Module 2.5

Clinical Overview

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ATV	atazanavir
AST	Aspartate aminotransferase
ART	Antiretroviral therapy
AUC	Area under the curve
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable concentration
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-24)	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose or over 24 hours
BE	Bioequivalence
BID	Twice daily
C24	Concentration at 24 hours post dose
CART	Combination antiretroviral therapy
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
C0	Pre-dose concentration
C0_avg	Average of concentrations at time 0
Cτ	Concentration at the end of the dosing period
c/mL	copies per milliliter
CDC	Centers for Disease Control and Prevention
CSF	Cerebrospinal fluid
CI	Confidence Interval
COBI	cobicistat
CrCL	Creatinine clearance
CSR	Clinical Study Report
CYP	Cytochrome P450
CV%	Coefficient of variance
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir, S/GSK1349572
EFV	efavirenz
EMA	European Medicines Agency
Emax	Maximum effect
ERPF	Effective renal plasma flow
ETR	Etravirine
EVG	elvitegravir

FC	Fold change
FDA	(US) Food and Drug Administration
FDC	Fixed dose combination
FPV	fosamprenavir
FTC	emtricitabine
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HIV-2	Human Immunodeficiency Virus Type 2
IC50	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IN	Integrase
IND	Investigational New Drug
INI	Integrase inhibitor
ITT-E	Intent-to-Treat Exposed
LOCFDB	Last observation carried forward (discontinuation equals Baseline)
LPV	Lopinavir
mg	Milligram
mITT-E	Modified Intent-to-Treat Exposed
mm^3	Cubic millimeter
MSDF	Missing, Switch or Discontinuation = Failure
ng	Nanogram
NOAEL	No Observable Adverse Effect Level
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OBR	Optimized background regimen
OCT2	Organic cation transporter 2
OMP	Omeprazole
PAH	Para-aminohippurate
PBMC	Peripheral blood mononuclear cell
PDVF	Protocol defined virologic failure
PI	Protease inhibitor
PK	Pharmacokinetic
PD	Pharmacodynamic
PP	Per-protocol
RAL	raltegravir
RIF	Rifampin
RNA	Ribonucleic acid
RTV	ritonavir
SE	Single Entity

SJS	Stevens Johnson Syndrome
SOC	System organ class
t1/2	Terminal phase half-life
TLOVR	Time to Loss of Virologic Response
TDF	tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
TPV	tipranavir
UGT	Uridine diphosphate glucuronyltransferase
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
Vd/F	Apparent volume of distribution
VL	Viral load

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1. PRODUCT DEVELOPMENT RATIONALE

1.1. Introduction

A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) is being developed for use in the treatment of human immunodeficiency virus (HIV) infection.

DTG is a novel INI currently under clinical development by GlaxoSmithKline (GSK) on behalf of ViiV Healthcare (ViiV). It is a potent, low nanomolar inhibitor of HIV integrase that provides the excellent antiviral activity and tolerability demonstrated for the INI class, while also offering once-daily dosing without the need for pharmacokinetic (PK) boosting. DTG is available in the United States (US) and has marketing applications under review in the European Union (EU) and other countries worldwide; it received US approval in August 2013 and is marketed as TIVICAY™. Co-formulated ABC 600 mg/3TC 300 mg is available as a once-daily FDC in the US, EU and many countries worldwide; it was first approved in 2004 and is marketed as KIVEXA™ (EPZICOM™ in the US and Japan).

The new STR being developed is a FDC of DTG 50 mg + ABC 600 mg + 3TC 300 mg with once-daily dosing for antiretroviral therapy (ART)-naïve and ART-experienced (INI-naïve) patients, and is referred to in this document as the DTG/ABC/3TC FDC.

1.2. HIV Infection

An estimated 34.2 million adults and children worldwide were living with HIV/Acquired Immunodeficiency Syndrome (AIDS) in 2011 [UNAIDS, 2012a].

In 2011, the global adult (15 to 49 years) HIV prevalence rate was 0.8% [UNAIDS, 2012b]. During that year, 2.5 million people were newly infected with HIV, and there were 1.7 million deaths due to HIV/AIDS. Of newly infected people, an estimated 1.2 million were women and girls, and 330,000 were children. As well, 3.4 million children younger than 15 years were living with HIV in 2011 [UNAIDS, 2012a]. In 2009, an estimated 370,000 children contracted HIV during the perinatal and breastfeeding period. Overall, the epidemic appears to have stabilized in most regions, although prevalence continues to increase in Eastern Europe and Central Asia and in other parts of Asia due to a high rate of new HIV infections [UNAIDS, 2010]. In 2011, Sub-Saharan Africa remained the most heavily affected region, accounting for 68% (1.7 million) of all new HIV infections among adults and children [UNAIDS, 2012b].

1.3. Current Therapies and Unmet Clinical Need

Although combination ART with HIV protease inhibitors and reverse transcriptase inhibitors has demonstrated significant improvement in AIDS-related morbidity and mortality, a number of issues remain to be addressed that could lead to improvements in

our existing armamentarium of HIV therapy. Ideal characteristics for new treatment regimens in comparison to currently available therapies include: 1) activity against drug-resistant HIV, 2) less toxicity and greater tolerability, 3) durability and higher barrier to developing resistance, 4) fewer drug interactions, and 5) a convenient dosing schedule. Regimens that include INIs—the latest class of antiretroviral drugs to be developed for use in combination ART—can provide most, if not all, such improvements over existing regimens, particularly when combined with other antiretrovirals in an STR.

There is substantial evidence in the literature that supports the benefit of streamlined treatment regimens, including those with once-daily administration and a minimized pill burden. In addition, clinical data support patient acceptance of and preference for STRs, as well as improved compliance with STRs.

In a study to evaluate therapy simplification, DeJesus et al. [DeJesus, 2009] found that when subjects were switched in a 2:1 ratio to a STR administered once daily (i.e., Atripla [efavirenz/tenofovir/emtricitabine: EFV/TDF/FTC]), instead of staying on a 3-drug, multi-pill, once-daily regimen, the STR regimen led to improvement in self-reported outcomes, including perceived ease of taking the regimen and overall preference for the STR.

Airoldi and colleagues [Airoldi, 2010] had similar findings when switching from a dual NRTI plus EFV regimen to the STR Atripla. In this study, the adherence rate at 1 month was improved modestly, but statistically significantly ($p < 0.01$), and this continued through 6 months of follow up. Their results also indicated a better perceived quality of life and higher patient preference for the STR.

A study by Bangsberg et al. [Bangsberg, 2010] evaluated the use of an STR (Atripla) and showed that it was a key factor in improving treatment compliance and viral suppression in a high-risk, marginalized population of homeless or near-homeless HIV-infected people. These data support the benefit of an STR treatment for populations where compliance may be more challenging.

As HIV infection is an incurable, lifelong condition, the availability of durable treatment options is critical to the successful treatment of patients. Patient compliance features prominently in the long-term success of any antiretroviral regimen because poor compliance due to factors such as pill burden has been linked to the increased development of HIV drug resistance, which in turn, inevitably leads to the inability of a regimen to suppress the virus. The use of STRs in the treatment of HIV may decrease the potential for selective resistance to develop to any of the individual components as patients must either take an entire regimen via a single pill, or take none of the regimen; they cannot selectively take only 1 or 2 drugs of their multi-drug regimen. This is important given that monotherapy (or "virtual monotherapy" due to partial compliance with a regimen) is a risk for early development of viral resistance to that drug, eventual treatment failure, and the elimination of future treatment options due to within-class cross-resistance to other drugs.

Currently, the recommended STRs are non-nucleoside reverse transcriptase inhibitor (NNRTI)-based (i.e., Atripla and Complera) [DHHS, 2013]. The recently-approved STR Stribild is the first INI-based STR—it contains the INI elvitegravir (EVG), along with the

PK booster cobicistat (COBI), and the NRTIs tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). However, despite the availability of these STRs, there is still a need for the DTG/ABC/3TC FDC.

All of the current STR options, with the exception of TRIZIVIR™ (ABC, 3TC, and the NRTI zidovudine), contain the nucleotide reverse transcriptase inhibitor (NtRTI) TDF, which may not be a suitable treatment option for some patients, such as patients with/at risk for renal insufficiency or osteopenia, or those with resistance or intolerance to tenofovir.

Other potential treatment advantages for the DTG/ABC/3TC FDC versus most other available STRs include a lack of significant cytochrome P450 (CYP) 3A enzyme interactions, and the ability to dose without regard to food. NNRTIs are substrates and inducers of CYP enzymes, and the STR Stribild includes a CYP3A4 inhibitor in its formulation to provide PK boosting for its INI component elvitegravir. All components of the DTG/ABC/3TC FDC have few drug interactions, which would allow for co-administration of the DTG/ABC/3TC FDC with drugs used to treat co-morbid conditions.

The data summarized in this submission describes the performance of a DTG+ABC/3TC regimen vs. comparators; the pivotal randomized clinical trial ING114467 (SINGLE) has shown that the DTG+ABC/3TC regimen was statistically superior to the Atripla STR through 96 weeks of therapy. The DTG+ABC/3TC regimen has been used as a treatment option in other treatment-naïve studies in the DTG development program and this data is presented in this submission as well; importantly, none of the treatment-naïve subjects treated with this regimen have developed resistance to any of the components of the regimen. This is not the case for the NNRTI- and raltegravir (RAL)-based comparator arms in the DTG program (for which NRTI and 3rd agent resistance has been observed), and stands in contrast to the frequency of treatment-emergent resistance that has been observed with the other STRs that are currently marketed [Cohen, 2012; DeJesus, 2012; Zolopa, 2013].

Therefore, the Sponsor believes that the DTG/ABC/3TC FDC will be a valuable new therapeutic option for patients and prescribers, as it allows the benefits of a maximally simplified daily treatment (i.e., a once-daily single tablet regimen). Finally, the DTG/ABC/3TC FDC may represent the best choice for patients with HIV infection who would be optimally treated with a DTG-based regimen, either due to tolerance concerns or resistance concerns (e.g., those with virus resistant to NNRTIs or protease inhibitors [PIs]), and who would benefit from the adherence advantages associated with STRs. The Sponsor intends to file regulatory submissions to make the DTG/ABC/3TC FDC available worldwide.

1.4. Claimed Indication and Dosage

The proposed product labeling for DTG/ABC/3TC 50/600/300 mg FDC includes the following key elements:

DTG/ABC/3TC is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults as well as children over 12 years of age and of at least 40 kg body weight who are antiretroviral treatment-naive or

are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents in DTG/ABC/3TC FDC (applicable where ABC/3TC FDC is currently approved for use in adolescents).

DTG/ABC/3TC FDC is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments. Separate preparations of DTG (TIVICAY™), ABC (ZIAGEN™) or 3TC (EPIVIR™) should be administered in cases where discontinuation or dose adjustment is indicated. In these cases the physician should refer to the individual product information for these medicinal products.

Since the recommended dose of DTG is 50 mg twice daily for patients with resistance to integrase inhibitors, the use of DTG/ABC/3TC FDC is not recommended for patients with resistance to integrase inhibitors, ABC, and/or 3TC.

DTG/ABC/3TC FDC should be administered as presented below (with or without food):

ADULTS AND ADOLESCENTS:

The recommended dose of DTG/ABC/3TC FDC in adults and adolescents weighing at least 40 kg is one tablet once daily.

CHILDREN:

DTG/ABC/3TC FDC is not currently recommended for treatment of children less than 12 years of age as DTG and once daily dosing of ABC or 3TC are currently not approved in these children. Clinical data is currently not available for this combination. Physicians should refer to the individual product information for DTG, ABC, and 3TC.

1.5. Clinical Development Program

The Sponsor's strategy for the development of DTG/ABC/3TC FDC includes the discussion of results from clinical studies conducted under different development programs for DTG, ABC, 3TC, and the ABC/3TC FDC.

DTG is available in the United States (US) and has marketing applications under review in the European Union (EU) and other countries worldwide; it received US approval in August 2013 and is marketed as TIVICAY. Co-formulated ABC 600 mg/3TC 300 mg is available as a once-daily FDC in the US, EU and many countries worldwide; it was first approved in 2004 and is marketed as KIVEXA (EPZICOM in the US and Japan). The ABC/3TC FDC is approved for once daily dosing in some markets down to 12 years, while the individual components (ABC and 3TC) are approved down to 3 months of age [EPZICOM US Prescribing Information, 2012; KIVEXA EU Summary of Product Characteristics, 2013].

With regard to individual components of ABC/3TC FDC, recommended dosing of ABC and 3TC for the treatment of HIV infection in adults and adolescents was initially 300 mg twice daily for ABC (1998) and 150 mg twice daily for 3TC (1995). The pharmacokinetic profile of these products supported the likelihood that once daily dosing

would provide sustained antiretroviral activity, confirmed by clinical studies resulting in regulatory approval for once daily dosing in 2004 for ABC and 2002 for 3TC.

For the DTG/ABC/3TC FDC development program, one pivotal study and five supportive studies provide safety and efficacy data in support of this combination product. These studies were conducted in the intended populations, and they provide data from subjects taking all three DTG/ABC/3TC FDC components concomitantly and/or DTG + 2 NRTIs (or at least 1 fully-active agent in the case of the ART-experienced, INI-naive study ING111762). These studies are:

- **ING114467 (SINGLE)**, which is also part of the DTG single entity development program, is considered the pivotal DTG/ABC/3TC FDC study because this trial evaluated a regimen of once-daily DTG 50 mg + ABC/3TC 600/300 mg FDC as one of two randomized study treatments.

- **ING113086 (SPRING-2)**, **ING114915 (FLAMINGO)**, and **ING112276 (SPRING-1)**, which are clinical studies within the DTG single entity development program, are considered supportive in demonstrating the safety and efficacy of the DTG/ABC/3TC FDC as they all include subjects administered once-daily ABC/3TC 600/300 mg FDC as a background treatment option in combination with DTG 50 mg once daily.

- **ING116070 (CSF Study)** and **ING111762 (SAILING)**, which are clinical studies within the DTG single entity development program, are considered supportive in demonstrating the safety and efficacy of the DTG 50 mg tablet in combination with ABC/3TC or other active antiretroviral drugs. The numbers of subjects from these studies contributing data for once daily DTG 50 mg + ABC/3TC 600/300 mg are small for both of these studies.

Five other studies are considered a part of the clinical development of the individual DTG/ABC/3TC FDC components, including:

- **ING111521** provided proof of concept (POC) for the DTG component and was included in the original DTG submission.

- **CNA30021**, **EPV20001**, **EPV40001**, and **COLA4005** were included in regulatory submissions to gain approval for once daily dosing of ABC 600 mg or 3TC 300 mg in many regions. Other studies (CAL30001, ESS30008, EPZ104057, CNA109586, and COL101004) were conducted with the ABC/3TC FDC and are included in the description of clinical studies in approved ABC/3TC FDC labeling in some countries and provide relevant background information discussed in m2.7.3, Section 6.

Finally, clinical pharmacology studies have been conducted to bridge between the various formulations over time and form an important component to support the efficacy and safety of DTG/ABC/3TC FDC. Underpinning all the clinical efficacy studies is the bioequivalence (BE) study ING114580, establishing that the DTG/ABC/3TC FDC tablet is bioequivalent to DTG+ABC/3TC FDC administered concomitantly. The pivotal

biopharmaceutical study CAL10001 established the bioequivalence of the ABC/3TC FDC (600 mg/300 mg) and the marketed formulations as ABC 2x300 mg tablets and 3TC 2x150 mg tablets. The clinical pharmacology studies relevant to the DTG/ABC/3TC FDC as well as the individual components are discussed in m2.7.1 and in m2.7.2.

Other studies have been conducted with DTG, ABC, 3TC, and ABC/3TC FDC. A list of sponsored studies with DTG, ABC, 3TC, or ABC/3TC FDC not included in this submission is available in Appendix Table 1. Clinical Study Reports for these studies are available upon request. A full listing of studies included in this application is located in m5.2, Table of Studies.

1.5.1. Organization of Efficacy and Safety Data Presentation in this Clinical Overview

The Overview of Efficacy (Section 4) provides a summary of the ART-naïve subjects receiving DTG+ABC/3TC for pivotal Study ING114467, and supportive Studies ING113086 and ING114915. Due to the small sample size of ART-naïve subjects in ING116070 (n =13), results are presented in m2.7.3 Summary of Clinical Efficacy (Section 2.2.4) and not repeated in this clinical overview. For ART-experienced subjects in supportive Study ING111762, few subjects (n=8) were taking DTG+ABC/3TC, therefore, efficacy data for this subset of subjects was not compiled. In addition to the recent approval in the US for DTG for use in ART-experienced patients, ABC and 3TC single entity products and ABC/3TC FDC are all indicated in multiple markets for the treatment of HIV infection in ART-experienced patients, and provide long-standing clinical experience in this population. A brief summary of efficacy results of the ART-experienced population from ING111762 is presented to support the indication in ART-experienced subjects.

Furthermore, to provide pivotal efficacy data for the individual components of DTG/ABC/3TC FDC, the Overview of Efficacy (Section 4) will present brief summaries of studies supporting the DTG component including the entire population of ART-naïve subjects (i.e., who received DTG + 2 NRTIs) from IN113086 and ING114915 as well as, the entire ART-experienced population (i.e., who received DTG + background regimen [BR]) from ING111762. See module 2.7.3 for efficacy data on other supportive Studies ING112276 (m2.7.3, Section 2.2.3) and ING111521 (m2.7.3, Section 2.2.6). Finally, the Overview of Efficacy also presents a brief summary of ABC and 3TC studies: CNA30021, EPV20001, EPV40001, and COLA4005. Other studies (CAL30001, ESS30008, EPZ104057, CNA109586, and COL101004) are summarized in m2.7.3, Section 6 and not repeated this clinical overview.

Regarding the safety profile of DTG/ABC/3TC FDC, the Overview of Safety (Section 5) provides a summary of integrated analyses from the ART-Naïve Pooled Dataset (including ING114467, ING113086, ING114915, and ING112276) and further non-integrated safety data from healthy subjects who took DTG/ABC/3TC FDC from the Phase I Bioequivalence Study ING114580. Safety results from ING116070 results are presented in m2.7.4 Summary of Clinical Safety and not repeated in this clinical overview.

The Sponsor believes the DTG single entity study ING111762 provides robust safety data in the ART-experienced population. Similarly, the safety profiles in clinical use of ABC and 3TC are well-known and described in ZIAGEN, EPIVIR, and KIVEXA/EPZICOM labeling. Therefore, the summary of ART-experienced subjects in ING111762 and studies with ABC and 3TC (including ART-naïve studies CNA30021, EPV20001, EPV40001, and COLA4005 and other FDC combination in ART-experienced studies: CAL30001 and ESS30008) are presented in Summary of Clinical Safety (m2.7.4) and will not be repeated in this clinical overview. Studies in ART-experienced, INI-resistant subjects using DTG 50 mg twice daily (ING112961 and ING112574), which were discussed in the submission for single entity DTG, are not presented herein; the Sponsor is not seeking an indication in this population and thus, efficacy data from these studies are not relevant to this DTG/ABC/3TC FDC submission.

1.6. Regulatory History

The development program for DTG/ABC/3TC FDC has been formally discussed with key regulatory agencies at various milestones throughout the development program (See m2.2).

1.7. Compliance with Good Clinical Practice (GCP)

All studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

2. OVERVIEW OF BIOPHARMACEUTICS

For detailed information on biopharmaceutic data described in this section, refer to m2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods).

This application for the DTG/ABC/3TC FDC tablet is supported by the bioequivalence study ING114580, a single dose, 2-way crossover study conducted in healthy volunteers to evaluate the bioequivalence of a single combined formulated tablet of DTG 50 mg, ABC 600 mg and 3TC 300 mg compared to co-administration of the separate tablet formulations of DTG 50 mg and EPZICOM (ABC 600 mg/3TC 300 mg) in the fasted state, and to evaluate the effect of food on the bioavailability of the combined formulation (see Section 2.3.1.1, m2.7.1). The formulation of EPZICOM used was the same as KIVEXA tablets registered in other markets.

The FDC tablet formulation of DTG 50 mg, ABC 600 mg and 3TC 300 mg met the criteria for bioequivalence with the separate tablet formulations of DTG 50 mg plus EPZICOM. Given that bioequivalence was demonstrated in ING114580, the efficacy demonstrated in clinical trials using the combination of the separate DTG and ABC/3TC

tablet formulations represents the efficacy that would have been achieved with the DTG/ABC/3TC FDC formulation, had it been available at the time those studies were conducted.

For each of DTG, ABC, and 3TC, the 90% CIs for the GLS mean ratios for the AUC0-∞, AUC0-t, and Cmax are within the BE criteria range of 0.8 to 1.25. The statistical results from the treatment comparisons of DTG, ABC, and 3TC PK parameters for bioequivalence assessment are also graphically summarized Figure 14, m2.7.1. Furthermore, the effect of food on the exposures of the three component drugs in the FDC was consistent with historical data for the individual tablets.

2.1. DTG/ABC/3TC FDC Biopharmaceutical Classification

DTG sodium, Form 1, is a non-hygroscopic, crystalline solid with suitable solid state stability and oral bioavailability. DTG sodium has a solubility of 3.2 mg/ml in water at 25°C; in buffered solutions across the physiological pH range 1 to 7, the solubility is significantly lower (at or below 50 µg/ml). The measured permeability is approximately $3x10^{-4}$ cm/sec. The combination of low solubility with high predicted permeability puts DTG in Biopharmaceutics Classification System Class II (m2.7.2, Section 1.1).

ABC and 3TC are established drugs and both are highly soluble in water.

ABC is approximately 77 mg/mL at 25°C and 3TC is approximately 85 mg/mL at 25°C. ABC has an absolute oral bioavailability of ~83% [Yuen, 2008]. Consequently, ABC is a BCS class III drug with high solubility and low drug permeability.

3TC has an absolute bioavailability of ~82% in adults [Johnson, 1999]. Consequently, 3TC is also a BCS class III drug with high solubility and low permeability.

Abacavir Sulphate is a BCS I drug with high solubility and high drug permeability.

3TC is a BCS III drug with high solubility.

2.2. DTG/ABC/3TC FDC Formulation Development

DTG, ABC and 3TC tablets, 50 mg/600 mg/300 mg (DTG/ABC/3TC tablets) were formulated to deliver an accurate quantity of the three active ingredients in a form that is physically and chemically stable. The detailed information regarding the formulation development of the DTG/ABC/3TC tablet is provided in m3.2.P.2, Formulation Development.

A Phase I relative bioavailability study (ING114581) has been carried out using two different tablet formulations of DTG/ABC/3TC tablets, listed as Formulation 1 and 2. The bioavailability of these two formulations was compared with DTG tablets, 50 mg and EPZICOM (ABC 600 mg/3TC 300 mg) FDC tablets.

Formulation 1 was optimized and then the proposed commercial formulation was used in the bioequivalence study (ING114580).

The formulation used in pivotal BE study is identical to the commercial formulation with the following exception: The tablet used in ING114580 was debossed with 572 TRI and a score bar on both sides of the tablet. The proposed commercial formulation of DTG/ABC/3TC FDC tablet is a purple, oval, biconvex tablet debossed with '572 Trı' on one side and plain on the other side. This difference in de-bossing is not anticipated to significantly affect product performance.

The tablets contain 52.62 mg DTG sodium which is equivalent to 50 mg DTG free acid, 702 mg abacavir sulphate, which is equivalent to 600 mg ABC and 300 mg 3TC.

The tablets are packaged into HDPE bottles with child-resistant closures that include induction seals. The bottles contain a desiccant. The quantitative composition of the DTG/ABC/3TC FDC tablet is summarized in Table 5, m2.7.1.

Dissolution Profile

The DTG/ABC/3TC FDC tablets are immediate-release, solid oral-dosage form. The dissolution profiles for the proposed commercial tablet formulation (Batch 121363956 used in ING114580) showed that complete dissolution of the DTG/ABC/3TC tablets within the predefined specification by test methods is consistent with the results from the *in vivo* pivotal bioequivalence study ING114580.

2.3. Analytical Methods

The bioanalytical methods used to measure concentrations of DTG, ABC, and 3TC in human plasma were sensitive, selective, accurate and reproducible. Stability of the analyte was demonstrated during sample processing and long-term storage (m2.7.1, Section 1.3.3).

2.4. Biopharmaceutics Studies

The key results from biopharmaceutic studies for consideration in clinical use and detailed in m2.7.1 are as follows:

- No absolute (IV/PO) bioavailability studies have been carried out with the DTG/ABC/3TC FDC formulation;
- Complete dissolution of the DTG/ABC/3TC FDC tablets within the predefined specification by test methods is consistent with the results from the *in vivo* pivotal bioequivalence study ING114580;
- Bioequivalence was demonstrated between the DTG/ABC/3TC FDC tablet formulation and the separate co-administered tablet formulations of TIVICAY (DTG) plus EPZICOM (ABC/3TC FDC).
- The bioanalytical methods used to measure concentrations of DTG, ABC and 3TC in human plasma were sensitive, selective, accurate and reproducible. Stability of the analytes were demonstrated during sample processing and long-term storage;

- DTG/ABC/3TC FDC tablets use micronized DTG and non-micronized ABC and 3TC;
- DTG/ABC/3TC FDC can be taken with or without food based on the accumulated safety data in Phase IIb and III/b studies all of which permitted DTG, ABC or 3TC dosing without restriction to food or food content.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

Critical findings from the clinical pharmacology studies conducted with DTG, ABC or 3TC (the individual components of DTG/ABC/3TC FDC) are discussed below. For some variables, only the more recent DTG development program included formal analysis. No clinical pharmacology study was performed with DTG/ABC/3TC FDC. These studies are described in detail in m2.7.2 (Summary of Clinical Pharmacology).

3.1. Absorption, Distribution, Metabolism and Elimination of DTG, ABC, and 3TC

Absorption

DTG, ABC and 3TC are rapidly absorbed following oral administration. The absolute bioavailability of DTG has not been established. The absolute bioavailability of oral ABC and 3TC in adults is 83% and 80 to 85% respectively. The mean time to maximal serum concentrations (tmax) is about 2 to 3 hours (post dose for tablet formulation), 1.5 hours and 1.0 hours for DTG, ABC and 3TC respectively.

At steady state, the Cmax and AUC0-24 of DTG 50 mg once daily is 3.67 micrograms/mL and 53.6 μ.h/mL, respectively. Following a single oral dose of 600 mg of ABC, the mean Cmax is 4.26 micrograms/mL and the mean AUC∞ is 11.95 micrograms.h/mL. Following multiple-dose oral administration of 3TC 300 mg once daily for seven days the mean steady-state Cmax is 2.04 micrograms/ml and the mean AUC24 is 8.87 micrograms.h/mL.

Distribution

The apparent volume of distribution of DTG (following oral administration of tablet formulation, Vd/F) is estimated at 17.4 L based on population pharmacokinetic analysis. Intravenous studies with ABC and 3TC showed that the mean apparent volume of distribution is 0.8 and 1.3 l/kg respectively.

DTG is highly bound (approximately 99.3%) to human plasma proteins based on in vitro data. Binding of DTG to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. Free fraction of DTG in plasma is estimated at approximately 0.2 to 1.1% in healthy subjects, approximately 0.4 to 0.5% in subjects with moderate hepatic impairment, 0.8 to 1.0% in subjects with severe renal impairment and 0.5% in HIV-1 infected patients. Plasma protein binding studies *in vitro* indicate that ABC binds only low to moderately

(approximately 49%) to human plasma proteins at therapeutic concentrations. 3TC exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36%).

DTG, ABC, and 3TC are present in cerebrospinal fluid (CSF). In 12 treatment-naïve subjects receiving a regimen of DTG plus ABC/3TC for 16 weeks, DTG concentration in CSF averaged 16 ng/mL at Week 2 and 12.6 ng/mL at Week 16, ranging from 3.64 to 23.2 ng/mL (comparable to unbound plasma concentration). CSF:plasma concentration ratio of DTG ranged from 0.11 to 2.04%. DTG concentrations in CSF exceeded the 50% inhibitory concentration (IC50) in all subjects at both 2 and 16 weeks of therapy. Studies with ABC demonstrate a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9 fold greater than the IC_{50} of ABC of 0.08 micrograms/ml or 0.26 micromolar when ABC is given at 600 mg twice daily. The mean ratio of CSF/serum 3TC concentrations 2 to 4 h after oral administration was approximately 12%. The true extent of CNS penetration of 3TC and its relationship with any clinical efficacy is unknown.

DTG is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue, and vaginal tissue were 6 to 10% of that in corresponding plasma at steady-state. AUC was 7% in semen and 17% in rectal tissue, of those in corresponding plasma at steady-state.

Metabolism

DTG is primarily metabolized via UGT1A1 (glucuronosyltransferase 1 family, polypeptide A cluster) with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). DTG is the predominant circulating compound in plasma and renal elimination of unchanged drug is low (<1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the feces but it is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of DTG (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose) (2.7.2 Summary of clinical pharmacology studies).

ABC is primarily metabolized by the liver with less than 2% of the administered dose being renally excreted as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine.

Metabolism of 3TC is a minor route of elimination. 3TC is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions with 3TC is low due to the small extent of hepatic metabolism (less than 10%).

Elimination

DTG has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 1 L/hr following oral administration of tablet formulation based on population pharmacokinetic analyses.

The mean half-life of ABC is about 1.5 hours. The geometric mean terminal half-life of intracellular carbovir-TP at steady-state is 20.6 hours. Following multiple oral doses of ABC 300 mg twice a day, there is no significant accumulation of ABC. Elimination of ABC is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged ABC account for about 83% of the administered ABC dose in the urine. The remainder is eliminated in the feces.

The observed 3TC half-life of elimination is 5 to 7 hours. For subjects receiving 3TC 300 mg once daily, the terminal intracellular half-life of 3TC-TP was prolonged to 16 to 19 hours. The mean systemic clearance of 3TC is approximately 0.32 l/h/kg, predominantly by renal clearance (greater than 70%) via the organic cationic transport system.

3.2. Pharmacokinetics in Special Populations

3.2.1. Children

DTG/ABC/3TC has not been studied in pediatric subjects. PK, safety and/or efficacy data from the individual components support the use of DTG/ABC/3TC in HIV-infected, pediatric patients aged 12 to 18 years weighing at least 40 kg (applicable where ABC/3TC FDC is currently approved for use in adolescents).

The PK profiles of the adult DTG/ABC/3TC FDC tablet were tested in the pivotal BE study ING114580 comparing PK profiles of DTG, ABC, and 3TC from the FDC tablet (containing DTG 50 mg, ABC 600 mg, and 3TC 300 mg) to those from separate entities (50 mg DTG tablet + ABC/3TC FDC containing ABC 600 mg and 3TC 300 mg). This BE study bridges the separate drugs used in the Phase III/b adult and pediatric clinical studies to the FDC tablet. The DTG 50 mg tablets used in the adult studies are the same formulation used in the pediatric study ING112578.

In ING112578, Cohort I included 23 ART-experienced HIV-1 infected children and adolescents aged 12 to 18 years of age. The pharmacokinetics of DTG was evaluated in 10 children and showed that weight based dosing of DTG resulted in DTG exposure in pediatric subjects comparable to that observed in adults who received DTG 50 mg once daily (Table 1).

Table 1 Pediatric Pharmacokinetic Parameters (n=10)

Age/weight	DTG Dose	DTG Pharmacokinetic Parameter Estimates Geometric Mean (CV%)		
		AUC(0-24) µg.hr/mL	Cmax µg/mL	C24 µg/mL
12 to 18 yrs, ≥40 kg [a]	50 mg once daily [a]	46 (43)	3.49 (38)	0.90 (59)

Data Source: ING112578 CSR Table 13 (in-text)
a. One subject weighing 37 kg received 35 mg once daily.
Note: Consistent with adult data for DTG 50 mg once daily, Section 3.1.

A secondary objective of this study was an assessment of efficacy. Nineteen of twenty-three subjects achieved virologic suppression (HIV-1 RNA <400 copies/mL [c/mL]) at Week 24, with 16 of 23 (70%) subjects achieving HIV-1 RNA <50 c/mL. The efficacy data further support the validity of the dosing strategy for adolescent (12 to <18 years of age), HIV-infected patients (weighing at least 40 kg) of DTG 50 mg once daily.

Safety data for this study is summarized in Section 5.5. Overall, DTG was demonstrated to have a similar safety profile in HIV-infected children 12 to <18 years of age as has been demonstrated in HIV-infected adults in clinical studies.

Although only ART-experienced children were enrolled in this age cohort of ING112578 (Cohort I), the primary objective of this study was the assessment of PK and safety, which would be expected to be similar in ART-naïve patients. Consistent with adult data for DTG 50 mg once daily, variability in AUC and C24h were 43% and 59%, respectively, using an adult tablet formulation administered under modified fasting conditions in adolescents of 12 to <18 years. The Geometric Mean AUC24 for these 10 children in Cohort I was 46 µg*h/mL and the C24h was 0.902 µg/mL, meeting the pre-defined targeted PK exposure from adults receiving DTG 50 mg once daily (AUC0-24 37 to 67 µg*h/ml and C24h 0.77 to 2.26 µg/ml). These DTG exposures have been shown to be efficacious in both treatment-naïve and ART-experienced (INI-naïve) adults in ING113086 and ING111762, respectively, and support the use of DTG 50 mg once daily in ART-naïve and ART-experienced (INI-naïve) 12 to <18 year olds weighing at least 40 kg.

The virologic and immunologic principles underlying the use of ART are considered to be similar in adults and children. With the use of antiretroviral agents, the course of HIV infection is similar in children compared to adults [Gortmaker, 2001; Doerholt, 2006]. Therefore, efficacy data and exposure-response relationship from adult studies should be relevant for the prediction of antiviral response in HIV infected children. As HIV integrase is a viral target, not a host target, it is expected that the PK/PD relationship between DTG drug exposure and antiviral activity is similar between adults and pediatric populations. The guiding principles of disease management in children is similar to adults with the same goals of therapy, i.e., complete suppression of viral replication as measured by plasma HIV-1 RNA and restoration of the immune system.

Therefore, the PK data from ING112578 in adolescents aged 12 to <18 years are sufficiently similar to adults to permit extrapolation of efficacy data from pharmacokinetic correlation, which is in line with the International Conference on

Harmonization guidance for medicinal products in the pediatric population [European Medicines Agency (EMA), 2011].

Pharmacokinetic parameters of ABC and 3TC in adolescents are comparable to those reported in adults (see m2.7.2, Section 2.2.4.3 and Section 2.3.4.8) [EPZICOM US Prescribing Information, 2012; KIVEXA EU Summary of Product Characteristics, 2013]. The ABC/3TC FDC is approved for once daily dosing in some markets down to 12 years, while the individual components (ABC and 3TC) are approved down to 3 months of age.

3.2.2. Elderly

Pharmacokinetic data for DTG, ABC and 3TC in subjects of >65 years old are limited. However, population pharmacokinetic analysis of DTG using data in HIV-1 infected adults showed no clinically relevant effect of age on the PK profile of DTG (m2.7.2, Section 1.3.5.3). There is no evidence that a dose adjustment of DTG, ABC or 3TC would be required in adults based on the effects of age on PK parameters.

3.2.3. Hepatic impairment

Pharmacokinetic data has been obtained for DTG, ABC and 3TC alone. Based on the absence of data with ABC in patients with moderate or severe hepatic impairment, DTG/ABC/3TC FDC is not recommended in patients with moderate or severe hepatic impairment.

DTG is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of DTG was similar between the two groups. The effect of severe hepatic impairment on the pharmacokinetics of DTG has not been studied.

Data obtained for 3TC in patients with moderate to severe hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction.

ABC is metabolized primarily by the liver. The pharmacokinetics of ABC have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). The results showed that there was a mean increase of 1.89 fold in the ABC AUC and 1.58 fold in the half-life of ABC. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. No relationship has been identified between ABC exposure and incidence of adverse events.

Dosage reduction of ABC may be required in patients with mild hepatic impairment. The separate preparation of ABC and thus of 3TC and DTG should therefore be used to treat these patients requiring an ABC dose adjustment. The pharmacokinetics of ABC has not been studied in patients with moderate or severe hepatic impairment. Plasma concentrations of ABC are expected to be variable and substantially increased in these patients. DTG/ABC/3TC FDC is therefore not recommended in patients with moderate and severe hepatic impairment.

3.2.4. Renal impairment

Pharmacokinetic data have been obtained for DTG, ABC and 3TC separately. DTG/ABC/3TC FDC should not be used in patients with creatinine clearance of less than 50 mL/min because, whilst no dosage adjustment of DTG or ABC is necessary in patients with renal impairment, dose reduction is required for the 3TC component. Therefore the separate preparation of 3TC and thus of ABC and DTG should be used to treat these patients with this combination of ARVs.

Renal clearance of unchanged drug is a minor pathway of elimination for DTG. A study of the pharmacokinetics of DTG was performed in subjects with severe renal impairment (CLcr <30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr <30 mL/min) and matching healthy subjects were observed. DTG has not been studied in patients on dialysis, though differences in exposure are not expected.

ABC is primarily metabolized by the liver, with approximately 2% of ABC excreted unchanged in the urine. The pharmacokinetics of ABC in patients with end-stage renal disease is similar to patients with normal renal function.

Studies with 3TC show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Therefore, dose adjustment is required for patients with creatinine clearance <50 mL/min.

3.2.5. UGT1A1 Polymorphism

Data is available for DTG, and no genetic polymorphisms have been described that would significantly alter the pharmacokinetics of ABC or 3TC.

There is no evidence that common polymorphisms in drug metabolizing enzymes alter DTG pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor DTG metabolism had a 32% lower clearance of DTG and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41). This increase is not considered to be clinically significant given the accumulated safety data obtained in Phase III/b. No relationship between DTG exposure and AEs has been identified. Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of DTG.

3.2.6. Gender

The DTG exposure in healthy subjects appear to be slightly higher (~20%) in women than men based on data obtained in a healthy subject study (males n=17, females n=24). Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III/b adult trials revealed no clinically relevant effect of gender on the exposure of DTG.

A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) subjects showed no gender differences in ABC AUC normalized for lean body weight. A population PK analysis showed no gender differences in 3TC oral clearance. A pharmacokinetic trial in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in 3TC AUC normalized for body weight.

There is no evidence that a dose adjustment of DTG, ABC or 3TC would be required based on the effects of gender on PK parameters.

3.2.7. Race

Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III/b adult trials revealed no clinically relevant effect of race on the exposure of DTG. The pharmacokinetics of DTG following single dose oral administration to Japanese subjects appear similar to observed parameters in Western (US) subjects.

There are no significant differences between blacks and Caucasians in ABC pharmacokinetics. There are no significant racial differences in 3TC pharmacokinetics.

There is no evidence that a dose adjustment of DTG, ABC or 3TC would be required based on the effects of race on PK parameters.

3.2.8. Co-infection with Hepatitis B or C

Population pharmacokinetic analyses indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to DTG. There are limited pharmacokinetic data on subjects with hepatitis B co-infection. There are no PK data for hepatitis co-infection for ABC and 3TC.

3.3. Drug-Drug Interactions

Drug interaction trials were conducted with DTG, ABC, and/or 3TC, the components of DTG/ABC/3TC FDC. The drug-drug interaction studies are described in m2.7.2, Section 2 and Section 3.

3.3.1. Effect of DTG, ABC, 3TC on the Pharmacokinetics of Other Agents

In vitro, DTG demonstrated no direct, or weak inhibition (IC50>50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2, or MRP4. In vitro, DTG did not induce CYP1A2, CYP2B6 or CYP3A4. In vivo, DTG did not have an effect on midazolam, a CYP3A4 probe. Based on these data, DTG is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug interaction studies, DTG did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir, and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, DTG inhibited the renal organic cation transporter 2 (OCT2) (IC_{50} = 1.93 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 6.34 μM) and MATE2-K (IC50 = 24.8 μM). DTG has a low potential to affect the transport of MATE2-K substrates in vivo. In vivo, DTG may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 (dofetilide, pilsicainide, metformin) (see Table 2) or MATE1.

In vitro, DTG inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC50 = 2.12 μM) and OAT3 (IC50 = 1.97 μM). Based upon the DTG unbound plasma concentration, in silico modeling, and no notable effect on the pharmacokinetics in vivo of the OAT substrates tenofovir and para aminohippurate, DTG has low propensity to cause drug interactions via inhibition of OAT transporters.

ABC and 3TC do not inhibit or induce CYP enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6).

3.3.2. Effect of Other Agents on the Pharmacokinetics of DTG, ABC, 3TC and Dose Recommendations

DTG is eliminated mainly through metabolism by UGT1A1. DTG is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore drugs that induce those enzymes or transporters may theoretically decrease DTG plasma concentration and reduce the therapeutic effect of DTG. Co-administration of DTG and other drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase DTG plasma concentration (see Table 2).

Efavirenz, nevirapine, rifampicin and tipranavir/ritonavir each reduced or is expected to reduce the plasma concentrations of DTG significantly, and require DTG dose adjustment to 50 mg twice daily. Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir. Therefore no DTG dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir, decreased plasma concentrations of DTG and the need for dose adjustments differ based on regional labels. A drug interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of DTG. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on DTG pharmacokinetics, therefore no DTG dose adjustment is required when co-administered with these drugs.

The likelihood of metabolic interactions with ABC and 3TC is low. ABC and 3TC are not significantly metabolised by CYP enzymes. The primary pathways of ABC metabolism in human are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine. The likelihood of metabolic interactions with 3TC is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. 3TC is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is renal.

DTG/ABC/3TC FDC is a complete regimen for the treatment of HIV infection. It is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments due to interacting concomitant medications. Separate preparations of DTG (TIVICAY), ABC (ZIAGEN) or 3TC (EPIVIR) should be administered in cases where dose adjustment is required.

Selected drug interactions are presented in Table 2, Table 3, and Table 4. Recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 2 Drug Interactions Studied with DTG

Concomitant Drug Class: Drug Name	Effect on Concentration of DTG or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	DTG ↓ AUC ↓ 71% Cmax ↓ 52% Cτ ↓ 88% ETR ↔	Etravirine decreased plasma DTG concentration, which may result in loss of virologic response and possible resistance to DTG. DTG/ABC/3TC FDC should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	DTG ↓ AUC ↓ 57% Cmax ↓ 39% Cτ ↓ 75% EFV ↔	Efavirenz decreased DTG plasma concentrations. Since the dose of DTG is 50 mg twice daily when co-administered with efavirenz, the co-administration of efavirenz with DTG/ABC/3TC FDC is not recommended.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	DTG ↓	Co-administration with nevirapine has the potential to decrease DTG plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on DTG exposure is likely similar to or less than that of efavirenz. Since the dose of DTG is 50 mg twice daily when co-administered with nevirapine, the co-administration of nevirapine with DTG/ABC/3TC FDC is not recommended.
Protease Inhibitor: Atazanavir (ATV)	DTG ↑ AUC ↑ 91% Cmax ↑ 49% Cτ ↑ 180% ATV ↔	Atazanavir increased DTG plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV+RTV)	DTG ↑ AUC ↑ 62% Cmax ↑ 33% Cτ ↑ 121% ATV ↔ RTV ↔	Atazanavir/ritonavir increased DTG plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV+RTV)	DTG ↓ AUC ↓ 59% Cmax ↓ 47% Cτ ↓ 76% TPV ↔ RTV ↔	Tipranavir/ritonavir decreases DTG concentrations. Since the dose of DTG is 50 mg twice daily when co-administered with tipranavir/ritonavir, the co-administration of tipranavir/ritonavir with DTG/ABC/3TC FDC is not recommended.
Protease Inhibitor: Fosamprenavir/ritonavir (FPV+RTV)	DTG ↓ AUC ↓ 35% Cmax ↓ 24% Cτ ↓ 49% FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases DTG concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients.

Concomitant Drug Class: Drug Name	**Effect on Concentration of DTG or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Protease Inhibitor: Nelfinavir	DTG ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV+RTV)	DTG ↔ AUC ↔ Cmax ↔ Cτ ↔ LPV ↔ RTV ↔	Lopinavir/ritonavir did not change DTG plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV+RTV)	DTG ↓ AUC ↓ 32% Cmax ↓ 11% Cτ ↓ 38% DRV ↔ RTV ↔	Darunavir/ritonavir did not change DTG plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDF)	DTG ↔ TDF ↔	Tenofovir did not change DTG plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV+ETR)	DTG ↔ AUC ↑ 10% Cmax ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir co-administered with etravirine did not change DTG plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV+ETR)	DTG ↓ AUC ↓ 25% Cmax ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔ ETR ↔	Darunavir/ritonavir co-administered with etravirine did not change DTG plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Agents		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of DTG has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Co-administration of dofetilide or pilsicainide and DTG and is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentrations.
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine	DTG↓	Co-administration with these metabolic inducers may decrease DTG plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.

Concomitant Drug Class: Drug Name	**Effect on Concentration of DTG or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
St. John's wort		
Antacids containing polyvalent cations (e.g., Mg, Al)	DTG ↓ AUC ↓ 74% Cmax ↓ 72% C24 ↓ 74%	Co-administration of antacids containing polyvalent cations decreased DTG plasma concentration. DTG/ABC/3TC FDC is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	DTG ↓ AUC ↓ 39% Cmax ↓ 37% C24 ↓ 39%	DTG/ABC/3TC FDC is recommended to be administered 2 hours before or 6 hours after taking supplements containing calcium, or alternatively, administer with food.
Iron supplements	DTG ↓ AUC ↓ 54% Cmax ↓ 57% C24 ↓ 56%	DTG/ABC/3TC FDC is recommended to be administered 2 hours before or 6 hours after taking supplements containing iron, or alternatively, administer with food.
Metformin	Metformin ↑	Co-administration of DTG has the potential to increase metformin plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Lower metformin doses may be considered for patients treated with dolutegravir and metformin.
Rifampicin	DTG ↓ AUC ↓ 54% Cmax ↓ 43% Cτ ↓ 72%	Rifampicin decreased DTG plasma concentration. Since the dose of DTG is 50 mg twice daily when co-administered with rifampicin, the co-administration of rifampicin with DTG/ABC/3TC FDC is not recommended.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN))	Effect of DTG: EE ↔ AUC ↑ 3% Cmax ↓ 1% Cτ ↑ 2% Effect of DTG: NGMN ↔ AUC ↓ 2% Cmax ↓ 11% Cτ ↓ 7%	DTG did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with DTG/ABC/3TC FDC.
Methadone	Effect of DTG: Methadone ↔ AUC ↓ 2% Cmax ↔ 0% Cτ ↓ 1%	DTG did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with DTG.

Data Source: m2.7.2

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; Cmax = maximum observed concentration, Cτ=concentration at the end of dosing interval

Table 3 Drug Interactions Studied with ABC

Concomitant Drug Class: Drug Name	Effect on Concentration of ABC or Concomitant Drug	Clinical Comment
Methadone (40 to 90 mg once daily for 14 days/600 mg single dose, then 600 mg twice daily for 14 days)	ABC AUC ↔ Cmax ↓35% Methadone CL/F ↑22%	The changes in ABC pharmacokinetics are not considered clinically relevant. The changes in methadone pharmacokinetics is not considered clinically relevant for the majority of patients
Ethanol	ABC AUC ↑41% Ethanol AUC ↔	Given the safety profile of ABC, these findings are not considered clinically significant.

Data Source: m2.7.2
Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; Cmax = maximum observed concentration, CL/F = apparent clearance

Table 4 Drug Interactions Studied with 3TC

Concomitant Drug Class: Drug Name	Effect on Concentration of 3TC or Concomitant Drug	Clinical Comment
Trimethoprim/sulfamethoxazole (Co-trimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	3TC: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of 3TC is necessary (see Dosage and Administration). 3TC has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of 3TC with higher doses of co-trimoxazole used for the treatment of Pneumocystis jiroveci (P. carinii) pneumonia and toxoplasmosis has not been studied. DTG/ABC/3TC FDC is not recommended for subjects with CrCl of <50 ml/min.
Emtricitabine		3TC-containing products may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both 3TC and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. 3TC-containing products are not recommended for use in combination with emtricitabine.
Zalcitabine		3TC may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. DTG/ABC/3TC FDC is therefore not recommended to be used in combination with zalcitabine.

Data Source: m2.7.2
Abbreviations: ↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve

3.3.3. Lack of Interaction Between Individual Components of DTG/ABC/3TC

Due to different routes of metabolism and elimination and minimal effect of these agents on drug metabolizing enzymes or transporters, no clinically significant drug interactions are expected between DTG, ABC, and 3TC. The primary route of elimination of DTG is metabolism, with UGT1A1 as the primary route and CYP3A as the secondary route. The primary routes of elimination of ABC are metabolism by alcohol dehydrogenase and glucuronidation (UGT2B7). The primary route of elimination of 3TC is renal excretion. Although DTG is an inhibitor of OCT2 and has the potential to increase the exposure of 3TC as OCT2 may be involved in active secretion of 3TC in the urine [Moore, 1996], no clinically relevant drug interaction has been observed between DTG and 3TC. This is supported by the cross-study comparison, demonstrating that the PK of ABC and 3TC when given as a ABC/3TC FDC tablet co-administered with DTG from the pivotal bioequivalence study ING114580 (m2.7.1) were similar to those obtained when given as ABC/3TC FDC alone in study CAL10001, a bioequivalence study for EPZICOM/KIVEXA (m2.7.1). These data suggest that DTG does not have an effect on 3TC exposure nor on ABC exposure. Therefore no PK drug interaction study was conducted between the individual components of DTG/ABC/3TC.

The lack of any meaningful PK interaction is further supported by the favorable safety profile observed across the ART-naive studies, where subjects have received DTG in combination with 3TC and ABC for 48 to 96 weeks or longer (ING112276, ING113086, ING114467, and ING114915) (m2.7.4).

3.4. Pharmacodynamics

The pharmacodynamic studies are described in m2.7.2, Section 2.2.

3.4.1. Mechanism of Action

DTG inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. In vitro, DTG dissociates slowly from the active site of the wild type integrase-DNA complex (t½ 71 hours).

ABC and 3TC are NRTIs, and are potent, selective inhibitors of HIV-1 and HIV-2. Both ABC and 3TC are metabolized sequentially by intracellular kinases to the respective triphosphate (TP) which are the active moieties with extended intracellular half-lives supporting once daily dosing (see Pharmacokinetics, Elimination). 3TC-TP and carbovir-TP (the active triphosphate form of ABC) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. ABC and 3TC triphosphates show significantly less affinity for host cell DNA polymerases.

3.4.2. Effect of DTG on Cardiac Conduction

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single dose oral administrations of placebo, a supratherapeutic dose of DTG at 250 mg as suspension (exposures approximately 2-3-fold of the 50 mg twice daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. DTG did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec).

There was no requirement to conduct thorough QTc studies at the time of development and registration of the marketed ABC- and 3TC- containing products. AE preferred terms indicative of clinical manifestations of TdP are not listed in the Company RSI or any approved local country labeling for ABC/3TC or the individual single entities ABC and 3TC. There is no evidence for risk of TdP for ABC and 3TC base on non-clinical data (see [m2.4 Nonclinical Overview] for further details).

3.4.3. Effect of DTG on Renal Function

The effect of DTG on serum creatinine clearance (CrCL), glomerular filtration rate (GFR) using iohexol as the probe, and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomized, 3 arm, parallel, placebo-controlled study in 37 healthy subjects, who were administered DTG 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily (n=12) for 14 days. A modest decrease (about 10%) in CrCL was observed with DTG within the first week of treatment, consistent with that seen in clinical studies. DTG at both doses had no significant effect on actual GFR or ERPF. These data support in vitro studies which suggest that the small increases in creatinine observed in clinical studies are due to the likely benign inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

3.5. Clinical Pharmacology Conclusions

Overall, pharmacokinetics, pharmacodynamics, PK/PD relationship in various patient populations, and drug interaction profile of DTG, ABC, 3TC as a fixed dose combination support the following dose recommendations:

Treatment-naïve adults: DTG/ABC/3TC 50/600/300 mg FDC once daily.

Treatment-experienced but integrase inhibitor-naïve adults: DTG/ABC/3TC 50/600/300 mg FDC once daily.

Integrase inhibitor-naïve children of 12 to <18 years of age and weighing greater than or equal to 40 kg: DTG/ABC/3TC 50/600/300 mg FDC once daily.

The following should be considered when initiating treatment with the DTG/ABC/3TC FDC:

- Dose adjustment is not possible given that the full daily dose of each component is contained in a single tablet.
- DTG/ABC/3TC FDC may be taken with or without food (m2.7.1).
- No substantial differences in PK were observed across patient demographic groups (weight, gender, age, race/ethnicity, UGT1A1 genotype) and no clinical significant effect of HCV co-infection was observed; therefore there is no need for individualized dosing based on these factors.
- DTG/ABC/3TC is not recommended for use in patients with moderate or severe hepatic impairment due to insufficient data being available for the ABC component.
- DTG/ABC/3TC is not recommended for use in patients with creatinine clearance <50 mL/min due to the inability to adjust the dose of the 3TC component.
- Drug interaction studies were conducted with individual compounds. No drug interaction studies have been conducted with the DTG/ABC/3TC FDC tablet. DTG/ABC/3TC components have favorable drug interaction profile, with few interactions that require a dose adjustment or schedule change. If dose adjustments are required, these should be done with administration of the separate components. Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of DTG, ABC, or 3TC.
    - No clinically significant drug interactions between DTG, ABC, and 3TC have been observed or are expected based on in vitro data, in vivo data, or metabolic pathways. ING114580 demonstrated that the FDC will provide exposures consistent with the individual components.
    - The co-administration of DTG/ABC/3TC with etravirine is not recommended unless the patient is also receiving concomitant ATV/r, LPV/r or DRV/r.
    - EFV, RIF, nevirapine and TPV/r each reduce or are expected to reduce the plasma concentrations of DTG significantly, and require DTG dose adjustment to 50 mg twice daily. Therefore co-administration of DTG/ABC/3TC FDC with these agents is not recommended. Recommendations for concomitant use of fosamprenavir (FPV)/ritonavir (RTV) differ based on regional labeling.
    - Due to metabolic induction, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, and St. John's wort have the potential to reduce DTG drug concentration to a suboptimal level. Therefore DTG/ABC/3TC FDC should not be co-administered with these agents.
    - DTG/ABC/3TC should not be co-administered with polyvalent cation-containing antacids due to significant reduction in DTG exposure. DTG/ABC/3TC is recommended to be administered 2 hours before or 6 hours after these agents.
    - DTG/ABC/3TC should be administered at least 2 hours before or 6 hours after calcium and iron supplements in the fasting state; alternatively, DTG/ABC/3TC

can be given concurrently with calcium or iron supplements with food. Concomitant fasting administration of calcium carbonate and ferrous fumarate reduced DTG exposure 39-54%, however no significant interaction was observed when DTG was given concomitantly with these supplements taken with a meal.

- Metformin concentrations may be increased by the DTG component. Lower doses of metformin may be considered in subjects treated with DTG and metformin.
- Due to inhibition of OCT2 by DTG, co-administration of DTG/ABC/3TC with dofetilide or pilsicainide is prohibited.
- Due to a theoretical potential to reduce intracellular phosphorylated metabolites, caution should be exercised when ABC-containing drugs and ribavirin are co-administered.

4. OVERVIEW OF EFFICACY

Module 2.7.3 (Summary of Clinical Efficacy) provides details on the individual efficacy results from the clinical program.

The effectiveness of DTG/ABC/3TC FDC tablets for the treatment of HIV-1 infection is demonstrated with results from clinical studies conducted over many years under the development programs for DTG, ABC, 3TC, and the ABC/3TC FDC (see m2.7.3, Section 9: Appendix Table 1).

This Overview of Efficacy provides a summary of ART-naïve subjects receiving DTG+ABC/3TC for pivotal Study ING114467 and supportive Studies ING113086 and ING114915. See m2.7.3 for efficacy data on Study ING116070, which is not discussed in this summary due to the small size (n=13 DTG+ABC/3TC).

For ART-experienced subjects in supportive Study ING111762, few subjects (n=8) were taking a regimen of DTG+ABC/3TC (one of whom was also taking maraviroc), and therefore, efficacy data for this subset of subjects were not presented separately. In addition to the recent approval in the US for DTG, the ABC and 3TC single entity products and the ABC/3TC FDC are all indicated in multiple markets for the treatment of HIV infection in ART-experienced patients, supported by long-standing clinical experience since 1998 and 1995, respectively. A brief summary of efficacy results of the whole ART-experienced population from ING111762 is presented to support the indication in ART-experienced subjects.

Furthermore, to provide pivotal efficacy data for the individual components of DTG/ABC/3TC FDC, the Overview of Efficacy will present brief summaries of studies supporting the DTG component including the entire population of ART-naïve subjects (i.e., who received DTG + 2 NRTIs) from ING113086 and ING114915 as well as the entire ART-experienced population (i.e., who received DTG + background regimen [BR]) from ING111762. Finally, the Overview of Efficacy presents a brief summary of efficacy results from ABC and 3TC studies: CNA30021, EPV20001, EPV40001, and COLA4005.

4.1. Non-clinical Virology

A summary of non-clinical and clinical virology can be found in m2.7.2.4 (Special Studies). DTG inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. ABC and 3TC inhibit HIV Reverse Transcriptase, an essential enzyme for HIV replication. Key non-clinical virology data are as follows:

- DTG has activity across broad HIV-1 subtypes. In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, DTG demonstrated antiviral potency similar to that seen with laboratory strains, with a mean IC50 of 0.52 nM. In addition, when tested in peripheral blood mononuclear cell (PBMC) assays against a panel consisting of 24 HIV-1 clinical isolates (group M [clade A, B, C, D, E, F and G] and group O) and 3 HIV-2 clinical isolates, the geometric mean IC50 was 0.20 nM and IC50 values ranged from 0.02 to 2.14 nM for HIV-1, while the geometric mean IC50 was 0.18 nM and IC50 values ranged from 0.09 to 0.61 nM for HIV-2 isolates.
- DTG, ABC, and 3TC are all additive or synergistic when assayed in combination with other antiretroviral agents.
- The dissociation of DTG, RAL, and EVG from wild type and mutant IN proteins complexed with DNA was investigated to obtain a better understanding of INI dissociation kinetics. DTG demonstrated slower dissociation from all IN-DNA complexes tested, including those with single, double, and up to four residue IN substitutions. The prolonged DTG binding characteristics are consistent with its distinct resistance profile and its higher barrier to resistance.
- 3TC selects for RT mutation M184V in vitro, resulting in a 100 to 1000 FC increase in IC50. ABC selects for RT mutations M184V, K65R, L74V, and Y115F in vitro. For ABC, the single M184V change confers low (2 to 3) FC increase, which alone does not confer clinical resistance.
- The combination of ABC + 3TC has proven efficacy alone and when used as a nucleoside backbone for third drugs of multiple classes. The combination of ABC + 3TC has a well defined and clinically robust resistance profile.

4.2. Selection of Patient Populations in Pivotal and Supportive Efficacy Studies

The DTG/ABC/3TC FDC pivotal and supportive studies in adults supporting this submission recruited HIV-1 infected subjects aged 18 years and older who were able to provide written informed consent. Women of child-bearing potential were eligible for enrolment if using a reliable method of contraception as permitted by labeling of comparator agents. Subjects were excluded on the basis of medical history (e.g. active Centers for Disease Control and Prevention [CDC] Category C disease with certain exceptions, moderate to severe hepatic impairment, gastrointestinal bleeding, allergy to

study drugs, history of malignancies), concomitant or recent medical therapy (e.g. HIV-1 vaccines, treatments with activity against HIV-1 that are not licensed for that purpose, radiation therapy, immunomodulators, cytotoxic chemotherapeutic agents or recent use of experimental drugs) or screening laboratory values (e.g. any verified Grade 4 lab abnormalities, or liver chemistries above specified thresholds). Notwithstanding the minimum inclusion and exclusion criteria defined in each protocol, investigators were also required to follow any existing country-specific guidelines when making decisions about subjects who were eligible for study participation.

Detailed study criteria for the other studies included in this submission are not described here, but can be found in the CSRs.

The specific eligibility criteria implemented during each phase of development for the different DTG/ABC/3TC FDC components (see m2.7.3, Table 3) reflected the data that were available at that time, and are therefore slightly different between the studies presented in this Summary of Clinical Efficacy.

4.3. Rationale for Dose Selection in Clinical Development

The doses selected for the DTG+ABC/3TC pivotal study, ING114467, were based on the doses previously selected for once-daily dosing of DTG, ABC, and 3TC. Administration of DTG 50 mg once-daily was selected for ART-naïve and ART-experienced (INI-naïve) populations. ABC 600 mg and 3TC 300 mg are the approved once-daily doses in the intended populations, and these are also the approved doses for the ABC/3TC FDC. Refer to m2.7.3, Section 4 for more details concerning dosing recommendations.

4.3.1. DTG 50 mg Component

The 50 mg once daily dose for DTG in ART-naïve/ART-experienced (INI-naïve) subjects was selected based on the following:

- Results from ING111521, 10-day monotherapy study in ART-naive or ART-experienced and INI-naive subjects demonstrated that once daily dosing of DTG achieved viral load declines for 2 mg, 10 mg and 50 mg of 1.54, 2.04, and 2.48 $\log_{10}$ c/mL, respectively. The 50 mg once daily dose achieved an inhibitory quotient (observed DTG concentration at the end of the dosing interval [Cτ]/fold above PA-IC90) of 19, demonstrating considerable coverage above the in vitro protein adjusted target concentration of 0.064 ng/ml.
- A PK/PD analysis from ING111521 evaluated the relationship between Cτ and change in HIV RNA from Baseline. The data were fit to a maximum effect model and demonstrated that the 50 mg dose was on the plateau of the concentration-response curve after monotherapy.
- In ING112276, a Phase IIb dose-ranging study in ART-naive subjects that evaluated DTG at doses of 10 mg, 25 mg and 50 mg once daily with 2 NRTIs vs. EFV plus 2 NRTIs. DTG was well tolerated across all doses studied. A good safety and tolerability profile with a low discontinuation rate due to AEs was observed in all three arms with no significant dose-dependent trends in safety parameters. All three

doses showed similar robust antiviral responses and no apparent dose-response relationship was observed, suggesting DTG doses from 10 mg to 50 mg once daily in combination with 2 NRTIs achieved maximum virologic suppression. Therefore, the highest dose, DTG 50 mg once daily, was selected as the dose for the Phase III studies in INI-naive population. Selection of 50 mg once daily dose was also to accommodate decreases in DTG concentrations in light of drug interactions, poor absorption, imperfect adherence, or other cause.

- The efficacy and safety of the 50 mg once daily dose was confirmed in four Phase III/b studies in integrase inhibitor-naïve subjects (ING114467, ING113086, ING111762 and ING114915). DTG has demonstrated superiority to Atripla and DRV+RTV and non-inferiority to RAL in ART-naïve subjects, and superiority to RAL in ART-experienced, INI-naïve subjects.

In summary, a dose of 50 mg once daily demonstrated safety and efficacy in ART-naive and ART-experienced (INI-naïve) adult subjects.

4.3.2. ABC and 3TC Components

The currently approved ABC 600 mg and the 3TC 300 mg once daily dosing was demonstrated in efficacy studies included in this and prior submissions and is represented in current product labeling. Limited information on dose selection is provided in m2.7.2. As such, a reanalysis of data supporting the approved ABC 600 mg component and the 3TC 300 mg component is not provided here. In addition, the combination of DTG 50 mg and ABC 600/3TC 300 mg demonstrated safety and efficacy in ING114467.

4.4. Clinical Trial Methodology and Design

The study designs details including the primary objectives, treatment regimens and number of subjects randomized for pivotal and supportive efficacy studies are presented in m2.7.3, Section 1.5 and listed in (Table 5).

Table 5 Brief Summary of Clinical Efficacy Studies Presented in the Summary of Clinical Efficacy

Study Number	Phase	Study Design and Duration	Primary Objectives	Study Reporting Status	Regimens[a]	No. of Subjects by Group Entered/ Completed[b]
Pivotal DTG/ABC/3TC FDC Study						
ING114467 (SINGLE)	III	Randomized, double-blind, double-dummy, active-controlled, multicenter, parallel group, fully-powered non-inferiority study 96 weeks (with subsequent open-label, phase from Week 96-144)	To assess safety and efficacy of DTG + ABC/3TC fixed-dose combination therapy administered once daily compared to Atripla	Week 96 CSR complete	DTG 50 mg once daily + ABC/3TC 600/300 mg once daily EFV/TDF/FTC 600/200/300 mg once daily	DTG + ABC/3TC: 414 Randomized 342 Completed Randomized Phase 340 Ongoing in Open Label Phase EFV/TDF/FTC: 419 Randomized 310 Completed Randomized Phase 302 Ongoing in Open Label Phase
DTG 50 mg Component Studies						
ING113086 (SPRING-2)	III	Multicenter randomized, double blind, double-dummy, active-controlled, parallel group, fully-powered non-inferiority study 96 weeks (with subsequent optional, open-label continuation of DTG arm)	To assess safety and efficacy of DTG 50 mg once daily compared to RAL 400 mg twice daily both administered with fixed-dose dual NRTI therapy	Week 96 CSR complete	DTG 50 mg once daily; oral tablet or RAL 400 mg once daily; oral tablet + ABC/3TC 600 mg/ 300 mg once daily; oral tablet or + TDF/ FTC 300 mg/ 200 mg once daily; oral tablet	DTG: 411 Randomized 349 Completed Randomized Phase 336 Ongoing in Open Label Phase RAL: 411 Randomized 332 Completed Randomized Phase (Note: per the study design, subjects randomized to RAL discontinue the study at

Study Number	Phase	Study Design and Duration	Primary Objectives	Study Reporting Status	Regimens[a]	No. of Subjects by Group Entered/ Completed[b]
						Week 96, so none are ongoing)
ING114915 (FLAMINGO)	IIIb	Randomized, open-label, active-controlled, parallel group, non-inferiority, multicenter study 96 weeks (with subsequent optional, continuation of DTG arm)	To demonstrate the non-inferior antiviral activity of DTG compared to DRV+RTV	Week 48 CSR complete	DTG 50 mg once daily, or DRV+RTV 800 mg/100 mg, once daily + ABC/3TC 600 mg/ 300 mg once daily, or + TDF/ FTC 300 mg/ 200 mg once daily	DTG: 242 Randomized 224 Ongoing DRV+RTV: 242 Randomized 213 Ongoing
ING112276 (SPRING-1)	IIb	Randomized, multicenter, parallel group, dose-ranging study 96 weeks (with subsequent optional, open-label continuation of DTG arms on selected dose)	To select a once daily oral dose of DTG administered with either ABC/3TC or TDF/FTC and to evaluate antiviral activity, safety and PK over time	Week 96 CSR complete	DTG 10 mg once daily, or DTG 25 mg once daily, or DTG 50 mg once daily, or EFV 600 mg once daily + ABC/3TC 600 mg/ 300 mg once daily, or + TDF/ FTC 300 mg/ 200 mg once daily [At the Week 96 visit, all DTG subjects were switched to the selected dose of 50 mg once daily]	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 (Note: After Week 96, EFV subjects discontinued and all DTG subjects may switch to open-label DTG 50 mg.) DTG 50 mg Open Label: 138 Enrolled 127 Ongoing

Study Number	Phase	Study Design and Duration	Primary Objectives	Study Reporting Status	Regimens[a]	No. of Subjects by Group Entered/ Completed[b]
ING116070 (CSF Study)	IIIb	Single-arm, open-label, multicenter study 96 weeks	To determine plasma (total and unbound) DTG concentration and evaluate the relationship between DTG concentration in plasma and CSF	Week 16 CSR available	DTG 50 mg once daily + ABC/3TC 600/300 mg once daily	13 Enrolled 11 Ongoing
ING111762 (SAILING)	III	Multicenter randomized, double-blind, active-controlled, parallel group, non-inferiority study 48 weeks (with subsequent optional, open-label continuation of DTG arm)	To evaluate safety and efficacy of DTG 50 mg once daily vs. RAL 400 mg twice daily, both administered with an investigator-selected background regimen	Week 48 CSR complete	DTG 50 mg once daily or RAL 400 mg twice daily + Investigator-selected background regimen	DTG: 357 Randomized, 299 Completed Randomized Phase, 282 Ongoing in Open Label Phase RAL: 362 Randomized, 283 Completed Randomized Phase, 23 Ongoing in Open Label Phase (Note: per the study design, subjects randomized to RAL discontinue the study at Week 48 unless RAL is not locally available)
ING111521 (DTG POC Study)	IIa	Multicenter, randomized, parallel, double-blind, dose ranging, placebo-controlled study 10 days	To assess the safety, tolerability and efficacy of repeat dose DTG	Day 10 CPSR complete	DTG 2 mg once daily, fasted, or DTG 10 mg once daily, fasted, or DTG 50 mg once daily, fasted, or Placebo once daily, fasted	35 (including 7 placebo) Enrolled 35 Completed

Study Number	Phase	Study Design and Duration	Primary Objectives	Study Reporting Status	Regimens[a]	No. of Subjects by Group Entered/ Completed[b]
ABC 600 mg and/or 3TC 300 mg Component Studies						
CNA30021	III	Randomized, double-blind, multicenter study 48 weeks	To compare the efficacy of ABC 600 mg once daily versus ABC 300 mg TWICE DAILY in combination with 3TC 300 mg once daily and efavirenz 600 mg once daily	Week 48 CSR complete	Treatment Arm A: ABC 600 mg; tablet; oral; once daily + ABC placebo; tablet; oral; BID + 3TC 300 mg; tablet; oral; once daily + EFV 600 mg; tablet; oral; once daily ; all for 48 weeks Treatment Arm B: ABC 300 mg; tablet; oral; BID + ABC placebo; tablet; oral; once daily + 3TC 300 mg; tablet; oral; once daily + EFV 600 mg; tablet; oral; once daily; all for 48 weeks	Arm A: 384 Enrolled, 290 Completed Arm B: 386 Enrolled, 294 Completed
EPV40001	IV	Open-label, randomized, parallel group, multi-centre study 48 weeks (with subsequent extension to 96 weeks)	To demonstrate equivalence in efficacy of the 3TC and ABC once daily combination regimens versus the triple combination regimen administered twice daily	Week 48 CSR complete	Regimen 1: 3TC 150 mg; tablet; oral; TBID + ZDV 300 mg; tablet; oral; BID + ABC 300 mg; tablet; oral; BID; all for 48 weeks Regimen 2: 3TC 300 mg; tablet; oral; once daily + ZDV 300 mg; tablet; oral; BID + ABC 300 mg; tablet; oral; BID; all for 48 weeks Regimen 3: 3TC 150 mg; tablet; oral; BID + ZDV 300 mg; tablet; oral; BID + ABC 600 mg; tablet; oral; once daily; all for 48 weeks	Regimen 1: 50 Enrolled, 49 Completed Regimen 2: 50 Enrolled, 42 Completed Regimen 3: 51 Enrolled, 45 Completed
EPV20001	III	Double-blind, randomized, controlled, multicenter study	To compare the magnitude of viral suppression and immunological response over	Week 48 CSR complete	3TC 300 mg once daily + ZDV 300 mg twice daily + EFV 600 mg once	3TC once daily: Randomized, n=278 Completed, n=179

Study Number	Phase	Study Design and Duration	Primary Objectives	Study Reporting Status	Regimens[a]	No. of Subjects by Group Entered/ Completed[b]
		48 weeks	48 weeks of treatment with 3TC 300 mg once daily vs. 3TC 150 mg TWICE DAILY in combination with approved dosing of ZDV and EFV		daily, or 3TC 150 mg twice daily + ZDV 300 mg twice daily + EFV 600 mg once daily	3TC twice daily: Randomized, n=276 Completed, n=174
COLA4005	II	Open-label, randomized, multi-centre study 24 weeks	To compare the efficacy of 3TC 300 mg administered once daily versus 3TC 150 mg administered BID in combination with FDA-approved dosing regimens of both stavudine and either indinavir or nelfinavir	Week 24 CSR complete	3TC 300 mg once daily, or 3TC 150 mg twice daily + stavudine 30 mg or 40 mg twice daily (based on weight) + indinavir 400 mg three times daily, or + nelfinavir at FDA-approved dosing (3-250 mg tablets three tmes daily or 4-250 mg tablets twice daily)	3TC once daily: 39 Enrolled, 39 Completed 3TC twice daily: 42 Enrolled, 39 Completed

a. All regimens were administered as oral tablets.
b. "Completed" for ING114467, ING113086, ING114915, and ING111762 indicates the subjects completed the double-blind or randomized phase of the study; completion of the randomized phase was not technically defined for ING112276 wherein at Week 96, the DTG subjects continued open-label (with 10 mg and 25 mg subjects switched to 50 mg for the Open-Label Phase) and the EFV subjects discontinued on-study treatment.

4.5. Efficacy Endpoints and Statistical Considerations of Efficacy Analyses

4.5.1. DTG/ABC/3TC and DTG Component Studies

4.5.1.1. Primary and Secondary Efficacy Endpoints

The primary endpoint for pivotal study ING114467 and supportive studies ING113086, ING114915, and ING111762 was the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 analyzed using a Missing, Switch or Discontinuation = Failure (MSDF) algorithm as codified by the FDA's "snapshot" algorithm (m2.7.3, Section 1.7.1.4).

The primary endpoints for all DTG component studies are listed in m2.7.3, Table 8. Secondary endpoints are provided in m2.7.3, Section 1.6.

4.5.1.2. Statistical Considerations

Details of the statistical methodology are described in m2.7.3, Section 1.7.1.

Assumptions underlying the determination of study sample size requirements, varied across the pivotal and supportive trials:

- ING114467: Assuming a 75% response rate in the TDF/FTC/EFV arm, the study required 394 evaluable subjects per arm to have 90% power with a 10% non-inferiority margin and a one-sided 2.5% significance level. The study was stratified on the following factors: Screening HIV-1 RNA (≤100,000 vs. >100,000 c/mL) and CD4+ cell count (≤200 vs. >200 cells/mm^3).
- ING113086: Assuming a 75% response rate in the RAL arm, the study required 394 evaluable subjects per arm to have 90% power with a 10% non-inferiority margin and a one-sided 2.5% significance level. The selection of a 10% non-inferiority margin has been well described [Hill, 2008]. The study was stratified on the following factors: Screening HIV-1 RNA (≤100,000 vs. >100,000 c/mL) and investigator-selected NRTI backbone (ABC/ 3TC vs. TDF/FTC).
- ING114915: Assuming an 80% response rate at Week 48 for both DTG and DRV+RTV arms, the study required 234 evaluable subjects per arm to have 90% power with a 12% non-inferiority margin and a one-sided 2.5% significance level. This sample size also had 85% power under the assumption of a 75% response rate for both arms at Week 96. The study was stratified on the following factors: Screening HIV-1 RNA (≤100,000 vs. >100,000 c/mL) and investigator-selected NRTI backbone (ABC/ 3TC vs. TDF/FTC).
- ING111762: Assuming a 65% response rate in the RAL arm, the study required 333 subjects per arm to have 90% power with a 12% non-inferiority margin and a one-sided 2.5% significance level. Recruitment of subjects with fully PI/r susceptible virus who received DRV+RTV was capped at 170 subjects in order to help achieve at least 80% power to detect non-inferiority in the "added sensitivity (AS)"

population (defined in ING111762 Week 48 CSR Section 4.8.3). Assuming a response rate of 65% in that population, and a non-inferiority margin of 12%, this requires at least 249 subjects per arm. The study was stratified on the following factors: Screening HIV-1 RNA (≤50,000 vs. >50,000 c/mL), use of DRV+RTV with or without primary PI mutations (yes vs. either no DRV+RTV use or presence of primary PI mutations), and number of fully active background agents (2 vs. <2).

Across the pivotal and supportive studies the analysis populations upon which the efficacy analyses were based are defined in m2.7.3 Section 1.7.1.2.

The Intent-to-Treat Exposed population consisted of all randomized subjects who received at least one dose of investigational product. The Modified Intent-to-Treat Exposed population for ING114915 and ING111762 study consisted of all randomized subjects who received at least one dose of investigational product, and who were not at one study site (Investigator ID=096536, n=1 subject enrolled in ING114915 and n=4 subjects enrolled in ING111762) in Russia that was closed early after the sponsor became aware of GCP noncompliance issues in another ViiV Healthcare-sponsored study. No subjects were recruited at this site in ING11467. This issue arose after unblinding of ING113086 and therefore no modified population was planned, instead an adhoc sensitivity analysis was run excluding subjects from this site (n=14). The results from the sensitivity analysis were consistent with the ITT-E results. The ITT-E (ING114467 and ING113086) and mITT-E (ING114915 and ING111762) are the primary populations for efficacy analyses.

4.5.2. ABC 600 mg Component and 3TC 300 mg Component Studies

4.5.2.1. Primary and Efficacy Endpoints

The CNA30021 (refer to CNA30021 Week 48 CSR) primary efficacy endpoint was to test the non-inferiority of ABC once daily versus ABC twice daily using the comparison of the proportion of subjects with plasma HIV-1 RNA levels <50 c/mL through Week 48.

The EPV40001 (refer to EPV40001 Week 48 CSR) primary efficacy endpoint was to compare the antiviral activity of 3TC once daily/ZDV twice daily/ABC twice daily and 3TC twice daily/ZDV twice daily/ABC once daily versus 3TC twice daily/ZDV twice daily/ABC twice daily following 24 and 48 weeks of treatment as measured by time averaged change in $\log_{10}$ HIV-1 RNA minus baseline (average area under the curve minus Baseline [AAUCMB]).

The EPV20001 (refer to EPV20001 Week 48 CSR) primary efficacy endpoints were the proportions of subjects with HIV-1 RNA <400 c/mL at Week 24 and Week 48.

The COLA4005 (refer to COLA4005 Week 24 CSR) primary efficacy endpoint was the proportion of subjects with HIV-1 RNA <400 c/mL at Week 24.

Key secondary efficacy endpoints varied across studies and are defined in the Clinical Study Reports for each individual study.

4.5.2.2. Statistical Considerations

Due to various stages of development of these compounds at the time the studies were conducted, details of all statistical analyses for Studies CNA30021, EPV40001, EPV20001, and COLA4005 can be found in the CSRs for the individual studies (CNA30021 Week 48 CSR, EPV40001 Week 48 CSR, EPV20001 Week 48 CSR, and COLA4005 Week 24 CSR).

4.6. Efficacy Results in all Studies

The efficacy data were not integrated due to significant variations in study designs, previous submission of data to support the individual components, and the number of different comparator arms.

4.6.1. Subjects on DTG 50 mg + ABC 600 mg/3TC 300 mg

In addition to the efficacy data available for subjects on the DTG/ABC/3TC FDC components from the pivotal ING114467 study (i.e., DTG + ABC/3TC), efficacy data for subjects who initiated DTG + ABC/3TC from the other Phase III/b studies (ING113086 through Week 96 and ING114915 through Week 48) are summarized. Because ING113086 and ING114915 were not powered to evaluate responses based on background NRTI treatment assignment at Baseline, the data presented from these studies for subjects on DTG + ABC/3TC are considered descriptive.

As Week 48 was the primary analysis timepoint for the Phase III/b studies in ART-naïve subjects (i.e., Studies ING114467, ING113086, and ING114915), and all three of these studies have available analyses at that time point, the below cross-study presentations largely focus on the Week 48 data.

There were a total of 169 subjects in ING113086 and 79 subjects in ING114915 who initiated the DTG/ABC/3TC FDC components, whereas there were 414 subjects in the DTG+ABC/3TC FDC arm of ING114467.

For the study in ART-experienced (INI-naïve) subjects, ING111762, since background regimens received during the treatment phase were diverse (with over 60 different individual regimens being prescribed), few subjects (n=8) were taking DTG +ABC/3TC (one of whom was also taking maraviroc). Thus, efficacy data for this subgroup from ING111762 was not compiled. However, this study provides efficacy data in an ART-experienced (INI-naïve) population who take DTG + an effective background regimen of at least one fully-active drug, whether ABC/3TC or any other possible combination.

4.6.1.1. Enrolment of Key Demographic Subpopulations in ING114467, ING113086, and ING114915

Overall, enrolment into Studies ING114467, ING113086, and ING114915 reflects the demographic characteristic of the current general ART-naïve population with HIV infection. Median age was 36 years, 19% were female and 22% were of African American/ African Heritage (Table 6). In Study ING114467, a limiting factor to

enrolment of women was use of a blinded comparator with pregnancy warnings for women (Atripla, [EFV/TDF/FTC]). However, due to the size of the ART-naïve studies (>400 subjects in ING114915 and >800 in ING114467 and ING113086), a total of 124 women were treated on DTG+ABC/3TC-containing regimens in these three studies. Other key populations, such as those with advanced disease and viral hepatitis co-infected patients, were adequately represented.

Table 6 Proportion of Demographic and Baseline Sub-populations in ING114467, ING113086, and ING114915

	ING114467		ING113086		ING114915	
	DTG + ABC/3TC N=414 n (%)	EFV/ TDF/FTC N=419 n (%)	DTG + ABC/3TC N=169 n (%)	RAL + ABC/3TC N=164 n (%)	DTG + ABC/3TC N=79 n (%)	DRV + RTV + ABC/3TC N=80 n (%)
Median Age (range), years	36.0 (18-68)	35.0 (18-85)	35.0 (18-64)	35.0 (18-75)	36.0 (19-67)	32.0 (20-60)
Female	67 (16)	63 (15)	45 (27)	35 (21)	12 (15)	16 (20)
African American/ African heritage	98 (24)	99 (24)	26 (15)	21 (13)	21 (27)	12 (15)
Hepatitis B virus	1 (<1)	1 (<1)	1 (<1)	2 (1)	0	0
Hepatitis C virus	27 (7)	29 (7)	23 (14)	20 (12)	6 (8)	6 (8)
CDC category C	18 (4)	17 (4)	4 (2)	3 (2)	2 (3)	1 (1)

Data Source: FDC ISO Table 1.703, Table 1.705, Table 1.706, and Table 1.707

4.6.1.2. Primary Efficacy Results in Subjects on DTG+ABC/3TC

The primary efficacy analyses for ING114467, ING113086, and ING114915 occurred at the Week 48 time point, which is available for all three studies; a comparison across all three studies at Week 48, for subjects on DTG+ABC/3TC is presented below in this section. Furthermore, Week 96 efficacy results are also briefly summarized for Studies ING114467 and ING113086.

Comparison of Week 48 Primary Efficacy Results in Subjects on DTG+ABC/3TC

In the pivotal DTG/ABC/3TC FDC Study ING114467, 88% of subjects on the DTG+ABC/3TC arm achieved the primary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48. This is compared with 81% of subjects on the EFV/TDF/FTC arm (Adjusted Treatment Difference [95% CI] +7.4% [+2.5%, +12.3%], p=0.003, a result that demonstrated statistical superiority of the DTG-based regimen over the EFV-based one (m2.7.3 Section 3.1.1 Table 20). Per protocol and other sensitivity analyses support the primary endpoint. The statistically significant difference in response rates noted in ING114467 was primarily due to lower discontinuations due to AEs on the DTG regimen.

In the subset of subjects from ING113086 and ING114915 who initiated DTG+ABC/3TC, response rates at Week 48 were similar to those observed for the DTG+ABC/3TC arm of ING114467, with 86% and 90% respectively achieving HIV-1

RNA <50 c/mL (m2.7.3 Section 3.1.1 Table 21). These results are consistent with those observed for the overall DTG populations of these studies (see Section 4.6.2.1).

Comparison of Week 48 Efficacy Results by Further Subgroups in Subjects on DTG+ABC/3TC

Results of various subgroup analyses supported the findings of the primary analysis (m2.7.3, Section 3.1.2). To assess the generalizability of the Week 48 primary analysis results, consistency of the treatment difference was explored within subgroups.

Table 7 presents Week 48 response rates by Baseline HIV-1 RNA strata (≤100,000 vs. >100,000 c/mL) for ING114467. An identical 7% response difference in favor of the DTG-containing arm was observed in each of these strata supporting non-inferiority of DTG+ABC/3TC vs. EFV/TDF/FTC.

Table 7 ING114467 Summary of Proportion of Subjects Responding Based on HIV-1 RNA <50 c/mL by Baseline HIV-1 RNA Strata, Week 48 Snapshot (MSDF) Analysis

	DTG + ABC/3TC once daily N=414 n/N (%)	EFV/TDF/FTC once daily N=419 n/N (%)	Difference in Proportion (95% CI)[a]
Response <50 c/mL			
≤100,000 c/mL	253/280 (90)	238/288 (83)	7.7 (2.1, 13.3)
>100,000 c/mL	111/134 (83)	100/131 (76)	6.5 (-3.2, 16.2)
p-value[b]			0.831

Data Source: ING114467 Week 48 CSR Table 7.10

a. Difference: Proportion on DTG+ABC/3TC - Proportion on EFV/TDF/FTC (unadjusted).

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 will be used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Although the primary comparison in ING113086 and ING114915 was DTG versus comparator (RAL or DRV+RTV, respectively), response rates by Baseline HIV-1 RNA level and backbone NRTI were also evaluated. Subjects with low and high viral load who received ABC/3TC as their Baseline NRTI had generally similar results across the studies through Week 48. There was a difference in response rate in favor of DTG+ABC/3TC compared to DRV+RTV+ABC/3TC in ING114915 (Table 8) for the >100,000 c/mL stratum. However, given the small number of subjects in ING114915 with high Baseline viral load receiving ABC/3TC, no definitive conclusions about this difference in favor of DTG can be made.

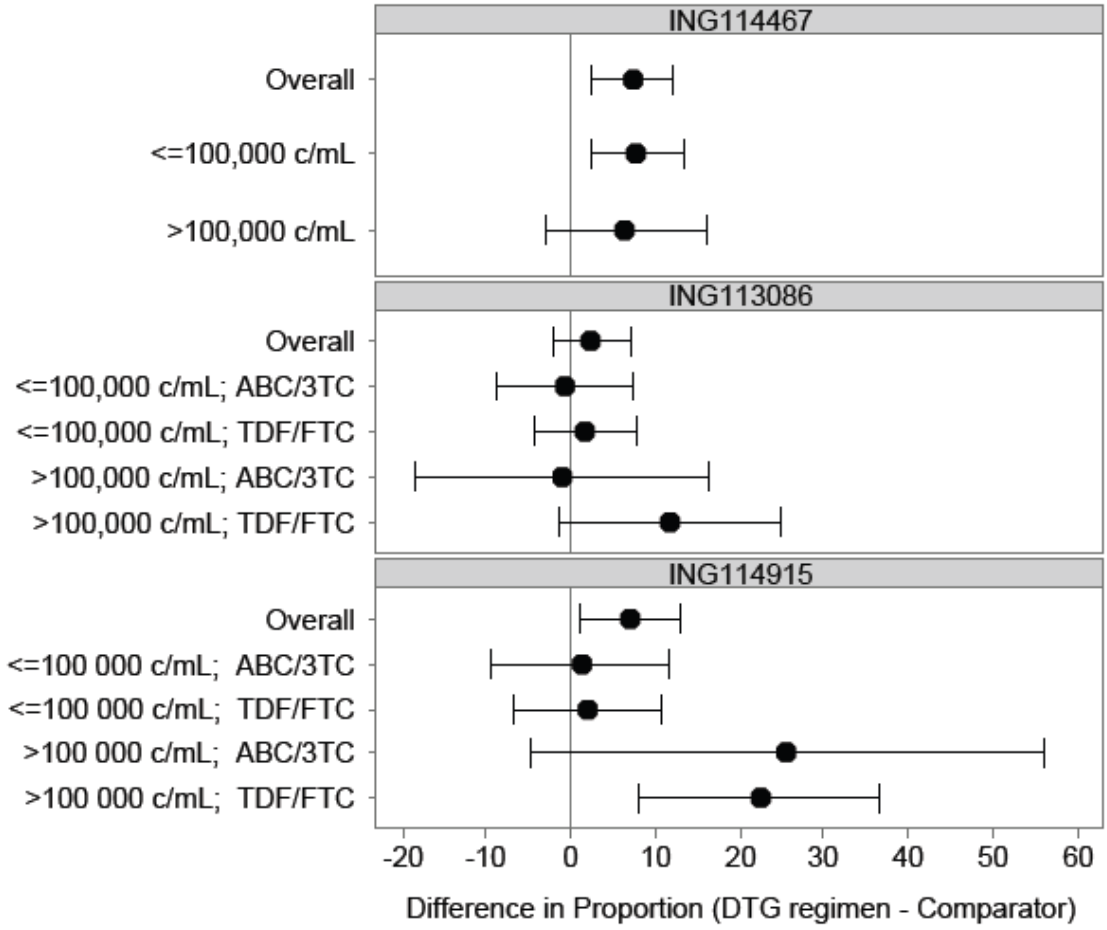
Table 8 Proportion of Subjects Initially Assigned to ABC/3TC Responding Based on Plasma HIV-1 RNA <50 c/mL by Baseline HIV-1 RNA at Week 48

Baseline HIV-1 RNA	ING113086 Week 48		ING114915 Week 48	
	DTG + ABC/3TC once daily N=169 n/N (%)	RAL + ABC/3TC once daily N=164 n/N (%)	DTG + ABC/3TC once daily N=79 n/N (%)	DRV + RTV + ABC/3TC once daily N=80 n/N (%)
Response <50 c/mL				
≤100,000 c/mL	115/132 (87)	110/125 (88)	59/66 (89)	60/68 (88)
>100,000 c/mL	30/37 (81)	32/39 (82)	12/13 (92)	8/12 (67)

Data Source:
ING113086 Week 48 CSR Table 7.7
ING114915 Week 48 CSR Table 7.9

The treatment differences observed across studies at Week 48 are presented below graphically by subgroup for each of the three studies (Figure 1). Some variability is apparent, as expected when looking at a large number of small subgroups. However, the treatment difference is around 0 or in favor of DTG+ABC/3TC versus the comparators, and the CIs of the differences always overlap.

Figure 1 **Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL by Baseline HIV-1 RNA and Background NRTI at Week 48 - Snapshot (MSDF) Analysis**



Data Source: ISE Figure 1.2

A subgroup analysis in age categories above and below age 36 years (based upon an approximation of the mid-point for the age range in ING114467) was conducted for the primary (Week 48) efficacy endpoint. The efficacy analyses for the ≥65 years age group was not conducted due to the limitation of the data. Analysis of subjects ≥50 years of age was performed to provide sufficient numbers of subjects for relevant assessment in older HIV-1 infected subjects.

In ING114467 there was no clinically meaningful difference between the proportion of subjects aged <50 years or ≥50 years in the DTG+ABC/3TC who achieved HIV-1 RNA <50 c/mL by Week 48. In addition, the studies showed similar responses in the DTG treatment groups for the primary efficacy endpoint in other categories including gender and race (White and non-White only; Table 9). The treatment differences between DTG+ABC/3TC and EFV/TDF/FTC were maintained across demographic subgroups including age (<36 years vs. ≥36), gender, and race (White vs. non-White) at Week 48.

Table 9 Primary Efficacy by Age, Gender, and Race in ING114467 at Week 48 (Snapshot [MSDF])

Subgroup of Interest	ING114467 Week 48	
	DTG + ABC/3TC n/N (%)	EFV/TDF/FTC n/N (%)
Age		
<36	175/202 (87)	171/215 (80)
≥36	189/212 (89)	167/204 (82)
Age		
<50 years	319/361 (88)	302/375 (81)
≥50 years	45/53 (85)	36/44 (82)
Gender		
Females	57/67 (85)	47/63 (75)
Males	307/347 (88)	291/356 (82)
Race		
White	255/284 (90)	238 285 (84)
Non-White	109/130 (84)	99/133 (74)

Data Source:
ING114467 Week 48 CSR Table 7.8 and ISE Table 1.2

For subjects who initiated ABC/3TC in ING113086 and ING114915, further breakdown for subgroup analyses by age, gender, or race categories were not conducted due to the limitation of the group sizes. For the overall DTG treatment groups in these studies, the treatment effects were generally similar across age, gender, and race.

Comparison of Week 96 Primary Efficacy Results in Subjects on DTG+ABC/3TC

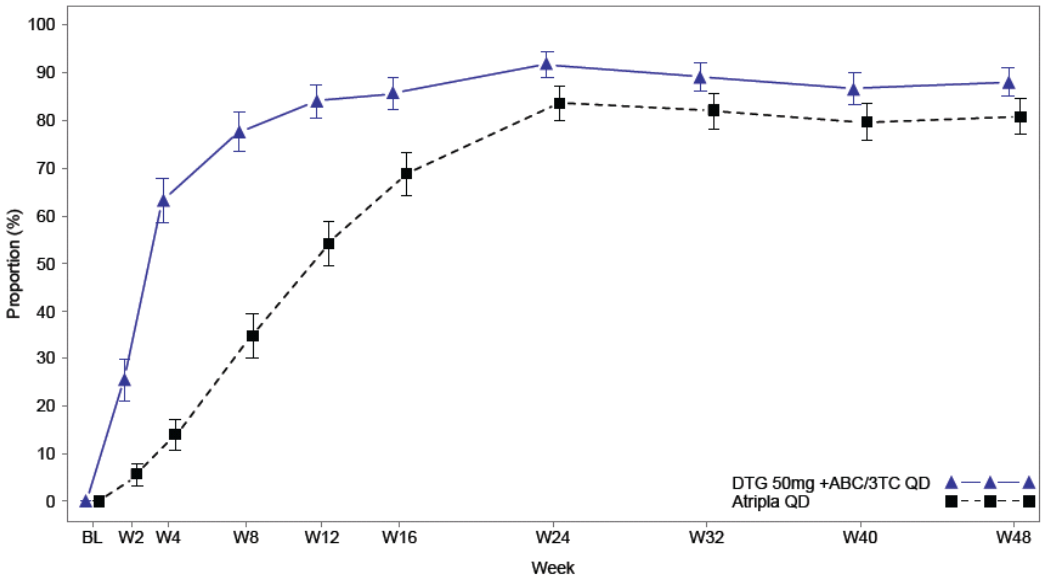
The Week 96 results of ING114467 and ING113086 provide longer-term efficacy data and further confirmation of the primary efficacy results from Week 48. Week 96 data are not yet available for ING114915. At Week 96 in ING114467, DTG+ABC/3TC (80%) maintained superiority over EFV/TDF/FTC (72%) for the primary endpoint of <50 c/mL plasma HIV-1 RNA based on outcomes of MSDF (Snapshot) algorithm (m2.7.3 Section 2.1.1). Supporting the ING114467 results, at Week 96, 74% of the subset of subjects from ING113086 who received DTG+ABC/3TC and 76% of subjects who received RAL+ABC/3TC responded (i.e., achieved HIV-1 RNA <50 c/mL; m2.7.3 Section 2.2.1.1).

4.6.1.3. Secondary Efficacy Results

In this section, key secondary efficacy results from Week 48 primary analysis are summarized for the pivotal Study ING114467 only. The Week 96 results from ING114467 provide further confirmation of the secondary efficacy results from Week 48 and are presented in the Week 96 CSR (ING114467 Week 96 CSR).

The time to virologic suppression was significantly faster on DTG+ABC/3TC (28 days) when compared to TDF/FTC/EFV (84 days), hazard ratio: 2.32 [2.00, 2.68], p<0.001. This analysis was pre-specified and adjusted for multiplicity.

Figure 2 ING114467 Week 48 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL Snapshot Analysis by Visit



Note: confidence intervals are derived using the normal approximation. (Triangles: DTG+ABC/3TC once daily, Squares: EFV/TDF/FTC once daily
Data Source: ING114467 48 Week CSR Figure 7.1

The rapid and significant viral load reductions seen with DTG+ABC/3TC were associated with sustained CD4 cell increases over 48 weeks (DTG+ABC/3TC: +246 cells/mm^3 vs. EFV/TDF/FTC: +187 cells/mm^3, m2.7.3, Table 33). Using the Repeated Measures Mixed Model Analysis, DTG+ABC/3TC was statistically superior to EFV/TDF/FTC with respect to change from Baseline in CD4 cell count at Week 48 (Adjusted mean change from Baseline: DTG+ABC/3TC 267 cells/mm^3 and EFV/TDF/FTC 208 cells/mm^3, difference 58.9 [33.4, 84.4] p <0.001). Differences in CD4 cell counts were seen as early as Week 4 and persisted through Week 48. This analysis was pre-specified and adjusted for multiplicity (ING114467 48 Week CSR).

HIV-associated conditions in subjects treated with DTG+ABC/3TC compared to EFV/TDF/FTC were assessed over time by summaries of the incidence of post-Baseline HIV conditions, and by the proportion of subjects with disease progression. There was a low incidence of HIV associated conditions (1% at Week 48; Data Source: ING114467 Week 48 CSR), and in the number of subjects with HIV disease progression (Data Source: ING114467 Week 48 CSR Section 6.3.5).

Secondary efficacy analyses in the subset of ART-naïve subjects receiving DTG+ABC/3TC in ING113086 and ING114915 were not conducted. In ING113086 overall, time to virologic suppression and change from Baseline in CD4 cell counts were similar between DTG and RAL arms. In ING114915, time to virologic suppression was faster on DTG than on DRV+RTV; CD4 change from Baseline was comparable between arms.

4.6.2. DTG Component Studies

Efficacy data from the Phase III/b supportive studies with DTG 50 mg once daily, ING113086, ING114915 and ING111762 (i.e., primary endpoint at Week 48) are included in this section to provide evidence of the efficacy of DTG for the treatment of HIV infection in ART-naïve and ART-experienced (INI-naïve) populations. Additional studies ING112276, ING116070, and DTG proof of concept study, ING111521, are presented in m2.7.3 Section 2.2.4 and Section 2.2.6, respectively.

4.6.2.1. ART-Naïve Subjects from ING113086 and ING114915

The efficacy of the DTG/ABC/3TC FDC is further supported by the overall results from Study ING113086 and ING114915 (m2.7.3, Section 2.2.1 and Section 2.2.2, respectively). In ING113086, 822 adults were randomized and received at least one dose of either DTG 50 mg once daily or RAL 400 mg twice daily, both administered with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC. In ING114915, an open-label and active-controlled study, 485 HIV-1 infected antiretroviral naïve adults were randomized and received at least one dose of either DTG 50 mg once daily or DRV+RTV 800 mg/100 mg once daily, both administered with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC).

In ING113086, virologic suppression (HIV-1 RNA <50 c/mL) in the DTG arm (88%) was non-inferior to the RAL arm (85%) at 48 weeks. The adjusted difference in proportion and 95% CI were 2.5 (-2.2, 7.1). At 96 weeks, virologic suppression in the DTG arm (81%) remained non-inferior to the RAL arm (76%). The adjusted difference in proportion and 95% CI were 4.5 (-1.1, 10.0). In ING114915, virologic suppression (HIV-1 RNA <50 c/mL) in the DTG arm (90%) was statistically superior to the DRV+RTV arm (83%) at 48 weeks. The adjusted difference in proportion and 95% CI was 7.1 (0.9, 13.2), p=0.025.

The median change in CD4+ T cell count from Baseline at Week 48 in ING113086 and ING114915 for the DTG arm was +230 cells/$mm^3$and +210 cells/mm^3, respectively.

4.6.2.2. ART-Experienced (INI-Naïve) Subjects from ING111762

The efficacy of the DTG/ABC/3TC FDC is also supported by data from ING111762, where 719 HIV-1 infected, ART-experienced adults were randomized and received either DTG 50 mg once daily or RAL 400 mg twice daily with investigator selected background regimen (BR) consisting of up to 2 agents (including at least one fully active agent) (m2.7.3 Section 2.2.5). A total of 8 subjects in this study were taking DTG+ABC/3TC once daily (one of whom was also taking maraviroc). Due to the small number, no analyses of responses by subject on this regimen were undertaken.

Virologic suppression (HIV-1 RNA <50 c/mL) in the DTG arm (71%) was statistically superior to the RAL arm (64%), based on a Week 48 primary analysis (p=0.030). Virologic suppression (HIV-1 RNA <50 c/mL) treatment differences were comparable across the Baseline characteristics of gender, race, and HIV sub type. The mean changes

in CD4+ cell count from Baseline were +162.4 cells/mm^3 in the DTG group and +153.2 cells/mm^3 in the RAL group at 48 weeks.

4.6.3. Treatment Emergent Resistance in INI-Naïve Subjects

A low rate of confirmed virological failure was observed in the DTG treatment arms compared to EFV/TDF/FTC in ING114467 (through Week 96), and compared to RAL in ING113086 (through Week 96) and ING111762 (through Week 48). Only two subjects in each of the DTG and DRV+RTV arms developed confirmed virologic failure through Week 48 in ING114915.

Through Week 48, protocol-defined virologic failure rates in ING114467, ING113086, and ING114915 were low and consistent for the DTG-containing regimens (4%, 5%, and <1%, respectively; m2.7.3 Table 36), despite stringent protocol defined virologic failure (PDVF) criteria (confirmed HIV-1 RNA at or after Week 24 of ≥50 c/mL [ING114467 and ING113086] or >200 c/mL [ING114915]). Rates of virologic failure remained low through Week 96 in the DTG arms of ING114467 and ING113086 (6% and 5%, respectively; Data Source: ING114467 Week 96 CSR Table 7.29 and ING113086 Week 96 CSR Table 7.23).

Across the Phase III ART-naïve studies, no subjects on DTG treatment arms developed treatment-emergent INI or NRTI resistance mutations through Week 48, whereas subjects on comparator agents EFV and RAL developed clinically relevant resistance mutations to these third agents and to NRTIs (Table 10). In the Phase IIb study ING112276 (ART-naïve subjects), no INI-resistant mutations or treatment-emergent resistance in NRTI background therapy were isolated with DTG 50 mg once daily through 96 week.

In the ING111762 Week 48 analysis, ART-experienced (INI-naïve) subjects receiving DTG were less likely to have genotypic or phenotypic evidence of treatment-emergent resistance at PDVF (confirmed plasma HIV-1 RNA ≥400 c/mL on or after Week 24; full definition in ING111762 Week 48 CSR, Section 7.1). In a pre-specified analysis, there was a statistically significant difference in favor of DTG for the proportion of mITT-E subjects harboring virus with evidence of treatment-emergent INI Resistance by Week 48 (DTG: 4/354 (1%); RAL: 17/361(5%); p=0.003).

In ING111762, there were four subjects in the DTG arm with emergent integrase-defined substitutions. One subject with RAL resistance pathway genotype Q148H/G140S/E138A at Baseline added T97A, and E138A became an E138A/T mixture at PDVF; this subject had extensive resistance to DTG and RAL at baseline. Otherwise, there was no emergence of primary or secondary RAL resistance mutations in the DTG group. Instead, one subject developed the polymorphic integrase substitution V151V/I with no increased DTG or RAL FC, and two subjects developed unique R263K or R263R/K substitutions, both with DTG or RAL FC <2, suggesting no high-level resistance to either drug conferred by R263K substitution. There were more examples of treatment-mergent genotypic and/or phenotypic resistance to the background regimen at PDVF in the RAL arm (12/361) versus the DTG arm (4/354) in ART-experienced subjects, suggesting that DTG as a third agent protected concomitant-ART well (see m2.7.2.4 for more details).

Table 10 Number of Protocol-Defined Virologic Failures (+/- Resistance[a] to integrase, NNRTI, BR) in ART-Naïve and ART-experienced Subjects

	ART-Naïve Adults					
	ING114467 Week 48		ING113086 Week 48		ING114915 Week 48	
	DTG + ABC/3TC N=414	EFV/ TDF/FTC N=419	DTG + 2 NRTI N=411	RAL + 2 NRTI N=411	DTG + 2 NRTI N=242	DRV + RTV + 2 NRTI N=242
Subjects with PDVF, n/N (%)	18/414 (4)	17/419 (4)	20/411 (5)	28/411 (7)	2/242 (<1)	2/242 (<1)
Resistance in PDVF Subjects with a Determinable Genotype/phenotype, n/N (%):						
INI-r Mutations Present	0	0	0	1/18 (6)	0	0
NNRTI-r Mutations Present	0	4/9 (44)	N/A	N/A	N/A	N/A
PI Mutations Present	N/A	N/A	N/A	N/A	0	0
NRTI-r Mutations Present	0	1/9 (11)	0	4/19 (21)	0	0

	ART-Experienced Adults	
	ING111762 Week 48	
	DTG 50 mg once daily + BR N=354	RAL 400 mg twice daily + BR N=361
Protocol-defined Virologic Failure, n (%)	21/354 (6)	45/361 (12)
Virologic non-response, n (%)	2/354 (<1)	19/361 (5)
Rebound	19/354 (5)	26/361 (7)
Genotype/phenotype Determinable	N=17	N=38
INI Substitutions Present	4/17 (24)[b]	16/38 (42)

Data Source:
ING114467 Week 48 CSR Table 7.7, Table 12.2, Table 12.4, and Listing 47;
ING113086 Week 48 CSR Table 7.22, Table 12.2, Table 12.4, and Listing 43;
ING114915 Week 48 CSR Table 7.7, Table 12.2 ,Table 12.4
ING111762 Week 48 CSR Table 12.12 and Table 7.10.

a. Predefined integrase inhibitor associated resistance mutations: H51Y, T66A, T66I, T66K, L68V, L68I, L74I, L74M, L74R4, E92Q, E92V, Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, Y143C, Y143H, Y143R, P145S, S147G, Q148H, Q148K, Q148R, V151I, V151L, S153F, S153Y, N155H, E157Q, G163R, G163K, G193E, R263K. Major resistance mutations to other classes (i.e., NRTI, NNRTI, PI) were as defined by the International Antiviral Society USA [IAS, 2011]. Topics in

b. Substitution(s), DTG FC: R263R/K, FC = 1.1; R263K, FC = 1.9; E138T/A and T97A, FC > max (Baseline sample testing showed this subject enrolled with preexisting RAL resistance [Q148] and FC > max for RAL and DTG); V151V/I, FC = 0.92.

4.6.4. ABC 600 mg Component and 3TC 300 mg Component Studies

No formal comparisons or analyses of results across studies were completed for the ABC and 3TC component studies for the Summary of Clinical Efficacy. Additional comparisons are presented in m2.7.3 Section 3.3.

Brief primary efficacy results for studies supporting the ABC and 3TC components, including studies CNA30021, EPV40001, EPV20001, and COLA4005, are shown in Table 11. Results across the four studies providing efficacy data for the ABC component and 3TC component showed that once daily dosing is effective in the treatment of HIV in the intended populations for the DTG/ABC/3TC FDC.

Other studies (CAL30001, ESS30008, EPZ104057, CNA109586, and COL101004) were conducted with the ABC/3TC FDC and are discussed in m2.7.3, Section 6. CAL30001 and ESS30008 evaluated the efficacy of the ABC/3TC FDC once-daily dosing as part of combination therapy in ART-experienced subjects.

Table 11 Results Across ABC and 3TC Component Efficacy Studies

Clinical Study	Treatment Groups	Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL	Point Estimate (Two-sided stratified 95% CI) or p-value	Proportion of Subjects with Plasma HIV-1 RNA <400 c/mL	Point Estimate (Two-sided stratified 95% CI) or p-value	Median Plasma HIV-1 RNA AAUCMB log_{10} c/mL	Median Difference in AAUCMB (95% CI)
CNA30021 ART-naïve population	ABC once daily ABC twice daily	253/384 (66%) 261/386 (68%)	-1.7% (-8.4%, 4.9%)	276/384 (72%) 279/386 (72%)	-0.4% (-6.7, 5.9)	-2.84 -2.76	-0.03 (-0.13, 0.07)
EPV40001 ART-naïve population	ABC twice daily + 3TC twice daily ABC twice daily + 3TC once daily ABC once daily + 3TC twice daily	35/50 (70%) 29/50 (58%) 29/51 (57%)		39/50 (78%) 33/50 (66%) 32/51 (63%)		-2.03 -1.98 -1.87	3TC once daily – twice daily[a] 0.11 (-0.09, 0.34) ABC once daily – twice daily[b] 0.14 (-0.06, 0.36)
EPV20001 ART-naïve population	3TC once daily 3TC twice daily	165/278 (59%) 168/276 (61%)	-1.5% (-9.7, 6.6)	178/278 (64%) 174/276 (63%)	1.0% (-7.0, 9.0)	-1.76 -1.78	-0.02 (-0.15, 0.12)
COLA4005 ART-experienced population/ switch study	3TC once daily 3TC twice daily	32/39 (82%) 34/42 (81%)	p=1.000	37/39 (95%) 38/42 (90%)	p=0.679	0.00 (–0.27 to 0.40) 0.00 (–0.38 to 0.59)	0

Data Source:
CNA30021 Week 48 CSR Table 13.1, Table 13.46, Table 13.15, and Table 13.16;
EPV40001 Week 48 CSR Table 13, Table 16, and Table 17;
EPV20001 Week 48 CSR Table 12.1, Table 12.2, Table 12.16, Table 12.17, Table 12.36 and Table 12.38;
COLA4005 Week 24 CSR Table 15. Table 16, and Table 19.

a. (3TC once daily + ABC twice daily regimen) minus (3TC twice daily + ABC twice daily regimen)
b. (3TC twice daily + ABC once daily regimen) minus (3TC twice daily + ABC twice daily regimen)

4.7. Efficacy Conclusions

The efficacy data support an indication for DTG/ABC/3TC FDC as a complete regimen for the treatment of HIV infection in patients without documented or suspected resistance to any of the three antiretroviral agents in the fixed dose combination.

For ART-naïve subjects, efficacy data in this submission establish the following:

- Superiority of DTG + ABC/3TC over EFV/TDF/FTC, the recommended first-line therapy in US Department of Health and Human Services (DHHS), European AIDS Clinical Society (EACS), World Health Organization (WHO), and other treatment guidelines for HIV-1-infected, ART-naïve subjects, was demonstrated at both Week 48 and 96 in ING114467, the pivotal trial supporting efficacy for the DTG/ABC/3TC FDC.
    - Differences in efficacy were primarily driven by a lower rate of discontinuation due to AEs on the DTG + ABC/3TC arm.
    - ING114467 Week 48 (the time point for the primary endpoint analysis) treatment differences between DTG + ABC/3TC and EFV/TDF/FTC were consistent across the Baseline stratification factors.
    - The results from the pivotal study ING114467 demonstrate that a treatment regimen with DTG/ABC/3TC is at least as effective as treatment regimens with EFV/TDF/FTC, including subjects with a Baseline viral load >100,000 c/mL.
- Data from the subgroups of subjects in ING113086 and ING114915 who initiated DTG + ABC/3TC support the pivotal study data, with response rates at Week 48 that were similar to those observed for the DTG + ABC/3TC arm of ING114467.
- In studies ING113086 and ING114915, the virologic efficacy at Week 96 and Week 48, respectively, was consistent when the investigator selected either ABC/3TC or TDF/FTC as the NRTI backbone.

For ART-experienced, INI-naïve subjects, efficacy data in this submission establish the following:

- Data from ING111762 are supportive of an indication in ART-experienced subjects for DTG in combination therapy.
- The demonstration of the efficacy of ABC, 3TC, and ABC/3TC FDC was supported by data in prior submissions, and has been validated by long-standing post approval clinical experience.

The broad experience with the constituent antiretroviral agents combined with confirmatory bioequivalence data (ING114580) establishes the efficacy of DTG/ABC/3TC FDC across all subjects with HIV infection without resistance to the components.

5. OVERVIEW OF SAFETY

For a full presentation of safety results presented within this Overview of Safety see the Clinical Summary of Safety (m2.7.4) and the Integrated Safety Summary (m5.3.5.3):

Regarding the safety profile of DTG/ABC/3TC FDC, the Overview of Safety provides a summary of integrated analyses from the ART-Naïve Pooled Dataset (including ING114467, ING113086, ING114915, and ING112276) and further non-integrated safety data from healthy subjects who took DTG/ABC/3TC FDC from the Phase I Bioequivalence Study ING114580. Safety results from ING116070 are presented in m2.7.4 Summary of Clinical Safety and not repeated in this clinical overview.

The Sponsor believes the DTG single entity submission provides robust safety data in the ART-experienced population from ING111762. Similarly, the safety profiles in the clinical use of ABC and 3TC are well-known and described in ZIAGEN, EPIVIR, and KIVEXA/EPZICOM labeling. Therefore, as there were limited numbers of subjects directly taking DTG+ABC/3TC in ING111762, the safety summary of ART-experienced subjects from both ING111762 and studies with ABC/3TC component are presented in the Summary of Clinical Safety (m2.7.4) and will not be repeated in this clinical overview.

5.1. Introduction

A full listing and description of individual studies providing safety data supporting the use of DTG/ABC/3TC FDC in the treatment of HIV infection are provided in m2.7.4, Section 1.1.4.

5.1.1. Data Cut-off Dates

This submission contains safety data collected and analyzed through [redacted]. Details of individual study cut-off dates are provided in m2.7.4, Section 1.1.5.

An additional cut off date for SAEs and pregnancies of [redacted] was applied to all subjects in ING114467, ING113086, ING114915, and ING112276 for complete disclosure of safety information. These data were not integrated, but are reported separately as listings in m5.3.5.3 and are described under corresponding sections of the m2.7.4 as applicable.

5.2. Non-Clinical 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 mg once daily.

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 DTG was gastrointestinal (GI) intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 38 and 1.5 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 no observable adverse effect level (NOAEL) for postnatal development of the offspring (F1) was 50 mg/kg/day. At this dose, the anticipated human exposure is approximately 32X a 50 mg once daily dose. Given that effects on offspring body weights were noted at doses where maternal toxicity was also observed, and the presence of considerable safety margins expected at the proposed clinical doses, there is minimal risk for adverse effects on post-natal development in offspring of mothers receiving DTG. In summary, there have been no demonstrable risks to the developing fetus exposed to DTG.

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.

The safety of ABC has been well characterized in a comprehensive battery of nonclinical studies and there is substantial clinical experience with this marketed product. The target organs in repeat dose toxicity studies with ABC were the liver and testes. Liver findings included hepatocellular hypertrophy (mice, rats, and monkeys) and individual cell necrosis (mice) with increases in cholesterol, triglycerides, total protein, bile acids, and/or alanine aminotransferase (ALT) across species. All findings were reversible or showed evidence of regression except hepatocellular hypertrophy in male mice at 1000 mg

(succinate)/kg/day for three months. ABC may be a weak enzyme inducer, and therefore hepatic changes may be associated with ABC-induced alterations in metabolic activity. Effects on the testes were only seen in rats, mainly in studies of short duration (30 days) and at dosages ≥135 mg (base)/kg/day. Findings included reduction in testicular size due to the loss of germ cells from the seminiferous tubules, which showed evidence of reversal following a treatment-free period.

The safety of 3TC has been well characterized in a comprehensive battery of nonclinical studies and there is substantial clinical experience with this marketed product. The main treatment related effects of 3TC in rats and dogs were hematological reductions in red cell counts. In dogs, these findings were associated with increased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), and reductions in total leukocyte, neutrophil, and lymphocyte counts. A chronic low-grade irritation of the cecum/anus was observed in the rat 6 month toxicity study with the highest dose of 3TC (4000 mg/kg/day). However, there was a clear no-effect level for the cecal changes at the intermediate dose (850 mg/kg/day), which is approximately 142 times higher than the therapeutic dose (300 mg, or 6 mg/kg for a 50 kg human) on a mg/kg basis.

ABC and 3TC were not mutagenic in bacterial tests but, like many other nucleoside analogues, showed activity in in vitro mammalian tests such as the mouse lymphoma assay. However, an in vivo rat micronucleus test with ABC and 3TC in combination was negative.

3TC was not carcinogenic in 2 year rat or mouse carcinogenicity studies. However, ABC showed an increase in the incidence of malignant and non-malignant tumors in mice and rats. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and in the liver, urinary bladder, lymph nodes and the subcutis of females. The majority of these tumors occurred at the highest ABC dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. The exception was the preputial gland tumor which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy.

ABC and 3TC both had no effect on male or female fertility in animals.

3TC was not teratogenic in animal studies, but a small increase in early embryonic loss was seen when administered to pregnant rabbits at exposure levels comparable to those achieved in humans. However, there was no indication of this effect in the rat. ABC produced fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) was observed in rats at a dose which produced 28 times the human exposure, based on AUC. However, in the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 7 times the human exposure for a 600 mg dose based on AUC.

In summary, the toxic potential of the individual compounds (DTG, ABC and 3TC) has been well characterized in comprehensive nonclinical development programs. New or enhanced toxicity is not expected from the co-administration of DTG with ABC and 3TC because there are no common target organ toxicities or metabolic pathways identified for

these compounds. NOAELs have been established for the 3 entities in general toxicity studies at exposure margins that are approximately at parity (DTG, ABC) or significantly higher (3TC) than expected clinical exposure.

Based on the DTG clinical experience from the Phase II/III program and ongoing safety analysis during the many years of post-marketing experience with ABC and 3TC (plus the absence of nonclinical toxicology and pharmacokinetic signals that might indicate the potential for an interaction producing increased toxicity), these data are considered adequate to support the proposed clinical use of DTG/ABC/3TC as a fixed-dose combination treatment for HIV.

5.3. Exposure in the Clinical Development Program

See m2.7.4, Section 1.2 for full presentation of exposure data.

As of the [redacted] analysis cut-off date, a total of 767 subjects (701 HIV-infected and 66 healthy) have been exposed to at least one dose of DTG+ABC/3TC FDC in the entire clinical development program for this product. This total includes:

- A total of 679 ART-naive subjects in the four randomized, controlled trials (ING114467, ING113086, ING114915, and ING112276) received DTG + ABC/3TC FDC (FDC ISO Table 1.701). The extent of exposure was 1066.5 subject-years. Median duration of exposure was 672.0 days (range 1 to 760 days) (FDC ISO Table 2.701).
- A total of 66 healthy adult subjects in the Phase I bioequivalence study ING114580 received the DTG/ABC/3TC combination tablet and DTG+ABC/3TC FDC (see Section 5.4 and ING114580 CSR).
- In addition, a total of 13 ART-naïve subjects received DTG + ABC/3TC FDC in ING116070 (ING116070 Week 16 CSR Table 6.3) and a total of 18 ART-experienced (INI-naïve) subjects in study ING111672 received ABC/3TC; of those, 9 subjects received DTG + ABC/3TC (one subject also received maraviroc [MVC]) and 9 subjects received RAL + ABC/3TC (one subject received ABC and 3TC as separate components (ING111762 Week 48 CSR Table 6.35).

5.4. Safety in Clinical Pharmacology Bioequivalence Study in Adults

Study ING114580 was a Phase I bioequivalence study of the combined formulated tablet (50 mg/600 mg/300 mg DTG/ABC/3TC FDC tablet) compared to one DTG 50 mg tablet + one ABC/3TC (600 mg/300 mg) tablet with and without food in healthy adult subjects. The treatment phase was divided into two parts (Part A and Part B). The EPZICOM tablet used in this study is identical to the KIVEXA tablet which is marketed globally in countries other than the US and Japan. Part A consisted of 2 single dose treatment sequences (AB, BA) in a randomized, two-period, crossover design with a ≥7 day washout between doses. Sixty-six subjects were enrolled in Part A. Twelve subjects who completed Part A participated in Part B and received a single dose of the combined

formulated tablet administered with a high fat meal (Treatment C). Treatments were as follows:

- Treatment A DTG 50 mg/ABC 600 mg/3TC 300 mg FDC tablet, fasted
- Treatment B DTG 50 mg tablet plus a single ABC/3TC tablet, fasted
- Treatment C DTG 50 mg/ABC 600 mg/3TC 300 mg FDC tablet with high fat meal

Bioequivalence was demonstrated between the DTG/ABC/3TC fixed dose combination tablet formulation and the separate co-administered tablet formulations of DTG plus ABC/3TC.

Dosing with DTG+ABC/3TC fasted and the FDC fasted demonstrated similar tolerability during Part A**.** The most commonly-reported AEs during Part A were nausea, abdominal pain, headache, and somnolence. Tolerability was similar between the two treatments, although the incidence of nausea was higher in the separate entities group (29%) compared to the FDC (17%). There were no Grade 3 or 4 AEs reported during the study. Dosing with FDC and a high fat meal was well-tolerated during Part B of the study. No AEs were reported during Part B, in healthy subjects already exposed to the FDC and DTG+ABC/3TC during Part A of the study.

No Grade 3 or 4 AEs, deaths or non-fatal SAEs were reported during the study. One subject was withdrawn from Part A of the study due to an AE (vomiting, considered related to FDC administration). No consistent, treatment related or clinically significant changes in mean or median hematology or clinical chemistry values were observed in the study. No clinically significant changes in vital signs or ECGs were observed during the study.

5.5. Safety in Pediatrics – ING112578

As agreed in the DTG/ABC/3TC Paediatric Investigation Plan (PIP) with the Paediatric Committee (PDCO) (EMEA-001219), the Sponsor does not currently plan to conduct a paediatric clinical study of the DTG/ABC/3TC (50 mg/600 mg/300 mg) FDC in adolescents. This tablet formulation is intended for adults and adolescent populations (i.e., ≥12 to <18 years) who weigh at least 40 kg.

The proposed adolescent indication for DTG/ABC/3TC is supported by the following safety data. The clinical data from Cohort I (12 to <18 years) in ING112578 (P1093) provides DTG PK and long term safety and efficacy (24 week) data and is the basis of the proposed INI-naïve (ART-naïve and experienced) adolescent indication for the DTG single entity (m2.7.4, Section 5.5.2). No subjects in this Cohort received ABC and 3TC alongside DTG. No safety signal has been identified in this study in adolescents that differs from the profile established in the larger Phase III program in adults.

ABC and 3TC are approved for twice daily (BID) use in children aged 3 months to 18 years dosed individually, and in some regions, from 12 to 18 years when given once daily as the ABC/3TC FDC, in all cases the indication includes ART naïve and ART experienced populations. The basis of these approvals is described in the Clinical

Summary of Safety (m2.7.4). Hence the safety profile of these components in this age group has been established and monitored for several years.

Finally, the adult Phase III data in subjects receiving DTG+ABC/3TC provides long term safety and efficacy which can be extrapolated to support adolescents who have similar absorption, distribution, metabolism and elimination of the individual entities.

5.6. Safety in DTG+ABC/3TC FDC Subjects

5.6.1. Safety Population DTG+ABC/3TC FDC Subjects

The Safety Population consists of all subjects who received at least one dose of investigational product, and for study ING114915 were not at one study site in Russia (Site 094861, Investigator ID 96536; enrolled one subject) that was closed early after the sponsor became aware of GCP noncompliance issues in another ViiV Healthcare-sponsored study at the same site. The Safety Population includes subjects from this site in ING113086, all of whom were receiving ABC/3TC as their NRTI backbone

In total, 1358 subjects from the integrated Phase IIb and III/b analysis are included in the integrated safety analysis: 679 subjects received DTG once daily and 679 subjects received comparator drug. The comparator group included all subjects in the Atripla arm of the pivotal study ING114467 and those subjects in the supportive studies who had ABC/3TC as their NRTI backbone to provide a safety analysis of DTG+ABC/3TC versus ABC/3TC combined with other third agents.

The majority of these subjects were still ongoing at the time of this analysis (≥82%). In the ART-naïve studies, patient populations with a broad set of Baseline characteristics were enrolled as follows (Data Source: ISO Table 1.703, Table 1.705, Table 1.706, and Table 1.707):

- In ING114467, 833 HIV-1 infected, ART-naive adults received at least one dose of DTG+ ABC/3TC or EFV/TDF/FTC. At Baseline, median subject age was 35 years, 16% were female, 31% non-white, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.
- In ING113086, 333 HIV-1 infected, ART-naïve adults were randomized and received at least one dose of DTG+ABC/3TC or RAL+ABC/3TC. At Baseline, median subject age was 35 years, 24% were female, 18% non-white, 13% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.
- In ING114915, 159 HIV-1 infected, ART-naïve adults received at least one dose of DTG+ABC/3TC or DRV+RTV+ABC/3TC. At Baseline, median subject age was 34 years, 18% were female, 26% non-white, 8% had hepatitis B and/or C co-infection and 2% were CDC Class C, these characteristics were similar between treatment groups.
- In ING112276, 33 HIV-1 infected, ART-naïve adults received at least one dose of DTG+ABC/3TC 50 mg once daily or EFV+ABC/3TC. At Baseline, median subject

age was 38 years, 9% were female, 24% non-white, 9% had hepatitis B and/or C co-infection and no subjects were CDC Class C, these characteristics were similar between treatment groups.

5.6.2. Common Adverse Events

For ART-naïve subjects, the safety profile for DTG+ABC/3TC was generally comparable or favorable to its comparators (m2.7.4, Section 2.1.1).

Diarrhea, nasopharyngitis, nausea, headache and fatigue were the most commonly reported clinical AEs occurring at similar rates in ART-naïve subjects treated with DTG and the ABC/3TC NRTI backbone or Atripla, across the treatment groups (Table 12; m2.7.4, Section 2.1.1). The only AE observed at higher frequency with DTG+ABC/3TC was insomnia, which was only observed in ING114467 and not replicated in any other Phase III study with DTG+ABC/3TC. Data on insomnia are further described under m2.7.4, Section 2.1.5.8, but in general, events were predominantly mild and did not result in treatment discontinuation. Otherwise, AE rates between DTG+ABC/3TC and RAL+ABC/3TC were generally similar, and AEs such as dizziness, rash, nightmare and abnormal dreams occurred at higher frequencies in the EFV and/or Atripla treatment groups. AEs of bronchitis, influenza and diarrhea occurred at higher frequencies in the DRV+RTV+ABC/3TC treatment group. Rates from Study ING112276 are included for integrative purposes, but individually should be interpreted with caution due to the limited number of subjects. 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 (m2.7.4, Section 2.1.1.2).

Table 12 Summary of Common Adverse Events by Frequency (in at least 5% of Subjects in the Total DTG population) – ART-Naïve Population

Preferred term	ING114467		ING113086		ING114915		ING112276		TOTAL
	DTG 50 mg + ABC/3TC once daily N=414	EFV/TDF/FTC once daily N=419	DTG 50 mg once daily + ABC/3TC N=169	RAL 400 mg BID + ABC/3TC N=164	DTG 50 mg once daily + ABC/3TC N=79	DRV + RTV 800 mg/100 mg + ABC/3TC once daily N=80	DTG 50 mg once daily + ABC/3TC N=17	EFV 600 mg once daily + ABC/3TC N=16	DTG 50 mg + ABC/3TC once daily N=679
	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Any event	**376 (91)**	**394 (94)**	**138 (82)**	**139 (85)**	**69 (87)**	**67 (84)**	**16 (94)**	**16 (100)**	**599 (88)**
Diarrhea	84 (20)	83 (20)	16 (9)	12 (7)	10 (13)	23 (29)	4 (24)	1 (6)	114 (17)
Nausea	65 (16)	61 (15)	30 (18)	25 (15)	16 (20)	22 (28)	3 (18)	2 (13)	114 (17)
Nasopharyngitis	74 (18)	66 (16)	21 (12)	17 (10)	8 (10)	8 (10)	2 (12)	0	105 (15)
Headache	63 (15)	63 (15)	21 (12)	19 (12)	7 (9)	6 (8)	1 (6)	1 (6)	92 (14)
Insomnia	69 (17)	46 (11)	8 (5)	9 (5)	4 (5)	5 (6)	3 (18)	4 (25)	84 (12)
Fatigue	63 (15)	53 (13)	7 (4)	7 (4)	3 (4)	3 (4)	0	2 (13)	73 (11)
Upper respiratory tract infection	50 (12)	53 (13)	10 (6)	16 (10)	3 (4)	7 (9)	4 (24)	0	67 (10)
Cough	36 (9)	36 (9)	11 (7)	5 (3)	4 (5)	5 (6)	2 (12)	0	53 (8)
Dizziness	40 (10)	153 (37)	10 (6)	10 (6)	5 (6)	8 (10)	1 (6)	4 (25)	56 (8)
Back pain	30 (7)	18 (4)	8 (5)	10 (6)	2 (3)	4 (5)	1 (6)	2 (13)	41 (6)
Bronchitis	28 (7)	26 (6)	11 (7)	7 (4)	0	4 (5)	0	2 (13)	39 (6)
Depression	31 (7)	34 (8)	7 (4)	6 (4)	4 (5)	2 (3)	0	0	42 (6)
Pyrexia	26 (6)	27 (6)	10 (6)	10 (6)	5 (6)	6 (8)	1 (6)	3 (19)	42 (6)
Vomiting	26 (6)	24 (6)	9 (5)	8 (5)	3 (4)	7 (9)	0	0	38 (6)
Syphilis	18 (4)	25 (6)	10 (6)	6 (4)	2 (3)	3 (4)	1 (6)	1 (6)	31 (5)
Gastroenteritis	21 (5)	17 (4)	9 (5)	6 (4)	5 (6)	6 (8)	1 (6)	0	36 (5)
Sinusitis	22 (5)	15 (4)	9 (5)	9 (5)	1 (1)	3 (4)	0	2 (13)	32 (5)
Influenza	22 (5)	10 (2)	9 (5)	8 (5)	0	6 (8)	1 (6)	0	32 (5)
Abnormal dreams	31 (7)	73 (17)	1 (<1)	2 (1)	0	0	0	1 (6)	32 (5)
Anxiety	26 (6)	30 (7)	5 (3)	11 (7)	5 (6)	3 (4)	0	0	36 (5)
Oropharyngeal pain	27 (7)	16 (4)	6 (4)	5 (3)	0	2 (3)	2 (12)	0	35 (5)

Data Source: ISO Table 2.705

a. Number and percent of subjects with adverse event.

The profile of AEs for the studies of DTG in ART-naïve subjects that included the TDF/FTC NRTI backbone was similar to that for the ABC/3TC NRTI backbone, Diarrhea, nasopharyngitis, nausea, headache, fatigue and upper respiratory tract infection were the most commonly reported clinical AEs, occurring at similar rates across the treatment groups (m2.7.4 Section 2.1.1). The majority of AEs were also Grade 1 or Grade 2, with few Grade 3 or 4 AEs reported.

The registrational studies (CNA30021 and EPV20001) for ABC/3TC in ART-naïve subjects included EFV, which resulted in reporting ofcommon EFV-related AEs including nausea, dizziness, insomnia/sleep disorders and diarrhea (m2.7.4 Section 2.1.1). The majority of AEs were Grade 1 or Grade 2; approximately 25% of subjects reporting Grade 3 or 4 AEs.

5.6.2.1. Labeling and Adverse Drug Reactions

Adverse reactions listed in the Company Reference Safety Information (RSI) and Local Country Labeling are events reported from clinical trial or post-marketing surveillance, which have been assessed as being at least possibly causally related to DTG, ABC and/or 3TC.

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 investigator was instructed to use clinical judgment 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 investigational product were to be considered and investigated. The investigator was 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 his/her assessment.

5.6.2.1.1. Company RSI and where Local Country Labeling require ADRs Presented from Integrated Data by SOC and Frequency

All of the adverse reactions and laboratory abnormalities listed in the RSI and Local Country Labeling for the individual active moieties (DTG, ABC and 3TC) are also presented in the RSI and Local Country Labeling for the combination product, even when not yet seen in humans with the combination product.

Furthermore, an analysis of pooled data for DTG+ABC/3TC has been conducted to identify any differences between the adverse reactions observed for the combination, compared to the existing adverse reaction profiles for the individual active moieties when each was administered with other antiretroviral agents.

Adverse reactions are listed by MedDRA body system organ class and by frequency category. Frequency 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
Rare:	≥1/10,000, <1/1000
Very Rare:	<1/10,000

The adverse reactions considered at least possibly related to treatment with the individual components of the DTG/ABC/3TC FDC from clinical trial data are tabulated in m2.7.4 Section 2.1.1.4.1.

DTG + ABC/3TC FDC: Adverse events judged by the investigator to be reasonably attributable to IMP with a frequency of at least 1% in the pooled DTG+ABC/3TC treatment group (n=679 ART naive subjects; Data Source: FDC ISO Table 2.708) were reviewed against those already listed in the labeling for the individual active moieties DTG, ABC and 3TC. Similarly, Grade 3 to 4 laboratory abnormalities of at least 1% in the pooled DTG+ABC/3TC treatment group were reviewed in the same way (Data Source: FDC ISO Table 2.738 and Table 2.740).

The adverse reactions observed for the combination of DTG + ABC/3TC were generally consistent with the adverse reaction profiles for the individual components dolutegravir, abacavir and lamivudine. However, some ADRs were observed with the combination at a reporting rate ≥1%, which were not listed in the company RSI for any of the individual components, as summarized below. The frequency categories for these additional ADRs were derived from the frequency of all adverse events in the pooled DTG+ABC/3TC population, regardless of causality, not just the frequency of events considered to be at least possibly related by the investigator (Data Source: FDC ISO Table 2.705).

Thus the following common treatment-emergent adverse reactions were observed with the combination but were not listed in the prescriber information for any of the individual components.

The following AEs were added as a result of this analysis with a frequency of 'common':

- *Gastrointestinal disorders:* abdominal distension, gastroesophageal reflux disease, dyspepsia
- *Nervous system disorders:* somnolence
- *Psychiatric disorders:* depression, nightmare and sleep disorder
- *Metabolism and nutrition disorders:* hypertriglyceridemia and hyperglycemia

In addition, abdominal discomfort, fatigue and insomnia were observed at a greater frequency with DTG+ABC/3TC when compared to the individual components. The frequency category for fatigue and insomnia was 'very common' with the combination

(previously 'common' with each individual component or with dolutegravir, respectively). The frequency category for abdominal discomfort was 'common' with the combination (previously 'uncommon' with dolutegravir). From analyses of data presented in subsequent sections of this document, the Sponsor does not consider there to be any events or laboratory anomalies observed with a different intensity with DTG+ABC/3TC than compared to the individual components.

Of note, more drug-related AEs were reported for the DTG+ABC/3TC treatment groups in studies with an EFV-containing treatment group (i.e., ING114467 and ING112276), than were observed for the DTG+ABC/3TC treatment groups in ING113086 and ING114915 (Data Source: FDC ISO Table 2.708). ING114467 accounted for 61% of the 679 subjects in the pooled DTG+ABC/3TC treatment group in the FDC ISO, whereas during analyses of data conducted for the original DTG 50 mg Single Entity (SE) marketing applications, ING114467 accounted for 26% of the 1571 INI-naive and resistant subjects in the total DTG pooled population (which also included the ART-naive subjects treated with a TDF/FTC backbone). Thus, reporting rates for the above ADRs in the pooled DTG+ABC/3TC treatment group appears to be higher than observed for the pooled DTG SE population, crossing the ≥1% threshold ADR reporting rate for inclusion in the Company CSI and proposed local labeling for DTG/ABC/3TC, despite not doing so for the Company CSI or local prescribing information for the DTG SE (Data Source: DTG SE ISO Table 2.511 and Table 2.508).

The safety profile for the DTG/ABC/3TC FDC is expected to be similar across the ART-naïve, and ART-experienced (INI- naïve) patient populations, based on the integrated analysis of clinical safety data for DTG from Phase IIb to Phase IIIb clinical trials and historic data for the ABC/3TC FDC from CAL30001 and ESS30008.

DTG: For DTG 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; including ART-naive and ART-experienced [both INI- naive and experienced]) for the initial DTG SE marketing applications, were selected for inclusion in the label (Data Source: DTG SE ISO Table 2.511).

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 Labeling. 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 DTG population, regardless of causality, not just the frequency of events considered to be at least possibly related by the investigator (Data Source: DTG SE ISO Table 2.508).

Grade 3 to 4 laboratory abnormalities of at least 1% in the pooled treatment group were included in the label (Data Source: DTG SE ISO Table 2.520).

ABC+3TC: For ABC/3TC all adverse reactions and laboratory abnormalities listed in the RSI and Local Country Labeling for the individual abacavir sulphate and lamivudine active moieties were included.

In addition to the adverse drug reactions included from clinical trial data, the events listed identified during post-approval use of ABC and 3TC (i.e., from spontaneous ADR report data, epidemiological data, review of the medical literature and/or aggregate review of subsequent clinical trial data) are tabulated separately in m2.7.4 Section 2.1.1.4.1. These events were chosen for inclusion due to a potential causal connection to ABC and/or 3TC.

The Applicant monitors the safety profile for each of its marketed products through the regular and systematic post-marketing surveillance/pharmacovigilance processes described in [m2.7.4 Section 6]. To date, there have been no additional relevant adverse reactions and/or laboratory abnormalities specific to the ABC/3TC FDC tablet, over and above those listed for the individual active moieties, identified by either the Sponsor or Regulatory Agencies. The safety profile for ABC and 3TC has been shown to be no different when administered either once or twice daily.

5.6.2.1.2. Local Country Labeling requiring ADRs presented 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 plus ABC/3TC in the pivotal Phase III clinical trial ING114467. A cut-off was applied to Grade 2 to 4 events with a frequency of ≥2% of subjects in any treatment arm within these four studies.

Events occurring in <2% of subjects receiving DTG in any clinical trial, 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.

Laboratory abnormalities with a worsening grade from Baseline, which met a specified reporting threshold (for Grades 2 to 4 combined), were provided where required.

5.6.3. Deaths

A complete discussion concerning deaths in the DTG+ABC/3TC FDC clinical development program can be found in m2.7.4, Section 2.1.2.

Nine deaths were reported from the DTG SE development program in INI-naive subjects up to the [redacted] data lock point.

- Six involved ART-naive subjects (ING112276, ING113086, and ING114467). Three received DTG, two received Atripla and one received RAL. Only one subject received DTG+ABC/3TC (motor vehicle accident, unrelated to IP) in ING112276.
- Three involved ART-experienced (INI-naive) subjects (ING111762). All had received RAL, with one also receiving ABC as a concurrent study treatment.

Only one fatality was associated with a drug related event (Subject 5315 in the Atripla treatment group from ING114467 (see m2.7.4, Section 2.1.2.1).

There were five deaths reported across the pivotal ABC+3TC studies. All deaths were reported in ART-naive subjects in CNA30021: two subjects in the ABC once daily group and three subjects in the ABC BID group. None of the deaths were considered by the investigator to be related to the study drug. No deaths were reported in EPV20001, CAL30001 or ESS30008 (m2.7.4, Section 2.1.2.3).

5.6.4. Serious Adverse Events

The definition of a Serious Adverse Event and details of the reported SAEs are provided in m2.7.4, Section 2.1.3.

In the ART-Naïve Pooled Data Set for the analysis of DTG+ABC/3TC, the proportion of subjects developing at least one SAE was low across treatment groups. Only drug hypersensitivity and suicide attempt were reported in >2 subjects treated with DTG+ABC/3TC (Table 13); these are discussed in Section 5.6.6.

Few SAEs were considered reasonably attributable to IP by reporting investigators across treatment groups, with no emerging trends for DTG+ABC/3TC apparent from these data. In ING114467 a higher frequency of drug related events was observed with the Atripla treatment population when compared with DTG+ABC/3TC (m2.7.4 Table 46).

Table 13 Summary of Serious Adverse Events in at least Two Subjects in any treatment group – ART-Naïve Population

Preferred term	ING114467		ING113086		ING114915		ING112276		TOTAL DTG 50 mg + ABC/3TC in ART Naïve Subjects N=679 n (%)
	DTG 50 mg + ABC/3TC once daily N=414 n (%)	EFV/TDF/FTC once daily N=419 n (%)	DTG 50 mg once daily + ABC/3TC N=169 n (%)	RAL 400 mg BID + ABC/3TC N=164 n (%)	DTG 50 mg once daily + ABC/3TC N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC once daily N=80 n (%)	DTG 50 mg once daily + ABC/3TC N=17 n (%)	EFV 600 mg once daily + ABC/3TC N=16 n (%)	
Any event	44 (11)	51 (12)	14 (8)	21 (13)	10 (13)	6 (8)	2 (12)	4 (25)	70 (10)
Drug hypersensitivity	1 (<1)	0	3 (2)	0	0	1 (1)	0	0	4 (<1)
Suicide attempt	2 (<1)	2 (<1)	1 (<1)	2 (1)	1 (1)	0	0	1 (6)	4 (<1)
Cerebrovascular accident	1 (<1)	1 (<1)	0	0	1 (1)	0	0	1 (6)	2 (<1)
Foot fracture	1 (<1)	1 (<1)	0	0	0	0	1 (6)	0	2 (<1)
Intentional overdose	2 (<1)	0	0	0	0	0	0	0	2 (<1)
Pneumonia	2 (<1)	2 (<1)	0	2 (1)	0	0	0	0	2 (<1)
Syphilis	2 (<1)	0	0	0	0	0	0	0	2 (<1)
Appendicitis	1 (<1)	1 (<1)	0	2 (1)	0	0	0	0	1 (<1)
Bronchitis	1 (<1)	3 (<1)	0	0	0	0	0	0	1 (<1)
Gastroenteritis	0	1 (<1)	1 (<1)	0	0	0	0	0	1 (<1)
Overdose	0	2 (<1)	0	0	1 (1)	0	0	0	1 (<1)
Suicidal ideation	1 (<1)	2 (<1)	0	2 (1)	0	0	0	0	1 (<1)
Syncope	0	3 (<1)	0	0	1 (1)	0	0	0	1 (<1)
Cellulitis	0	2 (<1)	0	0	0	0	0	0	0
Depression	0	3 (<1)	0	1 (<1)	0	1 (1)	0	0	0
Respiratory distress	0	2 (<1)	0	0	0	0	0	0	0
Sciatica	0	2 (<1)	0	0	0	0	0	0	0
Subcutaneous abscess	0	3 (<1)	0	1 (<1)	0	0	0	0	0

Data Source: ISO Table 2.711

For the DTG SE clinical program, no trends in SAEs were noted across the patient populations assessed (m2.7.4, Section 2.1.3.2). 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.

In ART-naive 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; with the exception of ING114915 (11% vs 5%), where the reporting rate was higher for the DTG treatment group (m2.7.4, Table 47). SAEs in the DTG treatment group were reported from a wider spectrum of SOCs compared to the DRV+RTV treatment group, but the frequencies in each SOC were low. Numerically, more SAEs were reported for the DTG treatment group from the GI disorders SOC, psychiatric disorders SOC, injury, poisoning and procedural complications SOC, and nervous system disorders SOC, compared to the DRV+RTV treatment group. In relation to psychiatric disorders, the three subjects with suicidality-related SAEs (suicide attempt or overdose) had a prior history of suicidality. For the GI disorders, none of the SAEs occurred in more than one subject and thus the increased rate of GI SAEs was likely a chance finding. Only one event (suicide attempt) was considered drug related.

For the remainder of the Phase IIb to IIIb studies the majority of individually-reported SAE preferred terms had a reporting rate of <1% across all treatment groups.

In the registrational studies for ABC/3TC the majority of SAEs were reported in 1% of subjects or less, except for drug hypersensitivity which was reported in 7% to 9% of subjects in CNA30021. These were due to abacavir HSR reactions and were considered drug-related. Subjects in this study were not screened for the *HLA-B*5701* allele and therefore the likelihood of ABC HSR was higher without exclusion for the presence of *HLA-B*5701* (m2.7.4, Section 2.1.3.3).

All cases of ABC HSR were to be reported as SAEs in any study using an ABC-containing product as protocol defined study medication (i.e., IP or background dual NRTI backbone), so that the sponsor could meet regulatory requirements for these products. This reporting was done regardless of whether any of the associated signs or symptoms actually met one of the standard ICH E2A definitions for serious. The SAE reporting rates from these studies are thus likely higher than they would have otherwise been without these additional specific reporting requirements.

In addition to the cumulative SAEs reported through to the data cut-off dates applied to individual studies for this integrated summary of safety, the Sponsor's global safety database (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 m2.7.4, Table 3) up to [redacted]. No reconciliation was performed between OCEANS and the clinical trials' databases in preparation for this analysis and as these studies are still ongoing, these cases are still subject to change.

Forty subjects reported additional SAEs through [redacted]. Thirty-five of these subjects were receiving DTG and five were receiving comparator. Review of these data

did not highlight any new signals for DTG. The most commonly reported SAEs in this dataset were infections and infestations, including respiratory tract infections, pneumonia, opportunistic infections, diverticulosis, abscesses, and sepsis (DTG n=10; RAL n=1) as would be expected in HIV-infected subjects. See m2.7.4 Section 2.1.3.4, "Additional SAEs (from date of last analysis to [redacted])".

It is concluded that SAE profile derived from clinical studies of DTG+ABC/3TC is consistent with the SAE profile derived from the DTG SE and ABC clinical studies.

5.6.5. Adverse Events Leading to Withdrawal

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. Rates were comparable to RAL+ABC/3TC and DRV+RTV+ABC/3TC (Table 14; m2.7.4, Section 2.1.4.1).

With the exception of dizziness, fatigue, abnormal dreams, depression and headache in the ING114467 Atripla group, all other individually reported AE preferred terms resulting in withdrawal or permanent discontinuation had a reporting rate of <1% across all treatment groups or were reported in one subject in ING112276, which had small treatment populations (Data Source: FDC ISO Table 2.713).

Table 14 Summary of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product by System Organ Class – ART-Naïve Population

System organ class	ING114467		ING113086		ING114915		ING112276		TOTAL DTG 50 mg + ABC/3TC in ART Naïve Subjects N=679 n (%)
	DTG 50 mg + ABC/3TC once daily N=414 n (%)	EFV/TDF/FTC once daily N=419 n (%)	DTG 50 mg once daily + ABC/3TC N=169 n (%)	RAL 400 mg BID + ABC/3TC N=164 n (%)	DTG 50 mg once daily + ABC/3TC N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC once daily N=80 n (%)	DTG 50 mg once daily + ABC/3TC N=17 n (%)	EFV 600 mg once daily + ABC/3TC N=16 n (%)	
Any event	14 (3)	52 (12)	5 (3)	4 (2)	3 (4)	3 (4)	1 (6)	4 (25)	23 (3)
Psychiatric disorders	4 (<1)	23 (5)	1 (<1)	0	0	0	0	2 (13)	5 (<1)
Nervous system disorders	1 (<1)	17 (4)	1 (<1)	0	2 (3)	0	0	0	4 (<1)
Immune system disorders	2 (<1)	3 (<1)	1 (<1)	1 (<1)	0	1 (1)	0	1 (6)	3 (<1)
Infections and infestations	2 (<1)	2 (<1)	1 (<1)	1 (<1)	0	1 (1)	0	0	3 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<1)	1 (<1)	0	0	1 (1)	0	1 (6)	0	3 (<1)
Gastrointestinal disorders	0	8 (2)	1 (<1)	0	1 (1)	1 (1)	0	0	2 (<1)
Injury, poisoning and procedural complications	2 (<1)	0	0	0	0	0	0	0	2 (<1)
Skin and subcutaneous tissue disorders	2 (<1)	9 (2)	0	1 (<1)	0	0	0	0	2 (<1)
General disorders and administration site conditions	0	10 (2)	1 (<1)	0	0	0	0	2 (13)	1 (<1)
Hepatobiliary disorders	0	0	1 (<1)	2 (1)	0	0	0	0	1 (<1)
Investigations	0	1 (<1)	1 (<1)	1 (<1)	0	0	0	0	1 (<1)
Renal and urinary disorders	1 (<1)	2 (<1)	0	0	0	0	0	0	1 (<1)
Blood and lymphatic system disorders	0	2 (<1)	0	0	0	0	0	0	0
Ear and labyrinth disorders	0	3 (<1)	0	0	0	0	0	0	0
Metabolism and nutrition disorders	0	2 (<1)	0	0	0	0	0	0	0
Musculoskeletal and	0	1 (<1)	0	0	0	0	0	0	0

System organ class	ING114467		ING113086		ING114915		ING112276		TOTAL DTG 50 mg + ABC/3TC in ART Naïve Subjects N=679 n (%)
	DTG 50 mg + ABC/3TC once daily N=414 n (%)	EFV/TDF/FTC once daily N=419 n (%)	DTG 50 mg once daily + ABC/3TC N=169 n (%)	RAL 400 mg BID + ABC/3TC N=164 n (%)	DTG 50 mg once daily + ABC/3TC N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC once daily N=80 n (%)	DTG 50 mg once daily + ABC/3TC N=17 n (%)	EFV 600 mg once daily + ABC/3TC N=16 n (%)	
connective tissue disorders									
Respiratory, thoracic and mediastinal disorders	0	2 (<1)	0	0	0	0	0	0	0

Data Source: ISO Table 2.713

The withdrawals from the studies in the DTG SE program showed the same pattern, with AEs leading to permanent discontinuation of IP and withdrawal from the study more commonly reported for the Atripla and EFV treatment groups, compared to DTG, and similar between DTG and RAL and DRV+RTV treatment groups (m2.7.4 Table 59).

Withdrawals due to liver stopping criteria were noted on DTG and comparator arms across the Phase IIb and III/b studies. However, these events were frequently confounded by concomitant medications or co-infection with hepatitis B or C virus.

5.6.6. Adverse Events by Organ System Class

Adverse events of special interest (AESI) for the DTG/ABC/3TC FDC are discussed in this section.

AESI have been determined for DTG based on nonclinical and/or clinical safety data for DTG, labeling and/or regulatory authority interest for approved integrase inhibitors and/or the INI class, and/or regulatory authority requirements.

For the ABC/3TC, AESI are based on the identified and potential ongoing risks recognized in the 2012 EU Risk Management Plan [GlaxoSmithKline Document number 2012N136605_00] for the ABC and 3TC actives formulated as the once daily ABC/3TC FDC tablet. These risks arose during the original non-clinical and clinical development program for ABC (i.e., carcinogenicity and hypersensitivity, respectively) or through post marketing surveillance activities (e.g., rash and ischemic cardiac disorders for ABC) and are discussed in this section. The hepatic impairment risk for ABC quantified during the original clinical pharmacology program for this asset is presented in Section 5.1.3.2 of m2.7.4.

Based on this information, the AESIs for the DTG/ABC/3TC FDC were identified as shown in the table below (see also m2.7.4, Table 64):

AESI	Applicable Component(s):	Discussed in Section of m2.7.4:
Hypersensitivity Reaction	ABC and DTG	2.1.5.1
Rash	DTG, ABC & 3TC	2.1.5.2
Hepatobiliary Disorders	DTG	2.1.5.3
Renal disorders	DTG	2.1.5.4
Ischaemic Cardiac Disorders	ABC	2.1.5.5
Gastrointestinal Disorders	DTG	2.1.5.6
Use during Pregnancy & Breast Feeding	All ART	2.1.5.7
Psychiatric disorders including Suicidality	DTG	2.1.5.8
Musculoskeletal, connective tissue and bone disorders	DTG	2.1.5.9
Immune Reconstitution Inflammatory Syndrome	DTG and all ART	2.1.5.10
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)	DTG and ABC	2.1.5.11
Torsades de Pointe	All medications	2.1.5.12
Mitochondrial dysfunction and related syndromes	NRTIs	2.1.5.13
Bone disorders	All ART	2.1.5.14

Details on the AEs of Special Interest section are included in m2.7.4, Section 2.1.5.

5.6.6.1. Hypersensitivity

Data on HSR for DTG and DTG+ABC/3TC FDC suggest that there will not be additional risk from HSR in *HLA-B*5701* negative subjects receiving the DTG/ABC/3TC FDC.

Few subjects receiving DTG+ABC/3TC FDC or comparator were reported with terms indicative of HSR (hypersensitivity, drug hypersensitivity and anaphylactic reaction) and reporting rates were similar across studies and treatment groups (m2.7.4, Table 60).

With the exception of the Atripla arm in ING114467 in, which 5/6 of the HSR events were considered of Grade 3 to 4 intensity, the majority of cases from each treatment group were considered of Grade 1 to 2 intensity. In the total DTG+ABC/3TC FDC treatment group, 2/10 HSR events were considered of Grade 3 to 4 intensity (Data Source: ISO Table 2.707). No HSR event resulted in a fatal outcome and cases of HSR infrequently resulted in the permanent discontinuation of IP and subject withdrawal (Data Source: FDC ISO Table 2.713).

The frequency of cases meeting the Market Authorization Holder (MAH) definition for suspected ABC HSR in ART-naive, *HLA-B*5701* negative subjects from the Phase IIb to IIIb clinical trials of DTG was <1% for the subjects treated with DTG+ABC/3TC and also the RAL+ABC/3TC and DRV+RTV+ABC/3TC treated subjects. This was comparable to or lower than the incidence for ABC HSR reported in *HLA-B*5701* negative subjects participating in large randomized MAH sponsored clinical trials investigating the marketed ABC-containing products. Although these data are limited, they suggest that there is no additional risk from HSR in *HLA-B*5701* negative subjects receiving the DTG/ABC/3TC single tablet FDC.

In ING113086, for 2/3 HSR cases involving DTG+ABC/3TC, symptoms resolved following a switch from ABC/3TC to TDF/FTC with continued DTG, suggesting that DTG was not causal. The remaining case involving DTG+ABC/3TC from this study also involved clinically significant liver chemistry elevations, and was reported as reasonably attributable to DTG by the reporting investigator (Subject 4529) and is considered to be the index case of possible DTG HSR by the Sponsor. Details of this case are provided in m2.7.4, Section 2.1.5.1.

The reporting rate of ABC HSR, calculated from spontaneous data and patient exposure estimates, has generally decreased on an annual basis since the ABC single entity was first introduced in 1999, and has remained at a plateau since 2008. Of the 1,880 cumulative spontaneous reports: 111 (6%) met the MAH definition for positive rechallenge ABC HSR with symptoms on initial exposure; see m2.7.4, Section 9.3 for the MAH ‘case definition’); and 28 resulted in fatal outcome (19 on initial ABC exposure, but prolonged despite evolving symptoms of HSR, and nine on rechallenge ABC exposure). As per the spontaneous reporting rate of all ABC HSR, the spontaneous reporting rate for all positive rechallenge ABC HSR and fatal ABC HSR has also decreased annually since the ABC single entity was first introduced in 1999, and has remained at a plateau since 2008 and 2003, respectively.

Due the identification of the case presented above of HSR with organ dysfunction in a ART-naïve subject in ING113086 and additional confounded cases identified in ART-experienced subjects, labeling for DTG containing product will include a warning about hypersensitivity reactions, including monitoring for liver enzymes if HSR is observed for a patient on a DTG containing product.

5.6.6.2. Rash

Overall, mild to moderate episodes of rash were commonly reported for DTG+ABC/3TC FDC (m2.7.4, Section 2.1.5.2.1). Episodes rarely required interruptions or discontinuations of therapy and tended to resolve within two to three weeks without recurrence of symptoms. The rate and nature of rash with DTG+ABC/3TC FDC was no different to that observed for comparators in the Phase III/b development program (with the exception of a significantly higher reporting rate observed for Atripla), or observed historically for the individual actives DTG, ABC and 3TC. The index case of hypersensitivity with DTG+ABC/3TC (ING113086 Subject 4529) involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including SJS, TEN and EM, were reported for DTG+ABC/3TC or comparator (Data Source: FDC ISO Table 2.705).

In the DTG SE clinical program, reporting rates for "Rash" of any grade for DTG, were comparable with RAL and DRV+RTV, but lower 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 (m2.7.4, Section 2.1.5.2.2).

Rash is listed as a common ADR for ABC and 3TC, occurring in ≥1% to <10% of patients (m2.7.4, Section 2.1.5.2.3). Rash frequently occurs as symptom of ABC HSR, but has also been commonly reported without systemic systems (i.e., outside of the context of HSR) post marketing. Serious skin reactions, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme have been uncommonly reported in patients taking ABC-containing products post marketing. These patients generally do not have the cluster of additional symptoms that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

5.6.6.3. Hepatobiliary Disorders

The frequency of assessments throughout the clinical programme was adequate to detect and characterize cases of possible drug induced liver injury (DILI) and included an additional two week assessment following the report of a hypersensitivity reaction with associated liver dysfunction early in the program from ING113086. There were no cases of severe DILI that were fatal or requiring transplantation. Cumulative data suggest a hepatic safety profile for DTG+ABC/3TC that is comparable to Atripla, RAL+ABC/3TC and DRV+RTV +ABC/3TC. 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.

In the DTG+ABC/3TC pooled dataset the percentage of subjects with post-baseline emergent ALT>3xULN was similar for DTG vs. RAL (ING113086) and lower for DTG+ABC/3TC compared with Atripla (ING114467). In ING114915 the percentage was greater for DTG+ABC/3TC compared with DRV+RTV, but the numbers were small. There were no subjects with ALT>3xULN in either treatment group (DTG or EFV)

receiving ABC/3TC in ING112276. Consideration of the full dataset for the DTG SE submission revealed the same trends in each study.

In the DTG+ABC/3TC pooled dataset, two subjects, both from study ING113086 and both in the DTG+ABC/3TC group had a combination of ALT >3xULN with total bilirubin >2xULN and ALP <2xULN. One was the index case of hypersensitivity, Subject 4529 discussed above. The subject was *HLA-B*5701* negative, but the Sponsor judged it was not possible to rule out a contribution by ABC, although features of the case would be considered atypical for ABC HSR. In addition the subject was taking a number of supplements including herbal extracts that may also be risk factors for severe reactions. The other case, Subject 4319, was confounded by concomitant biliary disease and was a subject participating in Russian site (Investigator ID=096536) that was closed early due to GCP violations.

Six subjects in the DTG+ABC/3TC pooled dataset had extreme elevations of transaminase (ALT>10xULN), two in each of the three ART-naïve studies (ING114467, ING113086 and ING114915). In each study one subject was treated with DTG+ABC/3TC and the other with comparator. There were definitive explanations other than DILI for all but two cases, one treated with DTG+ABC/3TC and one treated with RAL+ABC/3TC.

Subjects with HBV were excluded from the pivotal ING114467 study, thus there is limited data on use in this population (two subjects on DTG+ABC/3TC, two subjects on RAL+ABC/3TC and one subject on Atripla) and insufficient data for analysis.

In the DTG+ABC/3TC pooled dataset, subjects with HCV infection at Baseline had a higher incidence of post-Baseline emergent Grade 2 to 4 liver chemistry toxicities compared with subjects who were not co-infected in groups treated with DTG+ABC/3TC, Atripla and RAL+ABC/3TC. Only six subjects co-infected with HCV were randomized to treatment with DRV+RTV and none of them had Grade 2 to 4 liver chemistry toxicities. For ALT and AST laboratories the incidence of toxicities in subjects with hepatitis virus infection treated with DTG+ABC/3TC was lower than both the RAL+ABC/3TC and Atripla treated subjects. The incidence of liver chemistry toxicities for subjects without hepatitis virus infection was low in all treated groups.

In the full dataset for DTG SE submission, subjects with hepatitis B and/or C co-infection were noted to have immune reconstitution as a result of HIV virologic and immunologic responses and inadequate therapy for hepatitis B co-infected subjects as likely contributing factors to significant elevations in liver chemistries.

Across all patient populations, safety data supports the administration of DTG in HIV-infected patients co-infected with hepatitis B and/or hepatitis C, 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 labeling for DTG+ABC/3TC.

3TC is approved for the treatment of HBV, but monotherapy with 3TC in patients co-infected with HIV is not recommended as emergence of lamivudine resistant HBV has

been detected and has been associated with diminished treatment response. In addition, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of 3TC in patients infected with HBV. The Sponsor plans to include appropriate language to address these concerns in the proposed labelling for DTG+ABC/3TC.

ABC/3TC have NRTI class labeling, warning of the risk of lactic acidosis and severe hepatomegaly with steatosis. 3TC also has uncommon transient rises in liver enzymes (AST, ALT). As noted above, the incidence of liver enzyme elevations was modest, and no cases of lactic acidosis/steatosis were noted in the DTG + ABC/3TC treated subjects, hence, the combination does not appear to increase the known risk associated with ABC/3TC alone.

5.6.6.4. Renal Function

Overall, the renal safety profile of DTG+ABC/3TC is comparable to comparators in Phase III/b studies (i.e., RAL, DRV and EFV).

Mild elevations of serum creatinine have been observed with DTG. These are related to a likely benign effect on creatinine secretion via blockade of the OCT2 receptor, which is responsible for tubular secretion of creatinine. In a Phase I study to assess renal pharmacodynamic effects, 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 PAH clearance, a measure of effective renal plasma flow.

Small increases in mean serum creatinine were observed on the DTG arms in each of the Phase IIb and III/b studies (12.6 and 14.6 μmol/L at Week 96 for ING11467 and ING113086 respectively and 16.0 μmol/L at Week 48 in ING114915). These were evident from Week 1 but plateaued with no evidence of subsequent increase. Smaller mean increases in serum creatinine of 8.2 μmol/L on the RAL treatment arm of ING113086 and 1.4 μmol/L on Atripla in ING114467 at 96 Weeks and 5.4 μmol/L in the DRV+RTV arm of ING114915 at 48 Weeks were noted.

The changes in creatinine and creatinine clearance when DTG was combined with ABC/3TC were compared with DTG combined with TDF/FTC, using the DTG SE ISO of pooled data from ING112276, ING114467 and ING113086 and there was no evidence of deterioration in the renal tolerability of DTG due to concomitant TDF. A comparison of serum creatinine levels by background NRTI in ING114915 showed the changes were consistent with the overall results.A low incidence of graded creatinine elevations has been observed on DTG, and no Grade 3 to 4 toxicities have been observed in the 96 Week data from either ING113086 or ING114467.

Transient increases in urine protein by dipstick in a minority of subjects were noted in the Phase IIb studies, prompting quantitative measures of urine albumin in Phase IIb and III/b studies (albumin is the protein detected by the dipstick test). These changes were not progressive in nature, were not associated with clinically significant changes for individual subjects with respect to AEs, graded lab abnormalities or withdrawals, and

were not supported by more reliable, quantitative measures of albuminuria. Median increases in spot urine albumin/creatinine values were comparable between DTG and comparator treatment groups (RAL, EFV or DRV+RTV-containing regimens). Importantly, tubular and glomerular urine protein was evaluated in the Phase I study assessing the renal safety of DTG, and no association between DTG dosing at 50 mg once daily or BID and proteinuria was observed in this study.

No adverse effects on renal function have been identified for ABC/3TC in clinical trials or during post-marketing surveillance. However, the clearance of 3TC is reduced in patients with decreased GFR and dose adjustment is required for patients with a creatinine clearance of <50 ml/min. Therefore the DTG/ABC/3TC FDC would be unsuitable for use in such patients as it cannot be dose adjusted.

5.6.6.5. Ischemic Cardiac Disorders

No subjects receiving DTG+ABC/3TC were reported with myocardial infarction (MI) or any other ischemic cardiac events, after 1067 subject years of follow up in the pooled DTG+ABC/3TC treatment group (m2.7.4, Section 2.1.5.5).

Only two subjects developed ischemic cardiac disease related events in comparator treatment groups, and no subjects were reported with MI, with 636, 268 and 74 subject years of follow up for Atripla (coronary artery disease), RAL+ABC/3TC (angina pectoris) and DRV+RTV+ABC/3TC, respectively (Data Source: ISO Table 2.705 and ISO Table 2.701). One event of coronary artery disease was reported for Subject 5923 receiving Atripla in ING114467, with onset on Day 7. This subject was recorded with Framingham risk of <10% at Baseline and had a history of smoking. Subject 4337 receiving RAL+ABC/3TC in ING113086 developed angina pectoris 156 days after starting therapy. This case was confounded by medical history of hypertriglyceridemia and Framingham risk of <10% recorded at Baseline.

The frequency of events reported from the cardiac disorders SOC over all was generally low and comparable across studies and treatment groups. There was slight imbalance for DTG+ABC/3TC compared to DRV+RTV+ABC/3TC in ING114915 (2/79 [3%] and 0/80 subject reporting events from the cardiac disorders SOC), however these were non-ischemic in nature (tachycardia and cardiac failure) and the patient population and duration of exposure in subject years for this study were smaller than for ING114467 and ING113086 (Data Source: ISO Table 2.705 and ISO Table 2.701).

Although 1067 subject years of follow up have been accrued in the pooled DTG+ABC/3TC treatment group, clinical trials of 48 or 96 weeks duration are usually too short to characterize the cumulative cardiovascular risk for any drug. Thus, in line with the marketed ABC-containing products, the labeling for DTG/ABC/3TC FDC will summarize the available, inconclusive information on ABC and risk of MI and will recommend prescribers to consider underlying risk of coronary heart disease when prescribing antiretroviral therapies, including ABC, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

5.6.6.6. Gastrointestinal (GI) Disorders

As noted in Section 5.2, the primary effect of DTG in nonclinical studies was gastrointestinal intolerance or irritation. Additionally, gastrointestinal symptoms are frequent adverse events with antiretroviral medications [DHHS, 2012]. As noted in Section 5.6.2, diarrhea and nausea were some of the most frequently observed AEs across patient populations, which were typically Grade 1 or 2 in severity and typically did not lead to discontinuation from studies. Events indicative of general GI intolerance (i.e., diarrhea, nausea, vomiting, and abdominal pain with DTG+ABC/3TC in ING114467 and ING113086 were comparable to EFV- and RAL-containing regimens in ART-naïve subjects, respectively. Overall frequency of GI events was higher in DRV+RTV+ABC/3TC compared to DTG+ABC/3TC in the ING114915.

Few cases of gastric or peptic ulcer disease were reported in treatment-naïve subjects and were typically related to concomitant medications (e.g., aspirin) or medical conditions (Non-Hodgkin's lymphoma). Adverse events considered potentially indicative of GI ulcerative lesion as identified by Sponsor medical review were rarely reported.

Nonclinical evidence for GI ulceration with DTG did not translate into significant findings in double blinded randomized clinical trials; a similar rate and nature of GI events were reported for DTG compared to RAL and EFV-containing regimen, there was a lower rate compared with DRV+RTV, and there was no evidence for an increased risk of GI ulcerative lesions in any study.

The current RSI for ABC/3TC does not include GI ulceration as a potential adverse reaction.

5.6.6.7. Psychiatric Disorders

The Psychiatric adverse event profile for DTG was favorable compared with Atripla and similar to RAL and DRV +RTV (m2.7.4, Section 2.1.5.8). In the Psychiatric events SOC, nightmare, abnormal dreams, depression, bipolar disorder and suicidal events were more commonly reported for Atripla than the other treatment groups, which had similar lower rates. Insomnia was more common in the DTG+ABC/3TC group than Atripla in ING114467, but occurred at a lower rate in the DTG+ABC/3TC treatment groups in all other studies, and was similar to RAL+ABC/3TC and DRV+ RTV+ABC/3TC.

A meta-analysis of 54 MAH sponsored HIV clinical trials did not suggest that ABC-containing regimens were associated with an increased risk of neuropsychiatric events [GlaxoSmithKline Document number RM2009/00054/00].

5.6.6.8. Immune Reconstitution Inflammatory Syndrome (IRIS)

As detailed in m2.7.4, Section 2.1.5.10, for the Phase III clinical trials, potential IRIS cases were reviewed and adjudicated by senior ViiV Healthcare or GSK physicians (ING113086, ING114915) or the Independent Data Monitoring Committee (IDMC; ING114467). For the ART-naïve population, few cases of IRIS were identified and incidence rates were similar for DTG 50 mg once daily and comparators. Despite the

rapid decline in HIV RNA observed on DTG +ABC/3TC, IRIS cases were infrequent on DTG+ABC/3TC, and rates were comparable to those observed on Atripla, RAL+ABC/3TC and DRV+RTV+ABC/3TC.

5.6.6.9. Other

No clinically significant safety findings were identified in the following AEs of special interest (discussed in more detail in m2.7.4 Section 2.1.5):

- Musculoskeletal Disorders
- Neoplasms, Benign, Malignant, and Unspecified (including Cysts and Polyps)
- Torsades de Pointe
- Nervous System Disorders

5.6.7. Clinical Laboratory Evaluations

See m2.7.4, Section 3 for details of laboratory data.

5.6.7.1. Clinical Chemistry

Details of Clinical Chemistry safety findings can be found in m2.7.4, Section 3.1.

The majority of ART-naïve subjects in all groups reported graded chemistry toxicities, but only 16% in the total DTG+ABC/3TC group and 17 to 25% in the comparator groups had Grade 3 to 4 events.

Detailed discussion of renal, hepatic and lipid clinical chemistry results as well as CPK, lipase, electrolytes, metabolism indices and hematology are presented m2.7.4, Section 3.1. No pattern of toxicity for any of the other analytes was a cause for concern.

5.6.7.2. Hematology

Details of Hematology safety results can be found in m2.7.4, Section 3.2. There were no clinically significant trends in treatment emergent hematology abnormalities across all populations.

5.7. Vital Signs

There were no clinically significant patterns of changes in vital signs (weight, heart rate, systolic and diastolic blood pressure) across the studies (m2.7.4, Section 4.2).

5.8. Electrocardiograms

Few subjects had a QTcF >500 msec and few subjects had change from Baseline in QTcF or QTcB >60 msec. Additionally, few clinically significant ECG abnormalities were

reported, and no trends were observed in these abnormalities. ECGs are discussed in Section 4.2 of m2.7.4.

5.9. Safety in Special Groups and Situations

The effect of intrinsic factors (i.e., gender, age, race, and hepatitis co-infection) and extrinsic factors associated with the patient environment (i.e., the effect of food) are discussed in m2.7.4 Section 5.1 and Section 5.2, respectively.

In general, gender, age, and race did not significantly impact rates of AEs or laboratory abnormalities reported across treatment groups. The representation of special groups (i.e., women, African American/African heritage, age ≥50) allowed an analysis of safety in these groups. Minor exceptions for gender were noted, such as a higher incidence of vomiting in ART-naïve women receiving DTG+ABC+3TC FDC, and differences in laboratory abnormalities in men and women, including more anemia in women and more ALT and CPK increases in men. Minor exceptions were also noted for race, with more African heritage, ART-naïve subjects experiencing neutropenia; this is likely related to lower neutrophil counts in this racial group. These differences were not considered treatment-limiting.

Overall, the safety profile was similar across gender, age and race.

5.10. Pregnancies

No studies have been conducted with DTG+ABC/3TC in pregnant women, and pregnant women were excluded from the studies. Subjects who became pregnant (intrauterine) were required to discontinue from the clinical studies

Twenty-one pregnancies were reported across the pivotal and supporting study populations for the DTG/ABC/3TC FDC, see m2.7.4, Section 5.4. Few cases resulted in an adverse pregnancy outcome (e.g., spontaneous abortion or ectopic pregnancy), and were comparable for DTG+ABC/3TC, RAL+ABC/3TC and Atripla, and no congenital anomalies were reported.

DTG, ABC and 3TC have been shown to cross the placenta in reproductive toxicity studies in animals. 3TC and ABC have been associated with findings in animal reproductive studies. Therefore, administration of DTG/ABC/3TC in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the fetus.

5.11. Withdrawal Effects, Abuse Potential, Overdose

No studies to investigate the potential for withdrawal and rebound effects or the potential for abuse or dependency with DTG+ABC/3TC have been performed. There is currently limited experience with DTG+ABC/3TC overdose (i.e., any dose of DTG above 50 mg once daily in INI-naïve adults and 1 mg/kg once daily with a maximum daily dose of 50 mg in INI-naïve pediatric subjects). The INI class of compounds has no known drug abuse potential. There are no data suggesting that DTG has the potential to contribute to

illicit use, abuse, or dependency on DTG. In nonclinical studies, no effects related to DTG administration on central and peripheral nervous system or body temperature were noted following dosing withdrawal. There is no clinical evidence to suggest withdrawal or rebound effects of DTG.

There have been no studies to investigate the effect of DTG, ABC or 3TC on driving performance or the ability to operate machinery.

No specific symptoms or signs have been identified following acute overdose with ABC or 3TC, apart from those listed as adverse reactions.

5.12. Post-Marketing

There is no information available on DTG/ABC/3TC, as the product is currently not marketed.

DTG received its first approval in the US in August 2013, therefore no post-marketing data is available at the time of this data review.

Cumulatively post-marketing exposure to the ABC- and 3TC-containing products is extensive. Almost 2,000,000 and over 5,700,000 patient years post-marketing experience have been generated in total for the ABC- and 3TC-containing products, respectively, to 31 December 2012. Adverse events from post-marketing experience are presented in more detail in m2.7.4, Section 6.

5.13. Safety Conclusion

Overall the safety profile for DTG + /ABC/3TC, combined with the efficacy and virology profile captured in m2.7.3 and m.2.7.2.4 respectively, supports a favorable risk/benefit compared to other ARVs in the treatment of HIV infection in ART- naïve and ART-experienced (INI- naïve) adult and adolescent patients.

The risk of toxicity with DTG+ABC/3TC appears to be no different to that observed with either the DTG SE or the ABC/3TC FDC when used with other ARV-agents in combination antiretroviral therapy (CART).

- The short term data from the bioequivalence study (ING114580) showed no tolerability differences between the single entities and the FDC.

The safety profile for DTG + ABC/3TC was generally favorable compared with Atripla and comparable to RAL+ABC/3TC and DRV+RTV + ABC/3TC in ART- naïve HIV-infected patients.

- In the pivotal double blind study ING114467, where DTG 50 mg , ABC 600 mg and 3TC 300 mg once daily was compared to the leading ART FDC more subjects in the Atripla treatment group were reported to have AEs attributable to IP when compared to the DTG+ABC/3TC treatment group.

- The superiority of the DTG+ABC/3TC treatment response in ING114467 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. Both arms had low rates of virological non-response.
- The nervous system adverse event profile for DTG + ABC/3TC was improved compared with Atripla (mainly due to the increased incidence of dizziness with Atripla), and similar to RAL and DRV +RTV.
- The Psychiatric adverse event profile for DTG+ABC/3TC was improved compared with Atripla and similar to RAL and DRV +RTV. In the Psychiatric events SOC, nightmare, abnormal dreams, depression, bipolar disorder and suicidal events were more commonly reported for Atripla than the other treatment groups, which had similar lower rates. Insomnia was more common in the DTG+ABC/3TC group than Atripla in ING114467, but occurred at a lower rate in the DTG + ABC/3TC treatment groups in all other studies, and was similar to RAL+ABC/3TC and DRV+ RTV+ABC/3TC.

Cases of hypersensitivity reaction have been uncommon with DTG+ABC/3TC, with rates comparable to Atripla, RAL+ABC/3TC and DRV+RTV+ABC/3TC.

- The nature and incidence of HSR with DTG+ABC/3TC appears to be no different to such events observed with either the DTG SE or the ABC/3TC FDC when used with other ARV- agents in CART.
- ING114467 was the only study in which the dual nucleoside backbone was double-blinded, and the lower incidence of suspected HSR for DTG+ABC/3TC compared to Atripla prior to unblinding at Week 48, provides reassurance for a projected low rate of HSR when DTG and ABC/3TC are co-administered.
- In recent years, the practice of pre-therapy screening for *HLA-B*5701* and excluding individuals from ABC therapy who carry the allele reduces the risk of HSR. The risk of HSR has been managed proactively by clear and detailed labeling, the provision of patient Alert Cards with every pack of ABC-containing product, and an educational program; all of which are still maintained by the Applicant.

The incidence of rash with DTG+ABC/3TC FDC was lower than with Atripla but comparable to RAL+ABC/3TC and DRV+RTV+ABC/3TC.

- The nature and incidence of rash with DTG+ABC/3TC appears to be no different to such events observed with either the DTG SE or the ABC/3TC FDC when used with other ARV- agents in CART.
- No cases of SJS, EM or TEN have been observed in the DTG studies to date.

Cumulative data suggest a hepatic safety profile for DTG + ABC/3TC that is comparable to Atripla, RAL + ABC/3TC and DRV +RTV + ABC/3TC.

- 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, hepatitis virus co-infection was evident, and/or subjects had a medical history of alcohol abuse.

DTG+ABC/3TC is not recommended for use in patients with moderate to severe hepatic impairment (Child Pugh grade B or C)

- Pharmacokinetic studies of DTG showed that no dosage adjustment is necessary for patients with mild to moderate hepatic impairment or for lamivudine in patients with moderate to severe hepatic impairment. Data for ABC in patients with mild hepatic impairment showed an increase in mean AUC of 89% without clinical correlate; no data with ABC are available in patients with moderate or severe hepatic impairment.

The overall renal safety profile for DTG + ABC/3TC was comparable to marketed competitors in Phase III studies (i.e., Atripla, RAL + ABC/3TC and DRV +RTV + ABC/3TC) with a low incidence of adverse events in the Renal SOC for DTG+ABC/3TC and comparators and very few serious or Grade 3/4 events,

- Small, reversible elevations of serum creatinine are expected for DTG + ABC/3TC (appear to be related to a likely benign effect on creatinine secretion with DTG blockade of the OCT-2 receptor); these predictable 0.1 – 0.2 mg/dL changes occur in the first few weeks of therapy stabilize on continued treatment and are not of clinical concern (as they do not reflect changes in actual glomerular filtration rate).
- A low incidence of graded creatinine elevations has been observed, and no Grade 3 to 4 toxicities have been observed in data from either ING113086, ING114467 or ING114915.
- No clinically significant median increases in urine albumin/creatinine values (more accurate than dipstick measurements) were noted in the Phase III clinical studies When DTG+ABC/3TC was compared with Atripla, RAL or DRV+RTV+ABC/3TC.
- The risk of renal toxicity with DTG+ABC/3TC appears to be no different to that observed with either the DTG SE or the ABC/3TC FDC when used with other ARV- agents in CART.

DTG+ABC/3TC is not recommended for patients with a creatinine clearance <50 mL/min

- Whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance.

There is no evidence from the non-clinical and clinical trial program for an adverse effect of DTG + ABC/3TC on ischemic cardiac disorders or cardiovascular disease.

- No subjects receiving DTG+ABC/3TC were reported with myocardial infarction (MI) or any other ischemic cardiac events, after 1067 subject years of follow up in the pooled DTG+ABC/3TC treatment group.

Non-clinical evidence for ulcerative gastro intestinal (GI) toxicity with DTG did not translate into significant findings

- In randomized clinical trials there was a similar rate and nature of events suggestive of GI ulcerative lesion reported for DTG + ABC/3TC compared to Atripla, RAL + ABC/3TC and DRV +RTV + ABC/3TC.
- Hemoglobin concentrations were generally stable or increased over time on all regimens, suggesting positive ART effects.

The GI tolerability profile for DTG + ABC/3TC was similar to Atripla and RAL and improved compared with DRV +RTV.

- The incidence of events indicative of general GI intolerance for subjects treated with DTG+ ABC/3TC was similar to Atripla and RAL+ ABC/3TC and lower than for subjects treated with DRV+RTV+ABC/3TC.
- The risk of GI toxicity with DTG+ABC/3TC appears to be no different to that observed with either the DTG SE or the ABC/3TC FDC when used with other ARV- agents in CART.

Reproductive toxicity is not considered to be a risk for this asset based on non-clinical findings with DTG to date and Post-marketing experience with ABC/3TC.

The musculoskeletal adverse event profile for DTG+ABC/3TC was generally comparable to that observed for Atripla, RAL+ABC/3TC and DRV+ RTV+ABC/3TC treatment groups in ART-naive subjects.

Despite the rapid decline in HIV RNA observed on DTG +ABC/3TC, IRIS cases were infrequent on DTG+ABC/3TC, and rates were comparable to those observed on Atripla, RAL+ABC/3TC and DRV+RTV+ABC/3TC.

DTG+ABC/3TC does not appear to have an increased risk for treatment emergent lipase elevations or pancreatitis in these studies.

The effects of DTG+ABC/3TC on the lipid safety profile was modest and comparable to RAL+ABC/3TC and Atripla but improved compared with DRV + ABC/3TC.

- Post-Baseline changes in graded fasted lipids in all categories (all lipid parameters, cholesterol, triglycerides) were the same or similar when DTG + ABC/3TC treatment groups were compared to Atripla or RAL+ABC/3TC and lower when compared to DRV+RTV+ABC/3TC
- There were no clinically significant effects on the Total cholesterol/HDL cholesterol ratio in any group except for an increase in the ratio in the DRV+RTV+ABC/3TC treated group.

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

No effect of gender, age or race on safety profile of DTG + ABC/3TCis anticipated (beyond what might be expected for each sub group.

There are limited safety implications resulting from theoretical or actual drug: drug interactions with DTG, ABC and 3TC compared to other antiretroviral agents, including EFV and those requiring co-administration with a PK enhancer:

- In vitro, DTG inhibited the renal organic cation transporter (OCT2) and may increase plasma concentrations of drugs dependent on OCT2 for clearance (dofetilide, pilsicainide and metformin). The co-administration of DTG and dofetilide or pilsicainide is contraindicated. Lower metformin doses may be required to achieve glycaemic control when metformin is started in subjects on DTG; metformin dose adjustments may be considered for those currently on metformin who start DTG.

ABC and/or 3TC have a low propensity to cause many of the long-term safety issues historically associated with the NRTI class (e.g., mitochondrial dysfunction and associated clinical syndromes and metabolic disorders) and across ARV classes (e.g., bone disorders and carcinogenicity). Since DTG does not share these class-related risks and there is no PK effect of DTG co-administration with ABC/3TC, no additional risk is anticipated with use of the DTG/ABC/3TC FDC.

- Although clinical trial data for DTG+ABC/3TC have not suggested an increased risk of malignant neoplasms, mitochondrial dysfunction and bone disorders, it is acknowledged that the assessment of such longer-term toxicities require a more extended follow up period.

There are no data suggesting that the DTG/ABC/3TC FDC has the potential for illicit use, abuse, or dependency, nor risks associated with withdrawal or rebound effect.

Given the pharmacology of DTG + ABC/3TC and available clinical evidence, no detrimental effect is anticipated on the ability to drive or operate machinery, or on mental ability.

There is currently limited experience with DTG + ABC/3TC and overdose.

- Limited experience of single higher doses of DTG (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions for this asset. No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as undesirable effects adverse reactions.

Data in ART- experienced (INI- naïve) adults treated with DTG and/or ABC/3TC did not demonstrate a difference in the safety profile of these agents when compared with their effects in the treatment naive population.

The adverse event profile in children and adolescents is not expected to be significantly different from that of adults.

- 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.

- PK data in this age group demonstrated similar exposure levels to adult populations in the DTG 50 mg clinical studies, so there is no expected change in the safety profile in this age group.

6. BENEFITS AND RISKS CONCLUSIONS

Establishing the risk/benefit profile of an STR includes an assessment of the safety/efficacy of each individual component taken alone as well as the safety/efficacy of the components when used in combination. The DTG/ABC/3TC 50/600/300 mg FDC comprises a new chemical entity, DTG, plus two well-established marketed products, ABC and 3TC. The safety and efficacy profile of DTG has been described in the DTG clinical program, while the safety and efficacy profile of ABC/3TC has been established from years of marketed use. As found in the ING114580 bioequivalence study, there is no clinically significant difference in exposure of component drugs when they are dosed as an FDC.

6.1. Benefits of DTG/ABC/3TC FDC in the Treatment of HIV-1 Infection

The benefits of DTG/ABC/3TC FDC combine the benefits of the new INI drug DTG, with the long-established clinical benefits of ABC/3TC, in a convenient single tablet once daily treatment regimen.

New therapeutic options that combine potency, tolerability and ease of use are needed for all sectors of the HIV population, including treatment-naïve or experienced adults and adolescents. There is substantial evidence in the literature that supports the benefit of streamlined treatment regimens. Further, there is data to support patient acceptance and preference for STRs; adherence benefits are important given that HIV is a lifelong, incurable infection. The DTG/ABC/3TC FDC, which includes the novel INI DTG, is being developed as a treatment for those populations described above, and has distinct advantages over the many of the current widely-used therapies as follows:

- Convenience of a single tablet regimen, which may help improve overall treatment compliance and can be taken without regard to food
- Improved tolerability versus Atripla, with substantial reduction of treatment-limiting adverse drug reactions that translate to improved treatment outcomes through 96 weeks of therapy.
- Significant increase in efficacy with DTG-based combination therapy for ART-experienced (INI-naïve) patients over RAL.

- High barrier to resistance, with no INI or NRTI emergent resistance seen through 96 weeks in ART-naïve subjects on DTG regimens, and significantly lower emergent resistance in ART-experienced subjects when compared to RAL through 48 weeks.
- Convenient once-daily dosing (for ART-naïve and ART-experienced, INI naïve individuals), without the need for a pharmacokinetic booster, which may significantly decrease possible drug interactions with concomitant drugs. The potential for drug drug interactions are often a concern with NNRTI-based regimen and regimen that require boosting agents (including PIs and the cobicistat containing regimens).
- An STR treatment option for subjects for whom tenofovir is not considered appropriate, due to resistance, or safety concerns.

The results from the pivotal ING114467, with additional information provided by Phase III treatment-naïve (ING113086, ING114915, ING112276 [Phase IIb]) and ART-experienced, INI-naïve (ING111762) studies, provide evidence of effectiveness for DTG as a treatment for HIV-1 infection in combination with other antiretroviral agents. High rates of virologic suppression (HIV-1 RNA <50 c/mL) were observed in studies of ART-naïve and ART-experienced, INI-naïve subjects; and consistent responses were demonstrated in important subgroups as defined by Baseline HIV-1 RNA and CD4+cell count. In contrast to some historical studies, the use of ABC/3TC as NRTI backbone was equally effective in subjects with Baseline HIV-1 RNA >100,000 c/mL.

DTG+ABC/3TC achieved a statistically superior response through 96 weeks against Atripla (tenofovir/emtricitabine/efavirenz) in an *HLA-B*5701*-negative population, a result that was driven in large part by improved tolerability of the DTG-containing regimen. In ING114915, DTG+ 2 NRTIs was superior to DRV+RTV+2 NRTIs through 48 weeks. Finally, data from ING113086 demonstrated that DTG+ABC/3TC demonstrated comparable efficacy to RAL+ABC/3TC at Week 96.

In a study of ART-experienced, INI-naïve subjects, ING111762, virologic suppression (HIV-1 RNA <50 c/mL) in the DTG arm (71%) was statistically superior to the RAL arm (64%), based on the Week 48 pre-specified analysis (p=0.030). The difference in virologic response rate was driven by better overall virologic efficacy with DTG.

With regard to safety and tolerability, the DTG-containing regimen (DTG+ABC/3TC) in ING114467 was associated with significantly fewer withdrawals due to AEs in comparison with Atripla in an *HLA-B*5701*-negative population. In addition, subjects receiving DTG/ABC/3TC were significantly less likely to develop dizziness, abnormal dreams, rash, and somnolence (i.e., relative risk values and 95% confidence intervals were <1), with statistically significant differences also observed in pre-defined neuropsychiatric rates compared to DTG in a pre-specified, exploratory analysis conducted as part of ING114467. The safety profile for DTG was comparable to the well-tolerated RAL in both ART-naïve and ART-experienced (INI-naïve).

Another important benefit is the advantage of DTG as the INI in this STR. DTG has a different virologic profile versus other available INIs. Overall, the structural and electronic characteristics of DTG's metal-binding scaffold, along with its binding position within the integrase catalytic pocket, may contribute to the slower dissociation

kinetics observed *in vitro* for DTG compared with RAL and elvitegravir. The prolonged DTG binding to mutant integrase protein helps explain its distinct resistance profile; since prolonged binding is observed with mutant integrase protein, this may decrease the opportunity for resistance to develop, and would be consistent with a higher barrier to resistance. This may help explain the similar antiviral efficacy across the comparator studies, regardless of the NRTI backbone used and Baseline viral load.

Confirming these *in vitro* attributes, DTG-based regimens had a higher barrier to resistance in ART-experienced (INI-naïve patients), as demonstrated in ING111762 where significantly fewer virologic failures with INI resistance were observed when compared with RAL. Data from ING113086 and ING114467 were also supportive, as no subjects on the DTG regimens developed resistance to either the INI or the background NRTIs, whereas resistance to both the third agent and the background NRTIs was observed in both the RAL and EFV-based comparator arms.

DTG/ABC/3TC FDC offers once-daily dosing in patients without resistance to its components with no requirement for pharmacokinetic boosters. DTG/ABC/3TC FDC can also be dosed without regard to meals, as there is no significant food effect.

Across the DTG development program, no clinically significant effect of age, weight, gender, race, ethnicity, smoking, HCV co-infection, disease status (CDC classification of HIV infection), or polymorphism of drug-metabolizing enzymes on DTG concentration was observed, and no such effects have been previously identified for ABC or 3TC. Therefore, no dose adjustment for DTG/ABC/3TC FDC is required based on these patient characteristics.

6.2. Risks Associated with DTG/ABC/3TC FDC in the Treatment of HIV-1 Infection

There are no shared metabolic pathways between the components of DTG/ABC/3TC FDC, and no common target organs were identified in respective pre-clinical studies. As such, there is no pharmacologic data that would predict risk for the DTG/ABC/3TC FDC formulation beyond that identified for each component. Clinical data from the subjects treated with the DTG/ABC/3TC FDC components in larger Phase III studies further support this position, as the clinical safety data in the pivotal ING114467 study and in the subset of subjects exposed to the DTG+ABC/3TC regimen in ING113086 and ING114915 were consistent with the safety profile of the individual components..

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Considerations when using DTG/ABC/3TC FDC are as follows:

- The most common AEs seen in the DTG Phase II and III clinical program were diarrhea, nausea, and headache. These events occurred at similar rates across the treatment groups, were generally mild in intensity, and were typically not treatment limiting.
- In the pivotal ING114467 study, the only AE observed at significantly higher frequency with DTG+ABC/3TC versus EFV/TDF/FTC through Week 96 were

insomnia, pain in an extremity, and influenza (the latter two were reported at much lower rates). Insomnia was generally Grade 1 or 2 in ING114467 and did not lead to discontinuation in most cases. In all other studies, rates of insomnia were generally low and were comparable between DTG and RAL or DRV/RTV. Insomnia was not treatment-limiting in the clinical program.

- As well as extensive clinical trial data, the safety profile of ABC/3TC FDC is well defined and supported by 8.5 years of post-marketing experience for this product alone, and 14 to 17 years for the individual actives as ZIAGEN and EPIVIR, respectively.
- Hypersensitivity reactions are the most important risks associated with ABC use. The risk is well-characterized and can be managed clinically with appropriate patient counselling and close clinical follow-up. HSR, characterized by rash, constitutional findings, and in one case, organ dysfunction (including liver injury) have been observed in patients treated with DTG+ABC/3TC. The risk of ABC HSR has been managed proactively by clear and detailed labelling with guidance to healthcare professionals and patients, the provision of patient Alert Cards with all ABC-containing products, and an extensive educational program; all of which are still maintained by the Sponsor. These measures, which direct patients and physicians never to restart ABC-containing products after ABC-associated hypersensitivity reactions, have been highly effective. In recent years, the practice of pre-therapy screening for *HLA-B*5701* and excluding individuals from ABC therapy who carry the allele have further reduced the risk of HSR. This risk will be highlighted as a Warning and Precaution in the DTG/ABC/3TC FDC label and patient information, including a recommendation to immediately discontinue DTG/ABC/3TC FDC if HSR develops.
- Clinical data for DTG indicate the overall risk for IRIS with DTG-based therapy is not in excess of comparator agents. Few ART-experienced patients with hepatitis B virus and hepatitis C virus co-infection experienced IRIS with initiation of DTG-based therapy, which may reflect rapid HIV RNA decline and associated immune reconstitution. Few subjects with chronic HBV were treated with DTG+ABC/3TC in this clinical program, so a risk assessment specific to DTG/ABC/3TC cannot be made. The sponsor intends to describe the risk for immune reconstitution syndrome in general (and in particular for patients co-infected with HBV/HCV) and appropriate measures to manage this risk in the prescribing information and patient information.
- Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy when starting therapy with DTG/ABC/3TC FDC in hepatitis B co-infected patients. Clinical study and marketed use of 3TC have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC, which may have more severe consequences in patients with decompensated liver disease. If DTG/ABC/3TC FDC is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

- DTG/ABC/3TC FDC is not recommended in patients with moderate and severe hepatic impairment Further, ABC has not been evaluated in moderate or severe hepatic impairment. Mild and moderate hepatic impairment had no impact on DTG PK and DTG has not been evaluated in subjects with severe hepatic impairment. Mild, moderate or severe hepatic impairment had no impact on 3TC PK. The separate preparations of DTG, ABC, and 3TC will have to be used when this is judged necessary.
- DTG/ABC/3TC FDC will not be recommended in subjects with renal impairment (CrCL <50 mL/min), due to reduced 3TC clearance. 3TC dose adjustment according to renal function is recommended in the EPIVIR label [EPIVIR Prescribing Information, 2013]. Renal impairment has no impact on DTG or ABC PK. The separate preparations of DTG, ABC, and 3TC will have to be used when this is judged necessary.
- DTG inhibits OCT2 and thus may increase plasma concentrations of drugs that rely on OCT2 for clearance (e.g., dofetilide, pilsicainide and possibly metformin). Co-administration of DTG has the potential to increase metformin plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Metformin dose reductions may be possible for patients treated with dolutegravir and metformin.
- Overall the available data from observational cohorts and controlled clinical trials on the risk of myocardial infarction with ABC show some inconsistency and can neither confirm nor refute a causal relationship. There have been no adverse experience reports of myocardial infarction with ABC in the pivotal DTG studies mentioned above. To date, there is no established biological mechanism to explain a potential increase in cardiac ischemic risk with ABC. Nonetheless, increased risk of ischemic cardiac events with ABC exposure continues to be monitored by the Sponsor, and will be reflected in dosing guidance for DTG/ABC/3TC FDC.
- Other areas of potential risk associated with ABC and 3TC usage have been regularly monitored by ongoing pharmacovigilance activities, particularly those that are NRTI class-related, and include lactic acidosis, severe hepatomegaly with steatosis, and lipodystrophy. However, various studies have demonstrated that ABC+3TC has a low propensity to cause many of the long-term safety issues associated with other antiretrovirals both within the NRTI class and across classes. Since DTG does not share these class-related risks and there is no PK effect of DTG co-administration with ABC/3TC, no additional risk is anticipated with use of DTG/ABC/3TC FDC.
- Any DTG-specific ART drug:drug interactions [with NNRTI's, TPV+RTV, ETV (unless paired with a boosted PI)] will also apply to the DTG/ABC/3TC FDC formulation, and will be addressed with appropriate labelling. Further, it is anticipated that use this FDC will be as a single agent, as it is a complete three drug regimen. All drug:drug interactions for the three component drugs will apply to the FDC.

6.3. Overall Dosing Recommendations

The data collected in the clinical program suggests that in INI-naïve (ART-naïve or ART-experienced) adults patients, DTG/ABC/3TC FDC dosed once daily is safe and effective. The same once daily dose is recommended for INI-naïve adolescents 12 to 18 years of age and weighing at least 40 kg (applicable where ABC/3TC FDC is currently approved for use in adolescents).

6.4. Overall Conclusions

The safety and efficacy profile of the component drug DTG has been established from the DTG clinical program. The safety profile of ABC/3TC FDC is well defined and supported by years of post-marketing experience and extensive clinical trial data.

The results from the pivotal ING114467, with additional information provided by Phase III treatment-naïve (ING113086, ING114915, ING112276 [Phase IIb]) and ART-experienced, INI-naïve (ING111762) studies, provide evidence of effectiveness for DTG+ABC/3TC as a treatment for HIV-1 infection.

The studies showed that the safety/tolerability of the dosing regimen of DTG 50 mg plus ABC/ 3TC 600/300 mg was consistent with the established safety/tolerability profile of the three individual components.

As noted in the pivotal ING114467 study, the safety profile of DTG 50 mg+ABC/ 3TC 600 mg/ 300 mg was favorable when compared to the STR Atripla. This improved safety profile lead to fewer withdrawals from therapy, which led to significantly higher rates of virologic suppression through Week 96.

Other potential benefits of a DTG-based STR would include DTG's higher barrier to resistance versus other NNRTI or INI-based STRs. Across the program in ART-naïve subjects, no INI resistance mutations (or mutations to the NRTI backbone) were identified from patient isolates in three large comparator studies. In the ART-experienced study (ING111762), there were few subjects who developed any INI-associated mutations on DTG. Further, DTG's higher barrier to resistance has been observed to protect against the development of resistance to the other drugs in the ART regimen in both ART-naïve and ART-experienced patient populations.

Avoiding the development of resistance can lead to better long-term clinical outcomes. As a single table regimen, DTG/ABC/3TC FDC could offer maximal convenience, as well as help ensure adherence to all components of the multi-drug antiretroviral regimen. This could make DTG/ABC/3TC FDC a valuable option for ART-experienced subjects, in whom compliance may have been a prior issue, as this regimen could provide convenience in a regimen with a relatively high barrier to the development of further resistance.

Identified risks for the DTG/ABC/3TC FDC include hypersensitivity reactions, hepatitis, immune reconstitution syndrome (including in the setting of HBV/HCV co-infection), and a potentially serious drug interaction with dofetilide/pilsicainide. Appropriate

labeling and risk management activities, tailored to the geographic regions where DTG will be marketed, are described in this application, including education programs for the well characterized HSR with ABC. Mild to moderate gastrointestinal events and mild headache were the most commonly noted adverse reactions in subjects taking DTG + ABC/3TC in the clinical studies.

The DTG/ABC/3TC FDC compares well with other STRs in efficacy, tolerability, and drug interaction profile. There are a substantial number of patients who are in need of new STRs that offer the unique combination of efficacy and tolerability that encourage life-long adherence for this chronic infection. The DTG/ABC/3TC FDC has been developed to provide much needed improvements in the control of HIV disease.

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8. APPENDICES

Appendix Table 1 provides a listing of ViiV Healthcare or GlaxoSmithKline sponsored and significant collaborative clinical trials involving DTG, ABC and/or 3TC (as single agents or as the fixed dose combination of ABC/3TC, KIVEXA) which are not otherwise referenced in this dossier but have been previously reported to the EMA. Studies in which these agents have only been given as part of an undefined background therapy are not included. Studies in which these agents have been given only as part of the fixed dose combinations COMBIVIR™ and TRIZIVIR and not their components are also excluded except ACT5095 as it is cited in the ZIAGEN SPC. Population pharmacokinetic and epidemiological prevalence study reports are not included. Study reports are available to Regulatory Authorities on request.

Appendix Table 1 Table of Clinical Studies Not Referenced in Current DTG/ABC/3TC FDC Combination Submission

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
Biopharmaceutic Studies						
ARROW substudy	IV	ARROW (COL105677) pharmacokinetic substudy: relative bioavailability of scored tablets versus oral solution formulations of lamivudine (3TC), abacavir (ABC) and zidovudine (ZDV) in HIV infected African children	ABC (120-150 mg) + 3TC (60-75 mg)	19	PK day 1 (after at least 24 weeks), PK day 2 , (PK 1 + 4 weeks)	RM2010/00266/00
NUCB1004	IV	A study to investigate the comparative bioavailability of two oral formulations of GR109714X (lamivudine)	3TC 150 mg x2, 300 mg	24	Single doses	GCP/93/086
AZL10001	I	An evaluation of the bioequivalence of a combined formulated tablet (300/150/300 mg abacavir/lamivudine/zidovudine) compared to ZIAGEN (abacavir) 300 mg tablet EPIVIR (lamivudine) 150 mg tablet and RETROVIR (zidovudine) 300 mg tablet administered concurrently and the effect of food on absorption in subjects	ABC 300 mg, 3TC 150 mg	24	Single doses	RM1999/00252/01
NZTA1001	I	An evaluation of the bioequivalence of a combined formulated tablet compared to EPIVIR and RETROVIR administered concurrently and the effect of food on absorption	3TC 150 mg	24	Single doses	Synopsis, RM1997/00456/00
Pharmacokinetic Studies						
COL101665	I	A pharmacokinetic study of abacavir and its active intracellular anabolite, carbovir triphosphate, following administration of abacavir 600 mg once daily in HIV infected patients	ABC 600 mg once daily	15	Single dose	RM2004/00261/00
AZL10002	I	An evaluation of the steady-state pharmacokinetics of abacavir lamivudine and zidovudine following administration of a combined formulated tablet (300/150/300 mg abacavir/lamivudine/zidovudine) versus abacavir (300 mg tablet) and COMBIVIR (150/300 mg lamivudine/zidovudine) administered in subjects with HIV-1 infection	ABC 300 mg BID	12	7 days	PM1999/00009/00

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
CNAA1001	I	A phase I trial to evaluate the safety and pharmacokinetics of single oral doses of 1592U89 in HIV-infected children	ABC 4-8 mg/kg	22	Single dose	GM1997/00137/00
CNAA1013 (ACTG330)	I	A phase I safety and pharmacokinetic study of 1592U89 alone and in combination with other antiretroviral agents in infants and children with HIV infection	ABC 4-8 mg/kg BID	47	36 wks	RM1998/00100/00
PENTA15	I	Plasma pharmacokinetic study of once versus twice daily abacavir as part of combination antiretroviral therapy in children with HIV-1 infection aged 3 to <36 months	ABC 8 mg/kg with/without 3TC 4 mg/kg BID for ≥ 12 weeks; then ABC 16 mg/kg with/without 3TC 8 mg/kg once daily	18	4 weeks	GM2009/00161/00,
PENTA13	I	Plasma pharmacokinetics of once versus twice daily lamivudine and abacavir- simplification of combination treatment in HIV-1 infected children	3TC 4 mg/kg and/or ABC 8 mg/kg BID for ≥ 6 months, then 3TC 8 mg/kg and/or ABC 16 mg/kg once daily	19	24 weeks	Unnumbered report
COL105677	IV	Pharmacokinetic comparison of once vs twice daily administration of abacavir and lamivudine scored tablets in HIV-infected African children	3TC + ABC BID for 36 weeks, then 3TC + ABC once daily	36	40 weeks	RM2009/00368/00
NUCA1001	I	Pharmacokinetics of GR109714X (3TC) in asymptomatic HIV positive patients when administered orally with and without food	3TC 50 mg	13	Single doses	UCP/92/015
NUC10901	I	An open label study of the pharmacokinetics of lamivudine (GR109714X) in subjects receiving peritoneal dialysis in end-stage renal failure	3TC 10 mg/day	12	8 days	RM2001/00249/00

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
NUCB2018	II	A phase II pilot study to evaluate the safety and pharmacokinetics of lamivudine administered orally alone and in combination with zidovudine in HIV-infected pregnant women and their offspring	3TC: women 300 mg or 150 mg BID, neonates 4 mg/kg BID	20 women/20 neonates	3 weeks (week 38 of pregnancy to 1 week post birth)	GR1997/00012/00
COL10015	II/III	Safety, tolerability and pharmacokinetics of lamivudine plus zidovudine in HIV-1 infected pregnant women and their offspring: an open label uncontrolled study	3TC: women 3TC 150 mg BID, neonates 2 mg/kg BID	40 women/40 neonates	Women from week 20 of pregnancy , neonates 6 weeks	Executive Summary
ZDVB1003	I	A phase I study to evaluate the pharmacokinetics and safety of RETROVIR (zidovudine) administered orally in combination with 3TC (lamivudine) to HIV-1 infected pregnant women and their offspring	3TC: women 150 mg BID, neonates 2 mg/kg BID	17 women/16 neonates	Women from week 36 of pregnancy, neonates 1 week	RM1999/00018/00
CNAA2004	II	An open-label phase II trial to evaluate the steady-state pharmacokinetics, safety and efficacy of 1592U89 in combination with selected HIV-1 protease inhibitors in antiretroviral naive HIV-1 infected patients	ABC 300 mg BID	82	48 weeks	RM1998/00451/00
Human Pharmacodynamic Studies						
CNAA1004	I/II	A study to evaluate the single dose and steady state pharmacokinetics/ dynamics of 1592U89 and its active moiety, 1144U88 5.-triphosphate, following six different dosing regimen of 1592U89 in HIV-1 infected subjects	ABC 600 mg once daily, 300 mg BID, 600 mg BID, 100 mg TID, 200 mg TID, 300 mg TID	9	12 weeks	Synopsis only
COL100899	IV	Abacavir and tenofovir disoproxil fumarate co-administration results in a non-additive antiviral effect in HIV-1-infected patients	ABC 600mg once daily	21	53 weeks	Goicoechea M, Jain S, Bi L et al. AIDS 2010; 24: 707-716
Efficacy and Safety Studies: Controlled Clinical Studies						
ESS30009	III	Pharmacokinetic summary of plasma monitoring concentrations of abacavir, lamivudine and tenofovir from study ESS30009, a phase III, randomised, open-label, multicenter study of the safety and efficacy of efavirenz versus tenofovir when administered in combination with the	ABC/3TC FDC (fixed dose combination) once daily	16	16 weeks	RM2004/00030/00

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		abacavir/lamivudine fixed-dose combination tablet as a once-daily regimen in antiretroviral-naïve HIV-1 infected subjects				
ING116529	III	A phase III randomised, double-blind study to demonstrate the antiviral activity of dolutegravir (DTG) 50 mg twice daily vs 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 in HIV-1 Infected, integrase inhibitor therapy-experienced and resistant, adults: ING116529 day 8 primary analysis	DTG 50 mg BID	30	7 days	2012N151680_00
CNAB2002	II	A phase II randomised blinded dose-ranging multicentre study to evaluate the safety and efficacy of different regimens of abacavir monotherapy upon selected immunological and virological markers of HIV-1 infection in antiretroviral therapy naive patients.	ABC 100 mg, 300 mg, 600 mg all BID, then 300 mg BID	60	120 weeks	GM1999/00269/00
CNAB3002	III	A randomised double-blind parallel-group comparative parallel-group multicenter trial to evaluate the safety and efficacy of 1592U89 versus placebo in combination with background antiretroviral therapy in HIV-1 infected antiretroviral therapy experienced subjects with CD4+ cell counts ≤ 100 cells/mm^3 and plasma viral load between 400 copies/ml and 50,000 copies/ml	ABC 300 mg BID or placebo	185	48 weeks	GM1998/00223/00
CNAAB3003	III	A randomised double-blind parallel-group multicenter trial to evaluate the safety and efficacy of 1592U89 in combination with lamivudine (3TC) and zidovudine (ZDV) versus 3TC and ZDV in HIV infected antiretroviral therapy naive subjects with CD4+ cell counts > 100 cells/mm^3	ABC 300 mg BID or placebo	173	Last patient to 48 weeks	RM1997/00702/01
CNAAB3005	III	A phase III randomised double-blind multicenter study to evaluate the safety and efficacy of	ABC 300 mg BID or placebo	562	96 weeks	RM2000/00096/00

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		3TC/ZDV/1592U89 and 3TC/ZDV/IDV(indinavir) in HIV-1 infected antiretroviral therapy naive subjects				
CNAA3006	III	A double-blind randomised multicenter trial to evaluate the safety and efficacy of the combination of 1592U89/zidovudine/lamivudine versus the combination of zidovudine/lamivudine in HIV-1 therapy-experienced paediatric patients	ABC 8 mg/kg BID or placebo	205	48 weeks	RM1997/00749/01
CNAB3014	III	Randomised open multicentre study to evaluate the safety and efficacy and of 3TC/ZDV/ABC versus 3TV/ZDV/ IDV in HIV-1 infected antiretroviral naive subjects	ABC 300 mg BID	342	48 weeks	GM2001/00002/00
CNAB3015	III	A phase III, open Label, multicentre study to evaluate the safety and efficacy of the combination of 1592U89, 141W94 and nevirapine in HIV-1 infected NRTI and PI experienced subjects failing antiretroviral therapy	ABC 300 mg BID, ABC 600 mg BID	30	48 weeks	Synopsis only
CNA30017	III	A phase IIIb randomised open-label multicenter study to evaluate the safety and efficacy of 2 NRTI/1592U89 versus continued 2 NRTI/PI treatment in HIV-1 infected subjects with undetectable plasma HIV-1 RNA levels	ABC 300 mg BID	211	48 weeks	Clumeck N, Goebel F, Rosenbaum W et al. AIDS 2001; 15: 1517-1526
CNA30024	III	A phase III 1:1 randomised double-blind controlled multicenter trial comparing the efficacy and safety of abacavir versus zidovudine when combined with lamivudine and efavirenz for treatment of HIV-1 infection in antiretroviral therapy naive adults	ABC 300 mg BID + 3TC 150 mg BID	654	48 weeks	RM2002/00225/00
CNA30027	IIIb/IV	Key findings from the analysis of gene markers: a retrospective, case-control study to investigate genetic polymorphisms in HIV infected subjects who developed hypersensitivity following treatment with abacavir	N/A	229 (cases/ controls)	N/A	RM2001/00267/00
ABC107442	IV	A retrospective case-control study to estimate the sensitivity and specificity of a pharmacogenetic marker (HLA-B*5701) in	No treatment for therapeutic purpose	654	Not applicable	RM2006/00820/00

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		subjects with and without hypersensitivity to abacavir				
CNAF3007	III	An open label randomised study to investigate the safety and efficacy of COMBIVIR plus abacavir vs COMBIVIR plus VIRACEPT in HIV-1 infected antiretroviral therapy naive adults with a plasma HIV-1 RNA between 1000 and 500,000 copies/ml	ABC 300 mg BID	195	48 weeks	GWF/VHOO-05
CNAF3021	IV	Long term follow-up of 2 triple combinations COMBIVIR + ZIAGEN and COMBIVIR + VIRACEPT started in HIV-1 infected antiretroviral therapy naïve subjects within 2 years in study CNAF3007	ABC 300 mg BID	92	At least 1 year	Synopsis only
NZTA4002	IV	A comparison of a four-drug regimen comprised of 141W94, abacavir and COMBVIR with a three-drug regimen comprised of nelfinavir and COMBIVIR in antiretroviral-naive HIV-infected subjects	ABC 300 mg BID	302	64 weeks	Synopsis only
NZTA4006	IIIb	A phase IIIb, open-label, randomised study of the effect of an education intervention on virologic outcomes, adherence, immunologic outcome, and health outcomes in HIV-infected subjects from under-represented populations treated with triple nucleoside therapy (COMBIVIR, lamivudine 150 mg/zidovudine 300 mg, BID plus abacavir 300 mg BID), for 24 weeks	ABC 300 mg BID	209	24 weeks	Synopsis
NZTA4008	IV	A phase IV, 48-week, randomised, open-label, multicenter trial of abacavir (300 mg BID)/efavirenz (600 mg once daily)/didanosine (400 mg once daily) ± hydroxyurea (500 mg BID) in HIV-1 infected subjects failing initial therapy with 3TC/ZDV (or d4T) ± protease inhibitors	ABC 300 mg BID	54	24 weeks	Synopsis
APV30001	III	A phase III randomized, multicenter, parallel, open-label study to compare the efficacy safety and tolerability of GW433908 (1400 mg BID) and	ABC 300 mg BID + 3TC 150 mg BID	251	48 weeks	RM2002/00088/00

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		nelfinavir (1250 mg BID) in antiretroviral therapy-naive HIV-1 infected adults				
APV30002	III	A randomized open-label two arm trial to compare the safety and antiviral efficacy of GW433908/ritonavir once daily to nelfinavir BID when used in combination with abacavir and lamivudine BID for 48 weeks in antiretroviral therapy-naive HIV-1 infected subjects	ABC 300 mg BID + 3TC 150 mg BID	660	48 weeks	RM2002/00054/00
ESS40001	II	A phase II open-label randomised study to compare the efficacy and safety of EPIVIR, ZIAGEN, ZERIT (ABC/3TC/d4T) vs EPIVIR, ZIAGEN, SUSTIVA (ABC/3TC/EFV) vs EPIVIR, ZIAGEN,GW433908, NORVIR (ABC/3TC/908/RTV) for 96 weeks in the treatment of HIV-1 infected subjects who are antiretroviral therapy naive, 48 week interim analysis report	ABC 300 mg BID + 3TC 150 mg BID	291	48 weeks	RM2003/00004/00
ESS40003	IV	Randomised, multicenter, open-label trial to evaluate the reversibility of dyslipidemia upon substitution of abacavir for a protease inhibitor in virologically controlled HIV positive subjects with elevated cholesterol	ABC 300 mg BID	104	28 weeks	Keiser P, Sension M, DeJesus E et al. BMC Infectious Diseases 2005; 5:2
ESS40005	III	A phase IIIb randomised, multicenter, study of the efficacy and safety of COMBIVIR 1 tablet BID plus ZIAGEN 300 mg BID vs a TRIZIVIR tablet BID administered for 24 weeks in subjects with HIV-1 infection	ABC 300 mg BID	195	24 weeks	Fischl M, Burnside A, Farthing C et al. Pharmacotherapy 2003; 23: 1432-1440
ESS40010	IV	Trial to **a**ssess the regression of hyperlactatemia and to evaluate the regression of established lipodystrophy in HIV-1-positive subjects (TARHEEL)	ABC 300 mg BID, 3TC 150 mg BID	118	48 weeks	McComsey G, Ward D, Hessentaler S et al. Clin Inf Dis, 2004; 38: 363-370
ACTG368	II	A randomised phase II controlled trial of abacavir in combination with open label indinavir and efavirenz in HIV-infected subjects with nucleoside	ABC 300 mg BID	309	48 weeks	Unnumbered report

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		analogue experience: A rollover study for ACTG320				
ACTG372	II	A phase II study of prolongation of virologic success and options for virologic failure in HIV-infected subjects receiving indinavir in combination with nucleoside analogues: A rollover study for ACTG320	ABC 300 mg BID	94	48 weeks	Unnumbered report
CH-96-06	II	Simplified maintenance therapy in HIV infection: A prospective trial of the Swiss HIV cohort study	ABC 300 mg BID	172	48 weeks	Unnumbered report
COL30305	IV	A phase IV, randomised, open-label, multi-center, 24 week pilot study to evaluate the efficacy and safety of continued therapy with two nucleoside reverse transcriptase inhibitors plus one protease inhibitor versus switch to two NRTIs plus abacavir 300 mg BID in HIV-1 infected adults with HIV-1 RNA <50 copies/ml	ABC 300 mg BID	91	24 weeks	Synopsis
COL30345	III	Efficacy and safety of abacavir plus lamivudine vs didanosine plus stavudine when combined with a PI, an NNRTI or both in HIV-1 positive antiretroviral –naïve persons	ABC 300 mg BID, 3TC 150 mg BID	182	48 weeks	MacArthur R, Chen L, Peng G et al. HIV Clin Trials 2004; 5: 361-370
COL105677	IV	COMBIVIR, EPIVIR and ZIAGEN: Analysis of adverse event data from the ARROW study	3TC (4 mg/ml-150 mg BID), ABC (80mg total daily dose-300 mg BID) or ABC/3TC FDC once daily	1206	Determined by patient's physician	2013N158663_00
PENTA5	II	A randomised phase II trial to compare the toxicity, tolerability and activity of two drug combinations of the nucleoside analogue reverse transcriptase inhibitors lamivudine (3TC) and zidovudine (ZDV) and 1592U89 (abacavir, ABC) with or without the protease inhibitor, nelfinavir.	ABC 8 mg/kg BID, 3TC 4 mg/kg BID	128	48 weeks	GM2001/00069/00, PENTA AIDS 2007; 21: 947-955
NUCB2019	II	An open label randomised 2 arm pilot study of the safety and efficacy of the combination of zidovudine , 3TC and ritonavir in antiretroviral-	3TC 150 mg BID	33	24 weeks	Notermans D, Jurriaans S, De Wolf F et al. AIDS 1998; 12: 167-173

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		naive HIV-1 infected persons				
NUCA3001	III	A randomised double-blind multicenter trial to compare the safety and efficacy of 3TC monotherapy versus zidovudine (ZDV) monotherapy versus 3TC administered concurrently with ZDV in the treatment of HIV-1 infected patients who are ZDV naive (<4 weeks) with CD4 cell counts of 200-500/mm^3	3TC 300 mg BID	366	156 weeks then open label	UCR/95/002
NUCB3001	III	A randomised controlled trial to compare the safety and efficacy of lamivudine in combination with zidovudine (ZDV) vs zidovudine monotherapy in treating HIV infected patients who are zidovudine naive and have a CD4 count between 100-400 cells/mm^3	3TC 300 mg BID	129	24 weeks	GIO/94/003
NUCA3002	III	Randomised 3TC, ddC (dideoxycytidine) double-blinded (ZDV open-labelled) multi-centre trial to evaluate the safety and efficacy of 3TC (low dose) administered concurrently with zidovudine vs 3TC (high dose) administered concurrently with ZDV vs ddC administered concurrently with ZDV in the treatment of HIV-1-infected ZDV experienced patients with CD4 cell counts of 100-300 cells/mm^3	3TC 150 mg or 300 mg BID	254	156 weeks then open label	UCR/95/003
NUCB3002	III	A randomised controlled lamivudine (3TC) double-blinded trial to compare the safety and efficacy of zidovudine (ZDV) monotherapy vs lamivudine plus ZDV in combination in treating HIV-1-infected patients who are ZDV-experienced with a CD4 cell count between 100-400 cells/mm^3	3TC 150 mg or 300 mg BID	223	48 weeks	GIO/94/005
NUCB3007	III	A randomised controlled double-blinded trial to compare the efficacy and safety of 3TC versus 3TC + loviride versus placebo in the treatment of HIV-1 infected persons taking concurrent zidovudine –containing treatment regimens with CD4 counts between 25-25- cells/mm^3	3TC 150 mg BID	1895	52 weeks	GM1997/00088/00
NZTA4001	IV	A randomised, multicenter study of EPIVIR 150 mg	3TC 150 mg BID	223	Not specified	Synopsis

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		BID, RETROVIR 200 mg TID and a protease inhibitor versus 3TC 150 mg/ZDV 300 mg fixed-dose tablet given BID with a protease inhibitor in HIV-1 infected subjects				
PACTG300	III	A randomised comparative study of combined zidovudine-lamivudine vs the better of ddI (didanosine) monotherapy and zidovudine plus ddI in HIV-1 infected children	3TC 4 mg/kg BID	615	Median 9.3 months	RM1997/00632/00, McKinney R, Johnson GM, Stanley K. J Paediatrics 1998; 500: 500-508
PENTA4	II	A randomised double-blind placebo controlled trial to assess the safety and tolerability of adding lamivudine to current nucleoside analogue reverse transcriptase inhibitor therapy in children with HIV infection	3TC 4 mg/kg BID	162	48 weeks	Unnumbered reports, PENTA. AIDS 1998; 12: F151-F160
AVANTI 01	II	Randomised double-blind trial to evaluate the efficacy and safety of zidovudine plus lamivudine vs zidovudine plus lamivudine plus loviride in HIV infected antiretroviral naive patients	3TC 300 mg BID	106	52 weeks	Gartland M. Antiviral Therapy 1999; 4: 79-86 (manuscript submitted prior to publication)
AVANTI 02	II	Randomised, double-blind trial to evaluate the efficacy and safety of zidovudine plus lamivudine versus zidovudine plus lamivudine plus indinavir in HIV-infected antiretroviral-naive patients	3TC 150 mg BID	103	52 weeks	Gartland M, Gerstoft J and Goebel F.AIDS 2000; 14: 367-374
AVANTI 03	II	Randomised, double-blind trial to evaluate the efficacy and safety of zidovudine plus lamivudine versus zidovudine plus lamivudine plus nelfinavir in HIV-infected antiretroviral-naive patients	3TC 150 mg BID	102	52 weeks	Gartland M. Antiviral Therapy 2001; 6: 127-134 (manuscript submitted while in press)
ACTG320	II	A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 count of 200/mm^3 or less	3TC 150 mg BID	1156	Median 38 weeks	Hammer S, Squires K, Hughes M et al. NEJM 1997; 337:725-733

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
ESS30009	III	A phase III, randomised, open-label, multicenter study of the safety and efficacy of efavirenz versus tenofovir when administered in combination with the abacavir/lamivudine fixed-dose combination tablet as a once-daily regimen in antiretroviral-naïve HIV-1 infected subjects	ABC/3TC FDC once daily	282	48 weeks	RM2004/00586/00
ESS101822	III	A phase IIIb randomised, open-label, multicenter, parallel-arm study evaluating the short-term safety and tolerability of the ABC/3TC FDC tablet administered once daily versus the separate tablets of ABC (300 mg) and 3TC (150 mg) administered BID as part of a three or four drug regimen over a period of 12 weeks	ABC/3TC FDC once daily, ABC 300 mg BID, 3TC 150 mg BID	693	12 weeks + optional 12 weeks	RM2005/00435/00
APV109141	III	Study of once daily vs twice daily fosamprenavir plus ritonavir administered with abacavir/lamivudine once daily in antiretroviral naive HIV-1 infected adult subjects	ABC/3TC FDC once daily	214	48 week	Carosi G, Lazarrin A, Stellbrink H et al. ICAAC/IDSA 2008; Abstract: H-1244
COL100758	IV	A randomised trial of the efficacy, safety, and tolerability of two doses of GW433908/ritonavir with ABC/3TC fixed dose combination	ABC/3TC FDC once daily	115	96 weeks	Hicks C, DeJesus E, Sloan L et al. AIDS Research and Human Retroviruses 2009; 25: 395-403
COL103422	IV	A simplification trial switching from NRTIs to once daily fixed dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected patients with virologic suppression	ABC/3TC FDC once daily	333	96 weeks	Martinez E, Arranz J, Podzamczer D et al.: J AIDS 2009; 51: 290-297
COL110408	IIIb/IV	A multi-center, open-label, randomised, two-arm, 96 week pilot study comparing the tolerability and efficacy of fosamprenavir/ritonavir vs. EFV when administered once daily with KIVEXA for the treatment of HIV-1 infection in a ART(antiretroviral therapy)-naïve patient population that is underrepresented in US clinical research	ABC/3TC FDC once daily	101	96 weeks	Kumar P, DeJesus E, Huhn G et al. P7 10th ICDT-HIV, Glasgow, Scotland. Nov 7-11 2010

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
ACTG5095	III	A randomised, double-blind trial of three protease-inhibitor sparing regimens in therapy-naïve, HIV-infected patients conducted in the United States. The regimens studied included ZDV/3TC/ABC/EFV, ZDV/3TC/EFV and ZDV/3TC/ABC	ABC/3TC/ZDV FDC BID	1147	96 weeks	Unnumbered report (Executive Summary provided by ACTG)
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
CNAA2003	II	An exploratory study of the antiretroviral activity of abacavir when administered in combination with other specific nucleoside reverse transcriptase inhibitors (NRTIs) in NRTI experienced patients	ABC 300 mg BID	32	24 weeks + open label extension	RM1997/00701/00
CNAB2006	II	A phase II open-label observational study of changes in immune function and lymph node architecture during long term suppression of viraemia associated with early combination therapy with 1592U89 and 141W94 in antiretroviral naive HIV-1 infected subjects with a CD4+ cell count of >400 cells/mm^3	ABC 300 mg BID	47	72 weeks	GM1998/00289/00
CNAA2007	II	A phase II study evaluating the safety and antiviral activity of combination therapy with abacavir, amprenavir and efavirenz in HIV-1 infected subjects with detectable HIV-1 plasma RNA despite treatment with a protease inhibitor	ABC 300 mg BID	101	48 weeks	RM1998/00282/00
CNAB3004	III	An open-label phase III study to allow continued access to abacavir for HIV infected adults who have completed a clinical study from the GlaxoSmithKline international development programme for abacavir	ABC 300 mg BID	178	Determined by patient's physician	Synopsis only
CNAAB3007	III	1592U89 open label protocol for pediatric patients with HIV infection [paediatric expanded access program]	ABC 8 mg/kg BID	154	Determined by patient's physician	RM1999/00155/00
CNAAB3008	III	A 1592U89 open label protocol for adult patients with HIV-1 infection [adult - expanded access program]	ABC 300 mg BID	2113	Determined by patient's physician	RM1998/00225/01
CNAB3009	III	A phase III open-label study evaluating the efficacy	ABC 300 mg BID	53	48 weeks	GM1999/00267/00

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		and safety of abacavir (one 300 mg tablet BID) as an add on therapy in combination with zidovudine/lamivudine in patients who received zidovudine/lamivudine for at least 12 weeks in study NUCB3027				
CNA30018	III	Open-label trial to evaluate the efficacy, safety and tolerance of 1592U89 (abacavir) in paediatric infected patients with encephalopathy by HIV: virological and immunological markers in CSF	ABC 12 mg/kg BID	17	48 weeks	Synopsis only
CNA20010	II	ICC605 (A sub-protocol of ICC006): A phase II, 48-week, open-label study designed to evaluate the safety, tolerability, and efficacy of novel quadruple-combination therapy with PREVEON (adefovir dipivoxil; bis-POM PMEA), abacavir (1592U89), SUSTIVA (efavirenz; DMP 266), and amprenavir (141W94), with NORVIR (ritonavir), for the treatment of HIV-1 Infection in subjects who have failed previous protease inhibitor treatment	ABC 300 mg BID	25	48 weeks	RM2000/00442/00
CNA103964	IV	A study to evaluate the practical aspects of the use of the medication guide and warning card for abacavir-containing products	N/A	300	N/A	RTI-HS: 0301868
NZTA4005	IV	A triple nucleoside analogue regimen of COMBIVIR plus 1592U89 in antiretroviral-experienced HIV-infected patients	ABC 300 mg BID	87	48 weeks	RM1999/00364/00
NZTA4007	IIIb	A phase IIIB, open-label, pilot study to evaluate the efficacy, tolerability and health care resource use in HIV-infected incarcerated subjects treated twice daily for 24 weeks with COMBIVIR (lamivudine 150 mg/zidovudine 300 mg) plus ZIAGEN (abacavir) 300 mg	ABC 300 mg BID	108	24 weeks	Synopsis
CNAF3008	III	An open label pilot study to evaluate the efficacy and safety of a potent combination therapy (3TC+ZDV+abacavir +efavirenz) in antiretroviral naive adults with a plasma HIV-1 RNA <500 copies/ml	ABC 300 mg BID	31	48 weeks	GWF/VHOO-04

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
CNAF3010	III	Evaluation of efficacy and safety of a combination of COMBIVIR (AZT/3TC) and abacavir, in HIV-infected patients with an abacavir-susceptible phenotype and who had received ZERIT (d4T) as first-line treatment with some other antiretrovirals	ABC 300 mg BID	12	48 weeks	Synopsis only
CNAF3016	III	A pilot study to assess the efficacy and safety of a quadritherapy with COMBIVIR, abacavir, nelfinavir switching from week 16 to TRIZIVIR, nelfinavir for antiretroviral therapy in HIV-infected naive subjects with a viral load > 50 000 copies/ml	ABC 300 mg BID (for 16 weeks)	53	48 weeks	Synopsis only
ESS40009	IV	A phase IV, open-label study to assess the safety and tolerability of abacavir (ZIAGEN) in HIV-1 infected individuals and to investigate the effect of baseline genotype with virtual phenotype on the response to abacavir in therapy experienced subjects in the clinical setting	ABC 300mg BID	833	16 weeks	Synopsis only
EPZ111012	IV	The evaluation of attitudes and practice patterns when considering the use of HLA-B*5701 in clinical practice	N/A	874	N/A	RM2008/00345/00
COL30336	IV	A phase IV open-label multicenter 48 week study of the efficacy and safety of quadruple combination antiretroviral therapy with COMBIVIR BID, ZIAGEN 300 mg BID and SUSTIVA 600 mg once daily for 24 weeks followed by therapy with the triple nucleoside combination tablet (abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg) BID plus SUSTIVA 600 mg once daily for 24 weeks in HIV-infected adults	ABC 300 mg BID	38	48 weeks	Ruane P, Parenti D, Margolis D et al. HIV Clin Trials 2003; 4; 231-243
PROA2003	II	An open-label, single centre trial to evaluate the efficacy and safety of quadruple chemotherapy (zidovudine, lamivudine, 1592U89, and 141W94) in subjects infected with HIV-1 (GW QUAD)	ABC 300 mg BID, 3TC 150 mg BID	41	12 months, then at physician's discretion	GM1998/00073/00
COLA2012	II	A phase II, 192-week, uncontrolled, open-label study designed to evaluate the safety and efficacy	ABC 300 mg BID, 3TC 150 mg BID	42	192 weeks	Synopsis only

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		of novel and highly potent antiretroviral therapy (protease inhibitor and nucleoside reverse transcriptase inhibitor based) in subjects acutely infected with HIV-1				
COLA3003	II	A phase II, 48-week, uncontrolled, open-label study designed to evaluate cellular dynamics and immune restoration in peripheral blood and lymphoid tissue in antiretroviral-naïve, HIV-infected subjects receiving a triple-drug regimen comprised of amprenavir (600 mg BID), ritonavir (100 mg BID), abacavir (300 mg BID), and 3TC (150 mg BID)	ABC 300 mg BID, 3TC 150 mg BID	21	48 weeks	Synopsis only
NUCB3001C	III	An open label continuation to a randomised controlled trial to compare the safety and efficacy of lamivudine in combination with zidovudine vs zidovudine monotherapy in treating HIV infected patients who are zidovudine naive and have a CD4 between 100-400 cells/mm^3	3TC 300 mg BID	110	24 weeks	GIO/95/001
NUCA3003	III	Open Label Programme: An Interim Report on Serious Adverse Events Reported to [redacted]	3TC 300 mg BID	13	Determined by the patient's physician.	Synopsis
NUCA/B3004	III	Open label programme: Interim report on serious adverse events	3TC 150 mg or 300 mg BID	17,572	Determined by patient's physician	GIO/95/003
NUCB3004	III	3TC open label programme: interim analysis of safety data	3TC 300 mg BID (adults), 4 mg/kg BID (paediatrics)	1641	Determined by patient's physician	GIO/95/002
105816	IV	A post-marketing surveillance to monitor the safety of 3TC (lamivudine 150 mg) administered in Korean subjects according to the prescribing information	3TC 150 mg BID or 300 mg once daily	736	Determined by patient's physician	Synopsis only
COL102060	IV	An open-label multicenter study to evaluate the efficacy and safety of a fixed-dose combination of abacavir 600 mg/lamivudine 300 mg once-daily in combination with atazanavir 300 mg + ritonavir 100mg antiretroviral-naïve HIV-1 infected subjects	ABC/3TC FDC once daily	111	72 weeks	Elion R, DeJesus E, Sension M et al. HIV Clin Trials 2008; 9: 152-163

Protocol No.	Phase	Study Title	DTG, ABC &/or 3TC dose	No. of Study Subjects	Study Duration	Report No. or Publication Author
		over 48 weeks with continuing evaluation of abacavir/lamivudine plus atazanavir for maintenance over an additional 24 weeks				
COL111429	II	A multi-centre, open label, 96 week prospective pilot study of raltegravir 400 mg BID plus KIVEXA once daily in the treatment of ART-naïve HIV-infected subjects	ABC/3TC FDC once daily	35	96 weeks	Young B, Thanig T, DeJesus E et al. Clin Trials 2010; 11(5): 120-269
Reports of Analyses of Data from More Than One Study						
CNA30027 and CNA30032	IIIb/IV	Key findings from the analysis of genetic markers in two retrospective, case-control studies to investigate genetic polymorphisms in HIV infected subjects who developed hypersensitivity following treatment with abacavir	N/A	730 (cases/ controls)	N/A	RJ2004/00004/00
Other Clinical Study Reports						
ING114916	N/A	A GSK1349572 (dolutegravir, DTG) open label protocol for HIV infected, adult patients with integrase resistance	DTG 50 mg BID	0	Until DTG available commercially locally	2012N148028_00
ING115502	III	GSK1349572 (dolutegravir, DTG) for named patient/compassionate use in HIV: Physician's guidance document	DTG 50 mg BID	50	Not defined	2012N148022_00

3TC = lamivudine
ABC = abacavir
ART = antiretroviral therapy
BID = twice daily
d4T = stavudine
ddC = dideoxycytidine
ddI = didanosine
DTG = dolutegravir
EFV = efavirenz
FDC = fixed dose combination
HIV = human immunodeficiency virus
IDV = indinavir
NRTI = nucleoside reverse transcriptase inhibitor
NNRTI = non- nucleoside reverse transcriptase inhibitor
PI = protease inhibitor
PK = pharmacokinetics
RNA = ribonucleic acid
RTV = ritonavir
TID = three times daily
ZDV = zidovudine