUT 300 mg; capsule; oral; once daily; 14 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING115696</td>
<td>PK</td>
<td>To investigate the effects of prednisone on the steady-state PK of DTG</td>
<td>Open-label, repeat dose, two-period, single-sequence</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>12 subjects 5M/7F 28.5yrs (23-38)</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily; Days 1-10 + prednisone; tablet; oral; once daily (60 mg Days 1-5; 50 mg Day 6; 40 mg Day 7; 30 mg Day 8; 20 mg Day 9; 10 mg Day 10)</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING115697</td>
<td>PK</td>
<td>To assess the potential for a drug interaction</td>
<td>Randomized, open-label, two-period,</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>32 subjects 19M/13F 42.5yrs (19-65)</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
</tbody>
</table>
## 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Type of Study</th>
<th>Study Objective(s)</th>
<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING115698 PK</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and methadone</td>
<td>Open-label, repeat dose, two-period, single-sequence</td>
<td>18-65yrs, Healthy subjects enrolled in a methadone maintenance program, male / female</td>
<td>11 subjects 6M/5F 34.5yrs (24-44)</td>
<td>DTG 50 mg; tablet; oral; once daily + TVR 750 mg; tablet; oral; q8h; 10 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING11405 PK</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and lopinavir (LPV)/ritonavir (RTV) and between DTG and darunavir (DRV)/RTV</td>
<td>Randomized, open-label, two-period, single-sequence, two cohort study</td>
<td>18-50yrs, Healthy subjects, male / female</td>
<td>31 subjects 31M/0F 29.4yrs (18-50)</td>
<td>DTG 30 mg; tablet; oral; once daily; 5 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING11602 PK</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and multivitamin and between DTG and</td>
<td>Open-label, single dose, randomized, four-period crossover study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>16 subjects 16M/0F 30.8yrs (18-53)</td>
<td>DTG 50 mg; tablet; oral; single dose</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
</tbody>
</table>
## 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Type of Study</th>
<th>Study Objective(s)</th>
<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING111603</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and etravirine (ETV)</td>
<td>Open-label, repeat dose, two-period, single-sequence study</td>
<td>18-65yrs, Healthy subjects, male/female</td>
<td>16 subjects 16M/0F 41.5yrs (19-64)</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + ETV 200 mg; tablet; oral; q12h; 14 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING111604</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and tenofovir (TDF)</td>
<td>Open-label, repeat-dose, single-sequence, three-period study</td>
<td>18-65yrs, Healthy subjects, male/female</td>
<td>16 subjects 15M/1F 38.6yrs (20-58)</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days TDF 300 mg; tablet; oral; once daily; 7 days DTG 50 mg; tablet; oral; once daily + TDF 300 mg; tablet; oral; once daily; 5 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING111854</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and atazanavir (ATV)</td>
<td>Randomized, open-label, repeat dose, two-period, single-</td>
<td>18-65yrs, Healthy subjects, male/female</td>
<td>24 subjects 21M/3F 37.2yrs (18-61)</td>
<td>Period 1: DTG 30 mg; tablet; oral; once daily; 5 days; fed Period 2:</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
</tbody>
</table>
### 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Type of Study</th>
<th>Study Objective(s)</th>
<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING111855</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and oral contraceptives (ethinyl estradiol (EE) /norgestimate (NGM))</td>
<td>Randomized, two-period, double-blind study</td>
<td>18-40yrs, Healthy subjects, female</td>
<td>16 subjects 0M/16F 31.1yrs (20-40)</td>
<td>DTG 30 mg; tablet; oral; once daily + ATV/RTV 300/100 mg; capsule; once daily; 14 days DTG 30 mg; tablet; oral; once daily + ATV 400mg; capsule; oral; once daily; 14 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING112934</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG, ETV, and LPV/RTV or DRV/RTV</td>
<td>Randomized, open-label, repeat dose, three-period, single-sequence, two-cohort adaptive study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>17 subjects 17M/0F 37.6yrs (20-61)</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + ETV/LPV/RTV 200/400/100 mg; tablet; oral; q12h; 14 days DTG 50 mg; tablet; oral; once daily + ETV (tablet) DRV (tablet)/RTV (capsule) 200/600/100 mg; oral; once daily; 14 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING112941</td>
<td>PK</td>
<td>To evaluate the effect of a high fat meal and</td>
<td>Part 1: Randomized, open-label, two</td>
<td>18-65yrs, healthy subjects, male / female</td>
<td>Part 1: 14 subjects 12M/2F</td>
<td>Part 1: DTG 50 mg; tablet; oral; single dose; fasted</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
</tbody>
</table>
## 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
<th>Protocol No.</th>
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<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
</table>
| ING113068 PK | PK            | To investigate the effects of fosamprenavir (FPV)/ RTV on the steady-state PK of DTG and to evaluate relative bioavailability of tablets with varying particle size | Part A: Open-label, repeat dose, two-period, single-sequence  
Part B: Open-label, single dose, randomized, three-period, cross over study | 18-65yrs, Healthy subjects, male / female | Part A: 12 subjects 10M/2F 33.4yrs (24-55)  
Part B: 15 subjects 4M/11F 34.7yrs (20-60) | Part A:  
DTG 50 mg; tablet; oral; once daily; 5 days  
DTG 50 mg; tablet; oral; once daily + FPV 700 mg; tablet / RTV 100 mg; capsule; oral; q12h; 10 days  
Part B:  
DTG 50 mg using 25 mg tablets with micronized drug substance; oral; single dose  
DTG 50 mg using 25 mg tablets with unmicronized drug substance; oral; single dose | Completed; CPSR | 5.3.3.4 |
## 2.7.6 Synopses of Individual Studies

<table>
<thead>
<tr>
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<th>Study Objective(s)</th>
<th>Study Design</th>
<th>Key Inclusion Criteria of Subjects</th>
<th>No. of Subjects: Gender M/F: Mean Age (Range)</th>
<th>Treatment Details (Drug/Dose/Form/Route/Frequency/Duration)</th>
<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>ING113096</td>
<td>PK</td>
<td>To assess the safety, tolerability and PK of repeat dose co-administration of DTG alone, tipranavir (TPV)/RTV alone, and DTG in combination with TPV/RTV</td>
<td>Randomized, open-label, repeat dose, three-period single-sequence, study</td>
<td>18-55yrs, Healthy subjects, male / female</td>
<td>18 subjects 14M/4F 29.3yrs (19-45)</td>
<td>DTG 50 mg using 25 mg tablets with intermediate particle size drug substance; oral; single dose</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
<tr>
<td>ING114005</td>
<td>PK</td>
<td>To evaluate PK of DTG 100 mg versus 50 mg and the effect of efavirenz (EFV) on the PK, safety and tolerability of DTG 50 mg</td>
<td>Open label, repeat dose, three period single-sequence</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>12 subjects 12M/0F 38.7yrs (20-65)</td>
<td>DTG 100 mg; tablet; oral; single dose DTG 50 mg; tablet; oral; once daily and TPV / RTV 500/200 mg; capsule; oral; BID; 5 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
</tr>
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## 2.7.6 Synopses of Individual Studies

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<tr>
<td>LAI116181</td>
<td>PK</td>
<td>To assess the potential for a drug interaction between DTG and rilpivirine (RPV)</td>
<td>Open label, repeat dose, single-sequence, 3-period study</td>
<td>18-55yrs Healthy subjects, male / female</td>
<td>28 subjects 24M/4F 31.4yrs (18-50)</td>
<td>Cohort 1: Treatment A = DTG 50 mg; tablet; oral; q24h; 5 days  Treatment B = RPV 25 mg; tablet; oral; q24h; 11 days  Treatment C = RPV 25 mg; tablet; oral; q24h + DTG 50 mg; tablet; oral; q24h; 5 days  Cohort 2: Treatment D = GSK1265744 30 mg; tablet; oral; q24h; 12 days  Treatment B = RPV 25 mg; tablet; oral; q24h; 12 days  Treatment E = RPV 25 mg; tablet; oral; q24h + GSK1265744 30 mg; tablet; oral; q24h; 12 days</td>
<td>Completed; CPSR</td>
<td>5.3.3.4</td>
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### Human Pharmacodynamic Studies

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<tr>
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<tr>
<td>ING111856</td>
<td>PD</td>
<td>To evaluate the effect of DTG on cardiac conduction as assessed by 12-lead electrocardiogram compared to placebo and</td>
<td>Randomized, partial-blind, single dose, three-period, cross-over study</td>
<td>18-55yrs Healthy subjects, male / female</td>
<td>42 subjects 17M/25F 34.5yrs (18-55)</td>
<td>DTG 250 mg; oral suspension; single dose  Placebo; oral suspension; single dose  Moxifloxacin 400 mg; tablet; oral; single dose</td>
<td>Completed; CPSR</td>
<td>5.3.4.1</td>
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<tbody>
<tr>
<td>ING114819</td>
<td>PD</td>
<td>To evaluate the effect of DTG on glomerular filtration rate as measured by iohexol and to evaluate creatinine clearance, extra-glomerular creatinine excretion, and renal plasma flow</td>
<td>Open-label, randomized, three-arm, parallel, placebo-controlled</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>38 subjects 28M/10F 31.8yrs (19-59)</td>
<td>DTG 50 mg; tablet; oral; once daily; 14 days</td>
<td>Completed; CPSR</td>
<td>5.3.4.1</td>
</tr>
<tr>
<td>ING111521</td>
<td>PD</td>
<td>To assess the safety, tolerability and efficacy of repeat dose DTG</td>
<td>Dose-ranging, 10-day, repeat dose, placebo-controlled monotherapy study</td>
<td>18-65yrs, HIV-infected subjects, male / female</td>
<td>35 subjects 35M/0F 38.4yrs (20-55)</td>
<td>DTG 2, 10, 50 mg tablet; oral; once daily; 10 days; fasted</td>
<td>Completed; CPSR</td>
<td>5.3.4.2</td>
</tr>
<tr>
<td>ING116070</td>
<td>PD</td>
<td>To determine plasma (total and unbound) DTG concentration and</td>
<td>Phase IIIb single-arm, open-label, multicenter</td>
<td>≥18yrs, HIV-infected, ART-naïve subjects, male / female</td>
<td>ITT-E 13 subjects 13M/0F 40.2yrs (28-52)</td>
<td>DTG 50 mg; tablet; oral; once daily + ABC/3TC 600/300 mg; tablet; oral; once daily; 96 weeks</td>
<td>Completed; Week 2 Synoptic</td>
<td>5.3.4.2</td>
</tr>
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<tr>
<td>ING112276</td>
<td>Efficacy and Safety</td>
<td>To select a once daily oral dose of DTG administered with either ABC/3TC or TDF/emtricitabine (FTC) and to evaluate antiviral activity, safety and PK over time</td>
<td>Phase IIb, Randomized, multicentre, parallel group, dose-ranging</td>
<td>≥18yrs, HIV-infected, ART-naïve subjects, male / female</td>
<td>205 subjects 177M/28F 37.2yrs (20-79)</td>
<td>DTG 10 mg; tablet; oral + ABC/3TC 600mg/300 mg or TDF/FTC 300mg/200mg; tablet; oral; once daily; 96 weeks</td>
<td>Ongoing; Week 16 Synoptic SR</td>
<td>5.3.5.1</td>
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<tr>
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<td></td>
<td></td>
<td>DTG 25 mg; tablet; oral + ABC/3TC 600mg/300mg or TDF/FTC 300mg/200mg; oral; once daily; 96 weeks</td>
<td>Week 24 Full CSR</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>DTG 50 mg; tablet; oral + ABC/3TC 800mg/300mg or TDF/FTC 300mg/200mg; oral; once daily; 96 weeks</td>
<td>Week 48 Abbreviated CSR</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>EFV 600 mg + ABC/3TC 600mg/300mg or TDF/FTC 300mg/200mg; oral; once daily; 96 weeks</td>
<td>Week 96 Full CSR</td>
<td></td>
</tr>
<tr>
<td>ING113086</td>
<td>Efficacy and Safety</td>
<td>To assess safety and efficacy of DTG 50 mg once daily to RAL 400 mg BID both administered with</td>
<td>Phase III, multicentre randomized, double blind, double-dummy, active-</td>
<td>≥18yrs, HIV-infected, ART-naïve subjects, male / female</td>
<td>822 subjects 703M/119F 37.0yrs (18-75)</td>
<td>DTG 50 mg; tablet; oral; once daily or RAL 400 mg; tablet; oral; once daily + ABC/3TC 600mg/300mg or TDF/FTC 300mg/200mg; tablet; oral; once daily; 96 weeks</td>
<td>Ongoing; Week 48 Full CSR</td>
<td>5.3.5.1</td>
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<tr>
<td>ING114467</td>
<td>Efficacy and Safety</td>
<td>To assess safety and efficacy of DTG plus ABC/3TC fixed-dose combination therapy administered once daily compared to Atripla</td>
<td>Phase III, randomized, double-blind, double-dummy, active-controlled, multicentre, parallel group, fully-powered non-inferiority study</td>
<td>≥18yrs, HIV-infected, ART-naïve subjects, male / female</td>
<td>833 subjects 703M/130F 36.4yrs (18-85)</td>
<td>DTG 50 mg; tablet; oral; once daily + ABC/3TC 600mg/300mg; tablet; oral; once daily; 144 weeks</td>
<td>Ongoing; Week 48 Full CSR</td>
<td>5.3.5.1</td>
</tr>
<tr>
<td>ING11762</td>
<td>Efficacy and Safety</td>
<td>To evaluate safety and efficacy of DTG 50 mg once daily vs. raltegravir (RAL) 400 mg BID, both administered with an investigator-selected background regimen</td>
<td>Phase III, multicentre randomized, double-blind, active-controlled, parallel group, non-inferiority study</td>
<td>≥18yrs, HIV-infected, ART-experienced subjects, integrase inhibitor naïve regimen, male / female</td>
<td>mITT-E 715 subjects 485M/230F 43.0yrs (18-73)</td>
<td>DTG 50 mg; tablet; oral; once daily or RAL 400 mg; tablet; oral; BID + investigator-selected background regimen; 48 weeks</td>
<td>Ongoing; Week 24 Full CSR</td>
<td>5.3.5.1</td>
</tr>
<tr>
<td>ING112961</td>
<td>Efficacy</td>
<td>To assess the antiviral activity of DTG containing regimen</td>
<td>Phase IIb, multicentre, open-label, single-arm,</td>
<td>≥18yrs, HIV-infected, ART-experienced subjects,</td>
<td>Cohort I: 27 subjects 25M/2F 46.7yrs (19-61)</td>
<td>Cohort I: DTG 50 mg; tablet; oral; once daily; 96 weeks</td>
<td>Ongoing; Week 24 Cohort I Full</td>
<td>5.3.5.2</td>
</tr>
</tbody>
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<tr>
<td>ING112574</td>
<td>Efficacy</td>
<td>To assess the antiviral activity of DTG administered with failing background therapy to Day 8 and thereafter with optimised background ART</td>
<td>Phase III, multicentre, single-arm, open-label study</td>
<td>≥18yrs, HIV-infected, ART-experienced subjects, integrate inhibitor regimen, male / female</td>
<td>183 subjects 141M/42F 47.0yrs (19-67)</td>
<td>DTG 50 mg; tablet; oral; BID; 24 weeks</td>
<td>Ongoing; Week 24 Full CSR</td>
<td>5.3.5.2</td>
</tr>
<tr>
<td>ING112578</td>
<td>Safety and PK</td>
<td>To select a DTG dose for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG adult dose</td>
<td>Phase I/II, multicenter, open-label, non-comparative intensive PK and safety study</td>
<td>≥6wks&lt;18yrs, HIV-1 infected subjects, male / female</td>
<td>Cohort I (Stage 1): 10 subjects 3M/7F 14.0yrs (12-17) Cohort I (Stage 2):</td>
<td>DTG once-a-day doses with target dose of ~1 mg/kg and with 4 weight bands, and maximum dose of 50 mg; 48 weeks</td>
<td>Ongoing; Week 24 Full CSR [10 subjects (Stage 1) from Cohort 1]</td>
<td>5.3.5.2</td>
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</table>
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<tr>
<td></td>
<td></td>
<td>selected from the Phase IIb clinical trial in ART-naive adult subjects (ING112276), to evaluate safety, tolerability, and steady-state PK of DTG in combination with other ARTs</td>
<td></td>
<td></td>
<td>12 Enrolled No data available</td>
<td></td>
<td>through 24 weeks]</td>
<td></td>
</tr>
</tbody>
</table>

**Reports of Analyses of Data from More Than One Study**

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<tr>
<td>ING116265</td>
<td>PK</td>
<td>To evaluate the effects of UGT and CYP polymorphisms on the PK of DTG</td>
<td>Meta-analysis of PGx and PK data from 9 Phase II studies</td>
<td>Healthy adult subjects</td>
<td>89 subjects 78M/11F 36.9yrs (19-64)</td>
<td>DTG 50 mg; tablet; oral; once daily; 5 days</td>
<td>Completed; Meta-analysis Report (therefore there is no synopsis)</td>
<td>5.3.5.3</td>
</tr>
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**Other Clinical Studies**

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<th>Study Status; Type of Report</th>
<th>Location of Study Report</th>
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<tr>
<td>ING114915</td>
<td>Efficacy</td>
<td>To demonstrate the non-inferior antiviral activity of DTG compared to DRV/RTV</td>
<td>Phase IIb, randomized, open-label, multicenter study</td>
<td>≥18yrs, HIV-infected, ART-naive subjects, male / female</td>
<td>483 subjects 412M/71F 36.0yrs (18-67)</td>
<td>DTG 50 mg; tablet; oral; once daily; 96 weeks</td>
<td>Ongoing; Brief Study Summary</td>
<td>5.3.5.4</td>
</tr>
<tr>
<td>ING114916</td>
<td>Patient Access</td>
<td>To provide access to patients who have documented RAL or ELV</td>
<td>Open-label, multicentre, study</td>
<td>≥18yrs, HIV-infected subjects, male / female</td>
<td>0 Enrolled</td>
<td>DTG 50 mg; tablet; oral; BID</td>
<td>Ongoing; Brief Study Summary</td>
<td>5.3.5.4</td>
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<tr>
<td>ING115502</td>
<td>Patient Access</td>
<td>To provide a mechanism to supply DTG on an individual named patient basis for treatment of individuals with integrase resistance who have no available treatment alternatives and/or limited treatment options</td>
<td>NA</td>
<td>≥18yrs, HIV-infected subjects, male / female</td>
<td>50 Enrolled 50 Ongoing No data available</td>
<td>DTG 50 mg; tablet; oral; BiD</td>
<td>Ongoing; Brief Study Summary</td>
<td>5.3.5.4</td>
</tr>
<tr>
<td>ING116529</td>
<td>Efficacy</td>
<td>To quantify the antiviral activity of DTG compared to placebo (PCB) when administered with failing background therapy for 7 days</td>
<td>Phase III, randomized, multicentre, placebo-controlled, double-blind followed by an open label phase</td>
<td>≥18yrs, HIV-infected, ART-experienced subjects, integrase inhibitor regimen, male / female</td>
<td>4 Randomized 4 Ongoing No data available</td>
<td>DTG 50 mg; tablet; oral; BiD or Placebo; tablet oral; BiD + current failing regimen; 7 days</td>
<td>Ongoing; Brief Study Summary</td>
<td>5.3.5.4</td>
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<tr>
<td>ING114580</td>
<td>Bioequivalence</td>
<td>To evaluate the bioequivalence between a single FDC tablet formulation of DTG 50mg, ABC 600 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus EPZICOM</td>
<td>Phase I, randomized, two part, open-label, crossover, single center study</td>
<td>18-65yrs, Healthy subjects, male / female</td>
<td>0 Enrolled</td>
<td>Part A: Treatment A = DTG 50 mg/ABC 600 mg/3TC 300 mg; FDC tablet; oral; single dose; fasted</td>
<td>Ongoing; Brief Study Summary</td>
<td>5.3.5.4</td>
</tr>
</tbody>
</table>

3TC = lamivudine  
ABC = abacavir  
ATV = atazanavir  
BA = bioavailability  
BID = twice daily  
CPSR = clinical pharmacology study report  
CSR = clinical study report  
DRV = darunavir  
DTG = dolutegravir  
EFV = efavirenz  
ETV = etravirine  
FTC = emtricitabine  
FPV = fosamprenavir  
IV = intravenous  
LPV = lopinavir  
PD = pharmacodynamics  
PGx = pharmacogenetics  
PK = pharmacokinetics  
RAL = raltegravir  
RTV = ritonavir  
TDF = tenofovir  
TPV = tipranavir  
M = Male  
F = Female  
NA = Not Applicable