Module 2.5

Clinical Overview

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ABBREVIATIONS

ABC	Abacavir sulfate
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV	Atazanavir
AUC(0-∞)	AUC from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	AUC from time zero (pre-dose) to last time of quantifiable concentration
BA	Bioavailability
BE	Bioequivalence
BMD	Bone Mineral Density
BMI	Body Mass Index
BSAP	Bone Specific Alkaline Phosphatase
CDC	Centers for Disease Control and Prevention
c/mL	Copies per milliliter
Cmax	Maximum observed concentration
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CAR	Current Antiretroviral Regimen
cART	Combination Antiretroviral Therapy
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COBI	Cobicistat
CTX	C-Terminal Telopeptides Type I Collagen
CVW	Confirmed Virologic Withdrawal
CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DEXA	Dual-Energy X-ray Absorptiometry
DILI	Drug Induced Liver Injury
DRV	Darunavir
DTG	Dolutegravir
DTG + RPV	Dolutegravir 50 mg Single Entity Tablet and Rilpivirine 25 mg Single Entity Tablet
DTG/RPV FDC	Dolutegravir 50 mg and Rilpivirine 25 mg Fixed Dose Combination Tablet
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eC-SSRS	electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz
EU	European Union
EVG	Elvitegravir
FDA	Food and Drug Administration

FDC	Fixed-dose combination
GCP	Good Clinical Practice
GDS	Global Data Sheet
GERD	Gastroesophageal Reflux Disease
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GLS	Geometric Least-Squares
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus type 1
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
INSTI	Integrase Strand Transfer Inhibitor
ISO	Integrated Safety Output
ITT	Intent-To-Treat
ITT-E	Intent-To-Treat Exposed
IVIVC	In Vitro – In Vivo Correlation
mg	milligram
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
P1NP	Procollagen Type 1 N-propeptide
PI	Protease Inhibitor
PK	Pharmacokinetic
PP	Per-protocol
pPVW	Possible Precautionary Virologic Withdrawal
PSRAE	Possible Suicide Related Adverse Events
PT	Preferred Term
PVW	Precautionary Virologic Withdrawal
RAL	Raltegravir
RNA	Ribonucleic acid
RPV	Rilpivirine
RSI	Reference Safety Information
RT	Reverse Transcriptase
RTV	Ritonavir
SAE	Serious Adverse Event
SE	Single Entity
SOC	System Organ Class
TDF	Tenofovir disoproxil fumarate
TQT	Thorough QT Study
ULN	Upper Limit of Normal
US	United States of America

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1. PRODUCT DEVELOPMENT RATIONALE

The efficacy and clinical safety and tolerability of the treatment regimen of DTG 50 mg / RPV 25 mg is being evaluated in 2 pivotal, identical, ongoing, randomized, parallel group, 148-week, Phase III studies (201636 [SWORD-1] and 201637 [SWORD-2]). Full CMC development and Bioequivalence data for DTG/RPV FDC have been completed.

Additional data to support the proposed marketing use (labeling) of DTG/RPV had been obtained in the SE development programs. These include areas of preclinical safety and virology, drug interaction studies, and safety in special populations. Based on the lack of drug interaction between the components, these prior studies were not repeated. They will be used as supporting information, and their use in the application has been described in this document.

1.1. Introduction

The use of NRTI-sparing regimens for the long-term treatment of HIV-1 infection has the potential to avoid known NRTI-associated adverse drug reactions and long-term toxicities. Treatment simplification has long been a goal to increase treatment adherence and improve the quality of life for patients with HIV. Currently there are no approved 2-drug regimens to maintain virologic suppression. Current therapies and unmet medical need are discussed further in Section 6.1.2.

DTG/RPV FDC is a 2-drug, NRTI-sparing regimen, differing from the current standard of care, which typically includes 2 NRTIs plus a third agent from the PI, NNRTI, or INSTI class. The proposed new 2-drug regimen of RPV and DTG targets HIV replication at the early and late stage of the virus life cycle, respectively, resulting in maintenance of viral suppression. Based on the established tolerability and combined resistance profiles of DTG and RPV, this simplified 2-drug regimen offers favorable tolerability and suppression of resistance similar to other DTG-based and RPV-based HIV-1 treatment regimens.

DTG is an HIV-1 INSTI with low to moderate intersubject PK variability, a predictable exposure-response relationship, and a 14 hour plasma half-life that supports once-daily dosing without the need for a PK booster. In addition, DTG lacks many of the associated drug interactions, specifically with oral contraceptives, statins, antidepressants, anxiolytics, anticoagulants, and other medications commonly taken by HIV-positive patients.

RPV is an NNRTI, with in vitro activity against wild type virus and a broad range of NNRTI-resistant viruses. RPV combines the convenience of once daily dosing with potent antiviral activity. RPV has been extensively studied through Phase III and a dosing regimen of 25 mg once daily was generally safe and well tolerated.

1.2. Summary of Clinical Development Program

ViiV Healthcare Company (ViiV Healthcare) in partnership with Janssen Research and Development LLC (Janssen) are developing the FDC containing DTG and RPV. ViiV Healthcare is the Sponsor of the development program; various aspects of the program are being conducted by GSK on behalf of ViiV Healthcare.

The goal of the clinical development program (Table 1) was to develop a DTG/RPV FDC tablet consisting of an NRTI-sparing, 2-drug regimen that is efficacious and offers a favorable safety and tolerability profile. The clinical Phase III studies were conducted with the single entities, DTG 50 mg + RPV 25 mg. The FDC tablet was developed in parallel and BE was established between SE and FDC. The proposed commercial product with this application is the FDC tablet.

Table 1 Summary of Clinical Studies

Study	Study Design	Population	Treatment details	Key conclusions
201636 (SWORD-1) GSK Document Number: 2016N287382_01 Status: Ongoing; 48 week CSR completed	Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1 infected ART-experienced subjects	DTG 50 mg + RPV 25 mg once daily with a meal CAR: 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	The primary analysis demonstrated that DTG + RPV is non-inferior to CAR, with 95% of subjects in the DTG + RPV group and 96% of subjects in the CAR group achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm [adjusted treatment difference and 95% CI; -0.6%, -4.3% to 3.0%] for the ITT E Population.
201637 (SWORD-2) GSK Document Number: 2016N287539_01 Status: Ongoing; 48 week CSR completed	Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1 infected ART-experienced subjects	DTG 50 mg + RPV 25 mg once daily with a meal CAR: 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	The primary analysis demonstrated that DTG + RPV is non-inferior to CAR, with 94% of subjects in both treatment groups achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA at Week 48 based on the (Snapshot) algorithm [adjusted treatment difference and 95% CI; 0.2%, -3.9% to 4.2%] for the ITT-E Population.
202094 (DEXA Sub-study) GSK Document Number: 2016N287399_00 Status: Ongoing; 48 week CSR completed	Open-label, parallel-group study	HIV-1 infected ART-experienced subjects	DTG 50 mg + RPV 25 mg once daily with a meal TFV-containing ART regimen CAR: 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	Switching to a once daily 2-drug regimen of DTG + RPV demonstrated significant improvement in BMD for virologically suppressed HIV-1-infected adults when compared with continuing treatment with a TDF containing ART regimen.
201676 (Pivotal BE) GSK Document Number: 2016N304981_00 Status: Complete	Randomized, open-label, 2-period, single-dose, crossover study	Healthy adult subjects	Reference Treatment = DTG 50 mg + RPV 25 mg once daily with a moderate fat meal Test Treatment = DTG/RPV FDC 50 mg/25 mg (Product Code AW) with a moderate fat meal	DTG/RPV FDC is bioequivalent to combined administration of the SEs. The 90% CI of the GLS mean PK parameter ratios was within 80 to 125% for all primary PK parameter endpoints (AUC(0-t), AUC(0-∞), and Cmax) for both DTG and RPV.

Study	Study Design	Population	Treatment details	Key conclusions
201674 (Relative bioavailability and food effect) GSK Document Number: 2015N257835_00 Status: Complete	2-part, single dose, open-label, randomized, crossover, relative oral bioavailability study in the fed and fasted states	Healthy adult subjects	Reference Treatment = DTG 50 mg + RPV 25 mg single dose 5 Test Formulations = DTG/RPV FDC 50 mg/25 mg (Product Codes AS, AM, AQ, AK, and AU) single dose	Part 1: The AUC(0-∞) and Cmax of DTG following administration of various FDC tablets in presence of high fat diet were comparable to those following the reference DTG single agent co-administered with RPV. The AUC(0-∞) and Cmax of RPV following administration of various FDC tablets in presence of high fat diet were comparable to or ranged from 8% lower to 10% higher (depending on the FDC tablet) than those of the reference RPV single agent co-administered with DTG. Part 2: Systemic exposure of DTG following all DTG/RPV FDC formulations was lower than exposure following co-administration of the SE tablets under fasted conditions. Systemic exposure of RPV following all DTG/RPV FDC formulations was comparable to or higher than exposure following co-administration of the SE tablets under fasted conditions. Food Effect: All test DTG/RPV FDC formulations showed increases in DTG and RPV systemic exposures with a moderate fat meal (Part 2). This finding is consistent with previous food effect studies of the SEs. Cross-cohort comparisons between fed (High Fat Part 1) and fasted (Part 2) showed that a high-fat meal increased DTG and RPV systemic exposure following administration of 3 FDC formulations (AK, AM and AS/AU) and as co-administration as the SE tablets.
LAI116181 (DTG + RPV DDI) GSK Document Number: 2011N130484_00 Status: Complete	Cohort 1: Open-label, repeat-dose, single-sequence, 3-period study	Healthy adult subjects	Treatment A = DTG 50 mg with a moderate fat meal every 24 hours for 5 days Treatment B = RPV 25 mg with a moderate fat meal every 24 hours for 11 days Treatment C = DTG 50 mg + RPV 25 mg with a moderate fat meal every 24 hours for 5 days	Co-administration of DTG with RPV resulted in no change in DTG AUC(0-τ) and Cmax, and a 22% increase in Cτ. Co-administration of DTG with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and a 21% increase in Cτ. There was no significant drug interaction between DTG and RPV. DTV and RPV can be co-administered without dose adjustment.

1.2.1. Pivotal Efficacy and Safety Studies 201636 (SWORD-1) and 201637 (SWORD-2)

Studies 201636 (SWORD-1, Table 1) and 201637 (SWORD-2, Table 1) were conducted to provide evidence to support the efficacy, safety, and tolerability of the new 2-drug regimen combining DTG and RPV for the treatment of HIV-1 infection in ARV-experienced adult patients, with viral load suppressed to <50 c/mL, and who are switching from their CAR. These studies establish that HIV-1 infected adult subjects with current virologic suppression on a regimen with 2 NRTIs + a third agent remain suppressed upon switching to a 2-drug regimen with DTG + RPV and provide important information regarding efficacy, safety, tolerability and patient satisfaction.

1.2.1.1. DEXA Sub-Study 202094

Study 202094 (DEXA sub-study, Table 1) is an open-label, parallel group study, designed to evaluate the bone mineral density in HIV-1-infected adult subjects switching from a TDF-containing antiretroviral therapy regimen to a dolutegravir plus rilpivirine regimen. The primary endpoint evaluated the percentage change from Baseline at Week 48 in total hip (including the femoral neck, trochanter and inter-trochanter areas) BMD as assessed by areal density in g/cm^2. Study 202094 recruited eligible subjects from the Early Switch Phase DTG + RPV treatment group and from the Late Switch Phase who continued their TDF-based CAR through to Week 52 across Studies 201636 and 201637.

1.2.2. Bioequivalence Study 201676

Study 201676 (Table 1) was conducted to evaluate the pivotal bioequivalence of an oral DTG 50 mg/RPV 25 mg FDC tablet formulation proposed for commercial use compared with co-administration of the separate tablet formulations of DTG 50 mg (clinical trial material image) and RPV 25 mg (commercial), with each treatment administered in the fed state. The formulation selected for use in Study 201676, was based on in vitro testing, stability, and manufacturability considerations, and supported by the relative bioavailability study results from Study 201674.

1.2.3. Relative Bioavailability and Food Effect Study 201674

Study 201674 (Table 1) was a relative bioavailable study and food effect study that evaluated the PK of 5 prototype DTG/RPV FDC tablets compared with co-administration of the SE tablets in fasted and fed conditions. This study also served as a guide for pharmaceutical development and provided information on the study design and sample size required for pivotal bioequivalence Study 201676.

1.2.4. DTG and RPV DDI Study LAI116181

Study LAI116181 (Table 1) was a DDI study that demonstrated that there are no significant drug interactions between DTG and RPV, the 2 components of the FDC tablet.

1.2.5. DTG and RPV Single Entity Studies

Where no studies have been performed with DTG and RPV, additional previously submitted studies from DTG or RPV SE development programs support this application and are categorized as "key" studies or "supportive" studies:

- **Key SE Studies**: these studies provide data that may be included in labeling, and were conducted during the individual agent development programs. Key clinical studies are described in the module 2.7 summaries and CSRs for these studies have been previously submitted.
- **Supportive SE Studies**: these studies are not essential for the FDC Benefit Risk assessment, but are considered helpful to the reviewer and supportive on the proposed indication. Supportive studies are briefly tabulated in the module 2.7 summaries, but reports will be made available upon request for the convenience of the reviewer.

All single agent data that are considered not to be relevant to this DTG/RPV FDC application, e.g. efficacy data not related to the indication, will not be provided in this FDC submission.

1.3. Regulatory History

The DTG/RPV FDC development program has been formally discussed with key regulatory agencies at various milestones throughout development (see m1 and m2.2).

Both DTG and RPV are commercially available products in many markets worldwide. TIVICAY™ (DTG) Tablets, 50 mg are available in over 85 countries, including the US, EU, and Canada. DTG was developed by GSK on behalf of ViiV Healthcare. EDURANT (RPV) Tablets, 25 mg have been approved for the treatment of HIV-1 infection in ARV treatment-naïve adult patients in over 85 countries including the US, EU, and Canada. In most countries, the indication is further restricted to patients with plasma viral load ≤100,000 c/mL. RPV was developed by Janssen Sciences Ireland UC.

1.4. Claimed Indication and Dosage

DTG 50 mg/RPV 25 mg FDC is indicated for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) without known or suspected resistance to either antiretroviral component. The recommended oral dose for adults is 1 tablet administered once a day with a meal.

1.5. Compliance with GCP

All studies were undertaken in accordance with standard operating procedures of ViiV Healthcare and the GlaxoSmithKline Group of Companies, which comply with the principles of GCP. 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

DTG/RPV FDC met the criteria for bioequivalence with the reference SE tablet formulations of DTG 50 mg plus RPV 25 mg (Study 201676, Table 1). Since DTG/RPV FDC is bioequivalent to co-administration of the SEs, the efficacy and safety demonstrated in clinical trials using DTG + RPV represents the efficacy that would have been achieved with DTG/RPV FDC.

Co-administration of the DTG/RPV FDC with moderate- and high-fat meals increased exposures of DTG and RPV (Study 201674, Table 1). DTG/RPV FDC should be taken with a meal, as is recommended for RPV, and was done in the Phase III studies.

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

2.1. DTG/RPV FDC Formulation Development

DTG/RPV FDC Tablets 50 mg/25 mg are pink, oval, biconvex, [redacted], immediate release tablets for oral administration, debossed with 'SV J3T' on one side and plain on the other side. They contain 52.62 mg dolutegravir sodium (equivalent to 50 mg dolutegravir) and 27.5 mg rilpivirine hydrochloride (equivalent to 25 mg rilpivirine). The primary pack size will be a 30 count bottle.

[redacted]

There is a slight difference in the tablet shape between the DTG/RPV FDC tablet used in BE Study 201676 and the proposed commercial tablet, as described in m2.7.1 Section 1.3.3. This slight change in tablet shape is not expected to impact in vivo performance of the tablet. Dissolution data demonstrate that the change in tablet shape does not impact the dissolution profiles for DTG or RPV.

The formulation used in relative BA and food effect Study 201674 (AM) is slightly different from the formulation (AW) used in the pivotal BE study (201676) with respect to color, debossing, and site of manufacture for the RPV granules (m2.7.1 Section 1.3.1). These differences are not expected to alter the biopharmaceutic characteristics of the tablet in terms of systemic exposure. Therefore, food effect results of Study 201674 apply to the proposed commercial image tablet.

2.2. Analytical Methods

The bioanalytical methods used to measure concentrations of DTG in human plasma, in the presence of RPV, and RPV in the presence of DTG were sensitive, accurate and reproducible (m2.7.1 Section 1.4 and m2.7.1 Section 1.5).

2.3. Biopharmaceutics Studies

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

- Bioequivalence was confirmed in terms of both DTG and RPV for DTG/RPV FDC compared with separate tablet formulations of DTG and RPV when administered after a moderate fat meal (see m2.7.1 Section 2.1.1.1).
- DTG/RPV FDC should be taken with a meal, as recommended for RPV. Taking DTG/RPV FDC with a moderate- or high-fat meal increases exposures of DTG and RPV (see m2.7.1 Section 3.2).

In summary, results of the bioequivalence and food effect studies support use and posology of the DTG/RPV FDC in the proposed indication (Section 1.4).

3. OVERVIEW OF CLINICAL PHARMACOLOGY

The key characteristics of clinical pharmacology related to the DTG/RPV FDC product are based upon information obtained from the SE development programs for DTG and RPV, food effect and bioequivalence studies of the DTG/RPV FDC (201674 and 201676), and 2 Phase III studies (201636 and 201637) in HIV-1 infected subjects who had trough plasma concentration samples collected during co-administration of DTG with RPV (Table 1 and m2.7.2 Section 1.2).

A comprehensive set of clinical pharmacology studies was completed to support the initial marketing application and post-marketing commitments of the individual DTG or RPV component as TIVICAY or EDURANT, respectively (m2.7.2 Section 2). The steady-state RPV and DTG trough concentrations observed over Weeks 4 to 48 in the Phase III studies were comparable to those observed in SE studies in HIV-infected subjects (m2.7.2 Section 1.2) and there is no clinically relevant drug-drug interaction between DTG and RPV (LAI116181, Table 1). Since DTG/RPV FDC is bioequivalent to co-administration of the SEs, conclusions from prior drug-drug interaction, ADME, TQT, and special population studies can be applied to DTG/RPV FDC. The PK (ADME), drug-drug interaction and special population labelling for the SEs will be applied to establish the clinical pharmacology labelling for the DTG/RPV FDC tablet. These studies are described in m2.7.2 (Summary of Clinical Pharmacology).

In summary, results of SE drug-drug interaction, ADME, and special population studies and results of DTG/RPV FDC bioequivalence and food effect studies support use of the proposed FDC (m2.7.2 Section 5).

4. OVERVIEW OF EFFICACY

Pivotal studies 201636 and 201637 and the pooled data from the two each demonstrate that DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference for the ITT-E Population is greater than the pre-specified non-inferiority margin (Section 4.6.1). DTG + RPV is also non-inferior to CAR based on virologic failure since the upper bound of the 95% CI for the adjusted treatment difference is less than the non-inferiority margin of 4% for both studies and the pooled data (Section 4.6.2.2).

For a full presentation of efficacy results, see the Summary of Clinical Efficacy (m2.7.3).

4.1. Rationale for Dose Selection

The doses selected for DTG and RPV are equivalent to the doses used in the commercially available SE tablets (TIVICAY 50 mg and EDURANT 25 mg, respectively). The efficacy, PK, and safety of DTG and RPV as individual agents have been evaluated in 2 extensive clinical development programs of Phase I to III clinical trials. Additionally, clinical data showed the absence of a drug-drug interaction between DTG and RPV (Study LAI116181, Table 1). The study showed that co-administration of RPV with DTG had no clinically meaningful effect on DTG or RPV pharmacokinetics [Ford, 2013]. Hence, there is no need for a dose adjustment from approved doses when both products are used in combination.

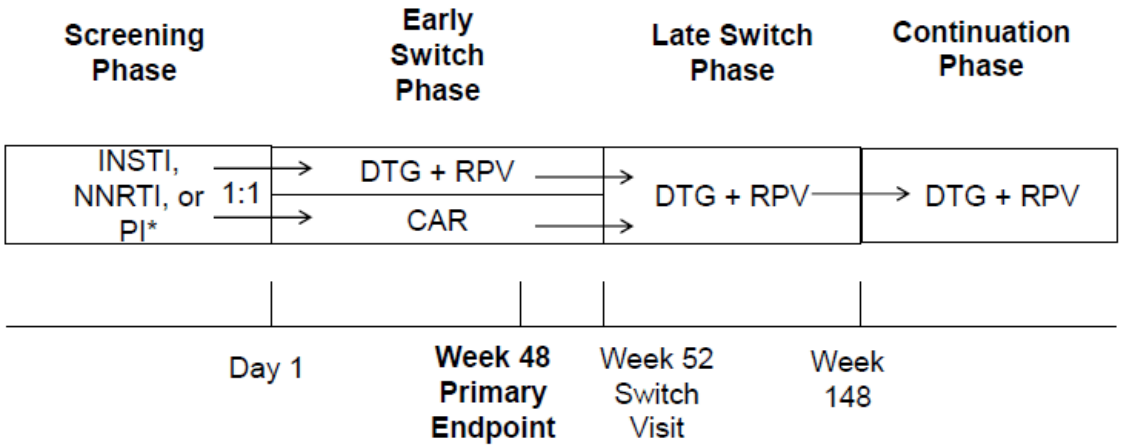
4.2. Clinical Trial Methodology and Design

The 2 ongoing pivotal efficacy studies, 201636 (SWORD-1) and 201637 (SWORD-2), are identical 148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority studies. They are being conducted in 508 (201636) and 516 (201637) adult HIV-1 infected patients who were on stable suppressive cART containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI. Eligible subjects were randomized 1:1 to continue their CAR or be switched to a 2-drug regimen DTG + RPV administered once daily. At Week 52, individuals who were originally assigned to continue their CAR and remained virologically suppressed switched to DTG + RPV and will be followed to Week 148 (Figure 1).

The primary analysis took place after the last subject completed the Week 48 visit. Additional analyses will be conducted after the last subject completes the Week 100 visit, the Week 148 visit, and after the last subject withdraws from the study or transitions to commercial supplies (i.e., completes the Continuation Phase).

The studies included a Screening Phase (up to 28 days), an Early Switch Phase (Day 1 up to Week 52), a Late Switch Phase (Week 52 to Week 148), and a Continuation Phase. No non-protocol defined dose reductions, modifications in dosage, or changes in the frequency of dosing were allowed at any time in these studies.

Figure 1 Study Schematic for 201636 (SWORD-1) and 201637 (SWORD-2)



*Plus 2 NRTIs
CAR = current antiretroviral regimen
N=508 (201636) and 516 (201637) randomized 1:1 to each treatment group and stratified by baseline 3rd Agent class, age group (< or ≥50 years old) and planned participation in Study 202094 (DEXA sub-study).

Must be on uninterrupted current regimen (either the initial or second CAR) for at least 6 months prior to Screening.
Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: 1 within the 6 to 12 month window, and 1 within 6 months prior to Screening.
No history of virologic failure.

No evidence of viral resistance based on the presence of any resistance-associated major PI, INSTI, NRTI, or NNRTI mutation and integrase resistance associated substitution R263K from prior resistance genotype assay results.
No current or prior history of etravirine use.

4.3. Selection of Patient Population(s)

Studies 201636 and 201637 enrolled a population of subjects who were stable and virologically suppressed, on their first or second regimen with no evidence of virologic non-response or failure.

Efficacy analyses were conducted based on the ITT-E population, which consisted of all randomly assigned subjects who received at least 1 dose of study drug.

Sensitivity analyses of the primary efficacy endpoint were conducted based on the ITT population and the PP population, defined as subjects in the ITT-E population with the exception of subjects with important protocol violations which could affect the assessment of antiviral activity, e.g., deviations from inclusion/exclusion criteria, taking of prohibited medications, treatment modifications/errors or where study drug compliance was known to be less than 90%.

4.4. Efficacy Endpoints and Statistical Considerations of Efficacy Analyses

4.4.1. Primary, Secondary, and Exploratory Efficacy Endpoint

The primary efficacy endpoint for Studies 201636 and 201637 was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population (m2.7.3 Section 1.6). Secondary and exploratory endpoints are provided in (m2.7.3 Section 1.6).

4.4.2. Statistical Considerations

For each study (201636 and 201637), non-inferiority could be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the 2 treatment groups was greater than -10%. If rg is the response rate on DTG + RPV and rr is the response rate on comparator group then the hypotheses can be written as follows:

$$H0: rg - rr \leq -10\% \qquad H1: rg - rr > -10\%$$

Assuming a true 87% response rate in each group, a non-inferiority margin of -10%, and a 2.5% one-sided significance level, each study (201636 and 201637) required 238 subjects per treatment group. This would provide 90% power to show non-inferiority for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48. If an 87% response rate was observed for the CAR group, then non-inferiority would be declared if the observed treatment difference was better than -3.5 percentage points.

Under the same assumptions, the pooled data from Studies 201636 and 201637 would provide >90% power to show non-inferiority for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using a non-inferiority margin of -8%.

Study recruitment was extended beyond the 476 subjects per study to allow for further recruitment into the DEXA sub-study, particularly in underrepresented populations.

4.5. Subject Disposition and Baseline Characteristics

For both studies combined, a total of 513 subjects were randomized and treated with DTG + RPV and 511 subjects were randomized and treated with CAR. Similar proportions of subjects in each treatment group withdrew from the study (DTG + RPV: 6%; CAR: 7%; m2.7.3 Section 3.1.1). The most common reasons for withdrawal were withdrew consent (DTG + RPV: 1%; CAR: 3%) and AE (DTG + RPV 3%; CAR <1%). Less than 1% of subjects from both groups were withdrawn from the study due to investigator's assessment of lack of efficacy.

Demographic characteristics were well balanced across treatment groups (m2.7.3 Section 3.1.2.1). Of note, >20% of subjects were women for both studies pooled (DTG + RPV 23%; CAR 21%) and 29% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. Baseline characteristics

were also well balanced across the treatment groups and randomization was stratified by age and Baseline third agent.

4.6. Efficacy Results

Refer to m2.7.3 Section 3 for a full presentation of the efficacy results.

4.6.1. Primary Efficacy Results

The primary endpoint for these studies was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population.

In the pooled analysis, the same proportion of subjects in the DTG + RPV and CAR groups (95% of subjects; 95% CI: 93%, 97%) achieved the primary efficacy response (Table 2, m2.7.3 Section 3.2.1) and thus response to treatment has been maintained with viral suppression greater than 90% at Week 48. The analysis demonstrated that DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.0%) is greater than -8% for the combined studies.

The primary efficacy endpoint was also achieved within each of the individual studies with the lower bound of the 95% CI for the adjusted treatment difference greater than -10% (Table 2).

Table 2 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (ITT-E Population)

Treatment	N	Number Responded/ Total Assessed	Difference in Proportion, % (95% CI)[a]	Adjusted Difference in Proportion, % (95% CI)[b]
201636				
DTG + RPV	252	240 / 252 (95%)	-0.5 (-4.1, 3.2)	-0.6 (-4.3, 3.0)
CAR	256	245 / 256 (96%)		
201637				
DTG + RPV	261	246 / 261 (94%)	0.1 (-3.9, 4.2)	0.2 (-3.9, 4.2)
CAR	255	240 / 255 (94%)		
Pooled Data				
DTG + RPV	513	486 / 513 (95%)	-0.2 (-2.9, 2.5)	-0.2 (-3.0, 2.5)
CAR	511	485 / 511 (95%)		

Data Source: 201636/201637 Table 2.011, Table 2.012, and Table 2.013

a. Difference: Proportion on (DTG + RPV) – Proportion on CAR.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: age (< vs. ≥50 years old) and Baseline third agent (PI, NNRTI, INSTI).

4.6.2. Secondary and Exploratory Efficacy Results

4.6.2.1. Study Outcomes at Week 48: Plasma HIV-1 RNA <50 c/mL (Snapshot Analysis)

Virologic response rates were the same between the DTG + RPV and CAR treatment groups (95%) (m2.7.3 Section 3.2.2.1).

For subjects in the Snapshot category of 'No virologic data', as would be expected in open-label switch studies, there were fewer discontinuations due to AEs or death in the CAR group (3 subjects) where subjects have already taken at least 6 months of stable treatment, compared with the DTG + RPV group (17 subjects) (m2.7.3 Section 3.2.2.1). In contrast there were fewer disconnections due for 'Other' reasons in the DTG + RPV group (7 subjects) compared with the CAR group (16 subjects).

4.6.2.2. Proportion of Subjects Classified as Snapshot Virological Failures at Week 48

The proportion of subjects who were classified as Snapshot virological failures at Week 48 is summarized in Table 3. These results indicate that the combined use of DTG + RPV is non-inferior to CAR based on Snapshot virologic failure within a non-inferiority margin of 4%. The upper bound of the 95% CI for the adjusted treatment difference (0.6%) is less than 4%.

Table 3 Analysis of Proportion of Subjects Classified as Virological Failures[a] at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (ITT-E Population)

Treatment	N	Number of Failures/ Total Assessed	Difference in Proportion % (95% CI)[b]	Adjusted Difference in Proportion % (95% CI)[c]
201636				
DTG + RPV	252	2 / 252 (<1%)	0.0 (-1.5, 1.5)	0.1 (-1.5, 1.6)
CAR	256	2 / 256 (<1%)		
201637				
DTG + RPV	261	1 / 261 (<1%)	-1.2 (-2.9, 0.5)	-1.1 (-2.8, 0.6)
CAR	255	4 / 255 (2%)		
Pooled Data				
DTG + RPV	513	3 / 513 (<1%)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
CAR	511	6 / 511 (1%)		

Data Source: 201636/201637 Table 2.181, Table 2.182, and Table 2.183

a. Virologic failures include subjects who had plasma HIV-1 RNA ≥50 c/mL at Week 48, who discontinued due to lack of efficacy, who discontinued for other reasons while not <50 c/mL, and who changed ART.
b. Difference: Proportion on DTG + RPV - Proportion on CAR
c. Based on Cochran-Mantel Haenszel stratified analysis adjusting for age (<50, ≥50 years old) and Baseline third agent class (PI, NNRTI, INSTI).

Note: Week 48 window is up to the end of on-treatment Early Switch Phase.

4.6.2.3. Incidence of HIV-1 Disease Progression (HIV-associated Conditions, AIDS, and Death)

A total of 3 subjects in the DTG + RPV group experienced HIV-1 disease progression to CDC Class C clinical conditions or death during the Early Switch Phase (m2.7.3 Section 3.2.2.7). Of these, 2 subjects progressed to Class C, and the other subject died (Section 5.3.2). HIV-1 associated conditions are discussed in m2.7.3 Section 3.2.2.7.

4.6.2.4. Subgroup Analysis (Including by Third Agent Class): Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis)

To assess the generalizability of the primary analysis results, consistency of the treatment difference was explored within subgroups. One-way homogeneity across the levels of each variable used to stratify randomization (age group [< or ≥50 years old] and Baseline third agent class) was tested. One-way homogeneity across the levels of gender and two categorizations of Race (White vs. non-White, African American/African Heritage vs. non-African American/African Heritage) was also tested. In addition, potential treatment-by-subgroup interactions were considered via the assessment of summaries of the treatment differences across subgroups.

Evidence of heterogeneity was observed for age subgroup in the pooled analysis and by race subgroup (White vs. non-White only) both in Study 201637 and in the pooled analysis. However, further exploration of the reasons for this finding did not reveal any pattern and was limited by the small number of Snapshot non-responders within subgroups. Regardless, treatment differences across age, Baseline third agent, race, and gender are consistent with primary endpoint conclusion of non-inferiority (m2.7.3 Section 3.3).

4.7. Virology

A summary of non-clinical and clinical virology can be found in m2.7.2.4 (Special Studies).

There is no increased risk of meeting CVW for DTG + RPV compared with CAR. There was a low and comparable incidence in the number of subjects in each treatment group that met CVW (2 per group, <1%; m2.7.2.4 Section 4.2.5.1.4).

4.7.1. Subjects Who Met Virologic Withdrawal Criteria

Virologic assessment was employed to ensure subjects remained suppressed to <50 c/mL. A value of ≥50 c/mL mandated repeat assessment of viral load. The CVW Population included all subjects in the ITT-E Population who had 2 consecutive viral loads ≥50 c/mL, with the second one being >200 c/mL (the second being the confirmatory virology sample). The studies allowed any subjects with a second virology sample of ≥50 c/mL and <200 c/mL to be evaluated for possible mitigating circumstances that could lead to low level elevations. They would be in the pPVW Population and also remained in the ITT-E population. If subjects in the pPVW Population failed to suppress

to <50 c/mL on a third viral load test, or, if there was no mitigating reason for the elevation, then they met virologic withdrawal criteria and were in the PVW Resistance Population.

Of the 4 subjects who met CVW criteria during the Early Switch Phase, only 1 subject in the DTG + RPV group who was noted as non-adherent had genotypic substitution K101K/E mixture in RT, no decrease in RPV susceptibility, and a greater than 3-log decrease in HIV-1 viral load on resumption of their DTG + RPV regimen (from 1,059,771 c/mL at suspected virologic withdrawal visit to 1,018 c/mL at the confirmatory visit, and decreased further to <50 c/mL at the withdrawal visit) (m2.7.2.4 Section 4.2.5.1.4).

Subjects with viral loads from 50 to 200 c/mL for more than 2 consecutive tests were deemed to have met a PVW criterion. In Studies 201636 and 201637, 1 subject in the DTG + RPV group and 2 subjects in the CAR treatment group met PVW criteria (m2.7.2.4 Section 4.2.5.1.6). Resistance testing was available for 1 subject in the CAR group, but was not available for the other two PVW subjects. No genotypic or phenotypic resistance to study drugs was observed.

4.8. Patient Reported Outcomes

A summary of patient reported change from Baseline in HIV related symptoms and in HIV treatment satisfaction can be found in m2.7.3 Section 3.4.

The DTG + RPV group had a small but statistically significant reduction in Symptom Bother score from Baseline compared with the CAR group at Weeks 4 and 48 (pooled results, m2.7.3 Section 3.4.1). Additionally, neither symptom count nor Symptom Bother scores worsened from Baseline at any time point suggesting that stable subjects receiving CAR were able to switch to DTG + RPV with no associated introduction or exacerbation of bothersome symptoms reported by subjects.

The DTG + RPV group had a small but statistically significant improvement from Baseline in patient reported treatment satisfaction at each assessed time point (pooled results, m2.7.3 Section 3.4.2).

4.9. Efficacy Conclusions

A switch to a novel, once daily 2-drug regimen of DTG + RPV was non-inferior to the continuation of CAR in virologically suppressed HIV-1-infected adults and maintained a high level of HIV-1 suppression. In the few subjects who had virological failure, only 1 non-adherent subject's plasma HIV-1 RNA was noted to have a single genotypic change, which was an NNRTI-class related substitution, and which conferred no decrease in phenotypic susceptibility.

A DTG + RPV regimen offers the potential for switching subjects to a well-tolerated 2-drug ART regimen, without an increased risk of virologic failure. The following conclusions can be made with regard to the pooled data:

- The pooled primary analysis demonstrated that DTG + RPV and CAR provided good clinical efficacy, with 95% of subjects in both treatment groups achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm for the ITT-E Population. The pooled analysis demonstrated that DTG + RPV met the predefined statistical conclusion of non-inferiority to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.0%) was greater than -8%. The predefined non-inferiority margins of -10% were also reached for each individual study (Studies 201636 and 201637).
- Non-inferiority in the primary endpoint is supported across demographic subgroups (age, race, and gender), Baseline CD4+ lymphocyte count subgroups, Baseline third agent treatment class, and for the PP Population.
- A dedicated analysis was performed on the rates of Snapshot virologic failure. The proportion of subjects who were classified as Snapshot virological failures at Week 48 demonstrates that the combined use of DTG + RPV is non-inferior to CAR for this endpoint with a non-inferiority margin of 4%. The 2-drug regimen effectively maintained virologic suppression, with few Snapshot virologic failures and no increased risk of resistance identified through Week 48.
- Of the 4 subjects who met CVW criteria, 1 subject in the DTG + RPV group, who was noted as non-adherent, had genotypic substitution K101K/E mixture in RT, no decrease in RPV susceptibility, and a greater than three log decrease in HIV-1 viral load on resumption of their DTG + RPV regimen. The other 3 subjects had no observed resistance on study.
- Results were similar across the two studies (201636 and 201637) indicating reproducibility of the data.

Taken together, these Week 48 results indicate that the DTG + RPV 2-drug regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL across a diverse spectrum of subjects and regardless of current third agent class. This simplified regimen is non-inferior to CAR without an increased risk of virologic failure. This NRTI- and PI-sparing regimen has the potential to avoid NRTI and PI class-related resistance, thereby preserving these ART classes as options for future use.

5. OVERVIEW OF SAFETY

For a full presentation of safety results, see the Summary of Clinical Safety (m2.7.4).

The safety database consists of safety data from 1024 (DTG + RPV 513; CAR 511) subjects from the 2 identical Phase III studies 201636 and 201637 (Table 1). Pooled safety data are presented for those studies, cumulative through the Week 48 primary endpoint. The safety data are not pooled with safety data previously reported for the individual components (DTG and RPV). To support the other safety information in the proposed label, we will use relevant SE safety data from non-clinical studies, and relevant clinical trials (including Phase III).

Establishing the risk/benefit profile of an FDC tablet includes an assessment of the safety of each individual component taken alone as well as the safety of the components when

used in combination. The safety data through Week 48 for patients switching to DTG + RPV in the pivotal Phase III studies (201636, 201637) is consistent with current labeling and the known safety profile for the SEs.

5.1. Introduction

The DTG + RPV clinical studies used to support the safety of DTG/RPV FDC (Studies 201636 and 201637) are presented in Table 1.

5.1.1. Population Included in Safety Analyses

Safety analyses were conducted based on the Safety Population, defined as all subjects who received at least 1 dose of study drug. The safety results presented are pooled data from Studies 201636 and 201637.

5.1.2. Data Cut-off Dates

This submission contains safety data collected and analyzed [redacted]. Details of individual study cut-off dates are provided in m2.7.4 Section 1.1.1.1.

5.1.3. Extent of Exposure in Studies 201636 and 201637

The median time of exposure to DTG + RPV was 364 days (52 weeks) (m2.7.4 Section 1.2).

5.2. Non-Clinical Data Relevant to Human Safety

The safety of DTG and RPV, separately, have been well characterized in a battery of nonclinical studies that are discussed in m2.4 (Nonclinical Overview). The overall nonclinical safety data support the clinical use of DTG and RPV as individual agents. There is no known effect on each other's exposure, and no known combined nonclinical safety risk. The nonclinical data for the individual agents support the use of the DTG/RPV FDC tablet in the treatment of HIV-1 infection in virologically-suppressed (HIV-1 RNA <50 copies/mL) adults without known or suspected resistance to either component at the recommended dose of DTG 50 mg and RPV 25 mg once daily.

5.3. Adverse Events

The clinical data obtained in the pivotal Phase III Studies 201636 and 201737 are summarized in Table 4. These data inform the safety profile of DTG + RPV as a treatment regimen in subjects switched from a stable 3-drug CAR regimen. In this open label switch-design study, the subjects in the comparator CAR group had been on a stable, and presumably tolerable ART regimen for at least 6 months (and an average of over 4 years). As expected, a higher proportion of subjects who switched to DTG + RPV reported at least 1 AE compared with subjects who continued their antiretroviral regimen. Overall, there was a difference of 6% observed between the treatment groups for Grade 2

to 4 AEs for the pooled data. The difference is driven by a difference between the treatment groups in Grade 2 to 4 AEs for Study 201637 that was not observed for Study 201636 (m2.7.4 Section 2.1.1). There were more drug-related events and more AEs leading to withdrawal in the DTG + RPV treatment group. These differences are expected given the influence of the study design.

Table 4 Overall Summary of Adverse Events during the Early Switch Phase for Pooled Data (Safety Population)

	Pooled	
	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any AE	395 (77)	364 (71)
Drug-related AEs	97 (19)	9 (2)
Any Grade 2 to 4 AEs	148 (29)	120 (23)
Any Drug-related Grade 2 to 4 AE	29 (6)	3 (<1)
AEs Leading to Withdrawal	21 (4)	3 (<1)
Drug-related AEs Leading to Withdrawal	14 (3)	4 (<1)
Any SAE	27 (5)	21 (4)
Drug-related SAEs	4 (<1)	1 (<1)
Fatal SAEs	1 (<1)	1 (<1)
Drug-related Fatal SAEs	0	0

Data Source: 201636/201637 Table 3.040, Table 3.100, Table 3.121, Table 3.122, Table 3.123, Table 3.150, Table 3.230, Table 3.291, and Listing 23
Note: Only on-treatment events are considered.

5.3.1. Common Adverse Events

While a higher proportion of subjects who switched to DTG + RPV reported at least 1 AE overall, the most commonly reported AEs occurring in ≥5% of subjects in either treatment group were similar, and reflect common AEs found in many subjects in a study of 1 year duration (m2.7.4 Section 2.1.1). The most commonly reported AEs for the DTG + RPV and CAR groups were nasopharyngitis (10% in both groups), headache (8% and 5%), upper respiratory tract infection (5% and 7%), diarrhea (6% and 5%), and back pain (3% and 6%) (m2.7.4 Section 2.1.1.1). The majority of events reported had an intensity of Grade 1 or Grade 2 (m2.7.4 Section 2.1.1.3).

5.3.1.1. Drug-Related Adverse Events

As expected for an open-label switch study where the subjects in the comparator CAR group had been on a stable and tolerable ART regimen for at least 6 months, drug-related AEs (as assessed by the reporting investigator) were more commonly reported for subjects who switched their regimen at Baseline compared with subjects who remained on CAR (m2.7.4 Section 2.1.1.4).

In the DTG + RPV treatment group, 19% of subjects (versus 2% of subjects in the CAR group) reported at least 1 drug-related AE during the Early Switch Phase

(m2.7.4 Section 2.1.1.4). No individual drug-related adverse event was reported in more than 2% of subjects. In both groups, the majority of AEs were Grade 1. A higher proportion of subjects who switched to DTG + RPV reported Grade 2 to 4 drug-related AEs (6% vs. <1%). The most frequently reported Grade 2 to 4 drug-related AEs in the DTG + RPV group were depression (4 subjects), asthenia (3 subjects) and diarrhea (3 subjects). All other Grade 2 to 4 drug-related AEs were reported in 2 subjects or fewer in the DTG + RPV group.

5.3.2. Deaths

Two deaths were reported at the time of the safety cut-off for the Week 48 analysis (m2.7.4 Section 2.1.2). In the Early Switch Phase, 1 subject in the DTG + RPV treatment group died due to an AE of Kaposi's sarcoma and 1 subject in the CAR treatment group died due to an AE of malignant lung neoplasm. Neither case was considered related to study drug by the investigator.

5.3.3. Other Serious Adverse Events

The incidences of subjects developing at least 1 SAE was low and similar between treatment groups in the Early Switch Phase (DTG + RPV 5%; CAR 4%) (m2.7.4 Section 2.1.3). The most frequently reported SAEs were pneumonia (reported in 3 subjects in the DTG + RPV group) and suicide attempt (reported in 1 subject each for the DTG + RPV and CAR groups). All other SAEs were reported in 1 subject each.

Fourteen subjects reported a total of 18 SAEs with an onset during the Late Switch Phase, none of which were considered related to study treatment (m2.7.4 Section 2.1.3).

5.3.4. Drug-Related Serious Adverse Events

Four subjects in the DTG + RPV treatment group reported drug-related SAEs during the Early Switch Phase compared with 1 subject in the CAR treatment group during the Early Switch Phase (m2.7.4 Section 2.1.4). In the DTG + RPV group, the 4 subjects experienced drug-related SAEs (as assessed by the reporting investigator) of acute pancreatitis, DILI (described further in Section 5.4.1.1), depression, and acute eosinophilic pneumonia. The 1 subject in the CAR group reported the drug-related SAE of suicide attempt.

There were no drug-related SAEs reported with an onset during the Late Switch Phase.

5.3.5. Other Significant Adverse Events

Adverse events leading to withdrawal of study drug are presented in Section 5.3.5.1. There were no other significant AEs.

5.3.5.1. Adverse Events Leading to Withdrawal

Twenty-one subjects in the DTG + RPV group and 3 subjects in the CAR group experienced AEs leading to withdrawal/permanent discontinuation of study drug during the Early Switch Phase (Table 5, m2.7.4 Section 2.1.5.1). All AEs leading to withdrawal had an incidence of <1%.

During the Late Switch Phase, an additional 6 subjects discontinued due to AEs (1 randomized to DTG + RPV at Baseline and 5 who switched to DTG + RPV at Week 52) (m2.7.4 Section 2.1.5.1).

Table 5 Listing of Subjects Who Experienced AEs Leading to Withdrawal/Permanent Discontinuation of Study Drug in Study 201636 and Study 201637 (Safety Population)

Subject ID	AE Preferred Term(s)	Phase[a]	Study Day (Days Since Switch[b])	Maximum Intensity	Serious AE	Drug Related	Baseline Third-Agent (Class)
Subjects Randomized to DTG + RPV at Baseline							
[redacted]	Pancreatitis acute	Early Switch	174	Grade 4	Yes	Yes	ATV/RTV (PI)
	Drug-induced liver injury	Early Switch	35	Grade 3	Yes	Yes	EFV (NNRTI)
	Eosinophilic pneumonia acute	Early Switch	195	Grade 3	Yes	Yes	DTG (INSTI)
	Depression	Early Switch	214	Grade 3	Yes	Yes	RAL (INSTI)
	Panic attack	Early Switch	313	Grade 3	Yes	No	EVG/COBI (INSTI)
	Anxiety	Early and Late Switch	313	Grade 4	No	Yes	
[redacted]	Plasmablastic lymphoma	Early Switch	29	Grade 3	Yes	No	DRV/RTV (PI)
	Hodgkin's disease mixed cellularity stage unspecified	Early and Late Switch	345	Grade 3	Yes	No	EVG/COBI (INSTI)
[redacted]	Kaposi's sarcoma[c]	Early Switch	207	Grade 4	Yes	No	DRV/RTV (PI)
	Gastrointestinal hemorrhage	Early Switch	12	Grade 3	Yes	No	EFV (NNRTI)
	Abscess	Late Switch	485	Grade 3	Yes	No	RAL (INSTI)
	Anal squamous cell carcinoma	Late Switch	457	Grade 3	Yes	No	
	Metastases to lymph nodes	Late Switch	457	Grade 3	Yes	No	
[redacted]	Depression	Early Switch	238	Grade 3	No	Yes	NVP (NNRTI)
	Peptic ulcer	Early Switch	128	Grade 3	No	No	DRV/RTV (PI)
	Abdominal distension	Early Switch	2	Grade 1	No	Yes	DRV/RTV (PI)
	Anxiety	Early Switch	119	Grade 1	No	Yes	
[redacted]	Tremor	Early Switch	31	Grade 3	No	Yes	EFV (NNRTI)
	Suicidal ideation	Early Switch	57	Grade 3	No	Yes	DRV/RTV (PI)
	Dyspepsia	Early Switch	12	Grade 2	No	Yes	RAL (INSTI)
	Headache	Early Switch	90	Grade 2	No	Yes	
[redacted]	Abdominal distension	Early Switch	1	Grade 2	No	Yes	EFV (NNRTI)
	Dyspepsia	Early Switch	59	Grade 2	No	Yes	RAL (INSTI)
	Anxiety (verbatim text: anguish)	Early Switch	6	Grade 2	No	Yes	LPV/RTV (PI)
	Anxiety (verbatim text: anxiety)	Early Switch	6	Grade 2	No	Yes	

Subject ID	AE Preferred Term(s)	Phase[a]	Study Day (Days Since Switch[b])	Maximum Intensity	Serious AE	Drug Related	Baseline Third-Agent (Class)
	Depression	Early Switch	6	Grade 2	No	Yes	
[redacted]	Depressed mood	Early Switch	2	Grade 2	No	Yes	EFV (NNRTI)
	Insomnia	Early Switch	2	Grade 1	No	No	
[redacted]	Insomnia	Early and Late Switch	331	Grade 1	No	No	EFV (NNRTI)
[redacted]	Anxiety	Early Switch	192	Grade 2	No	No	EFV (NNRTI)
Subjects Randomized to CAR at Baseline							
[redacted]	Suicide attempt	Early Switch	80	Grade 4	Yes	Yes	EFV (NNRTI)
[redacted]	Hodgkin's disease	Late Switch	447 (87)	Grade 2	Yes	No	EFV (NNRTI)
[redacted]	Lung neoplasm malignant[c]	Early Switch	164	Grade 3	Yes	No	ATV (unboosted PI)
[redacted]	Breast cancer	Early Switch	185	Grade 3	Yes	No	ATV (unboosted PI)
[redacted]	Blood glucose increased	Late Switch	391 (29)	Grade 2	No	Yes	NVP (NNRTI)
	Transaminases increased	Late Switch	391 (29)	Grade 2	No	Yes	
[redacted]	Pain in extremity (verbatim text: pain in finger left hand)	Late Switch	395 (31)	Grade 2	No	Yes	EFV (NNRTI)
	Eczema	Late Switch	399 (35)	Grade 1	No	Yes	
	Pain in extremity (verbatim text: foot plant pain)	Late Switch	419 (55)	Grade 2	No	Yes	
	Pain in extremity (verbatim text: pain in right hand)	Late Switch	419 (55)	Grade 2	No	Yes	
	Diarrhea	Late Switch	420 (56)	Grade 1	No	Yes	
	Abdominal distension	Late Switch	420 (56)	Grade 2	No	Yes	
	Constipation	Late Switch	424 (60)	Grade 2	No	Yes	
[redacted]	Abulia	Late Switch	370 (6)	Grade 2	No	Yes	DTG (INSTI)
	Aphasia	Late Switch	370 (6)	Grade 2	No	Yes	
	Chest discomfort	Late Switch	423 (59)	Grade 2	No	Yes	
	Confusional state	Late Switch	370 (6)	Grade 2	No	Yes	
	Disturbance in attention	Late Switch	370 (6)	Grade 2	No	Yes	
[redacted]	Abortion induced	Late Switch	406 (42)	Grade 1	No	No	NVP (NNRTI)

Data Source: 201636/201637 Listing 23 and Listing 48

a. Early Switch indicates the event occurred prior to the Week 52 visit; Late Switch indicates the event occurred at or after the Week 52 visit. Early and Late Switch indicates that the onset of the event was prior to Week 52 and that is was ongoing after Week 52.
b. Number of days from the switch to DTG + RPV to the onset of the event; For DTG + RPV subjects, this is calculated as the number of days since Baseline, for CAR subjects it is calculated as the number of days since switch to DTG + RPV at Week 52.
c. Outcome was fatal (see Section 5.3.2).

5.3.6. Adverse Events of Special Interest

AESI have been determined for DTG + RPV based on: non-clinical and/or clinical safety data for DTG and RPV; labeling and/or regulatory authority interest for approved INSTIs; and/or regulatory authority requirements. There is no expected or observed additive or synergistic effect on AESIs in subjects taking DTG/RPV FDC beyond that expected for the SEs. Details on AEs for the CAR group in the following categories are available in m2.7.4 Section 2.1.6.

5.3.6.1. Hypersensitivity

Two subjects in the Early Switch Phase (1 in each treatment group), and 2 subjects in the Late Switch Phase (DTG + RPV group) reported events coded to the PTs of 'hypersensitivity' or 'drug hypersensitivity' (m2.7.4 Section 2.1.6.1). The 3 events reported in subjects taking DTG + RPV were Grade 1. None of the events were considered related to study drug and none of the events resulted in withdrawal of study drug or withdrawal from the study. Two of these events were reported as an allergy to a drug other than study drug.

5.3.6.2. Hepatobiliary Disorders

See Clinical laboratory results in Section 5.4.

5.3.6.3. Psychiatric Disorders Including Depression and Suicidality

Adverse events in the psychiatric disorders SOC were reported more frequently in the DTG + RPV treatment group (DTG + RPV 12%; CAR 6%) (m2.7.4 Section 2.1.6.3). Insomnia (3%), depression (3%), anxiety (2%), and abnormal dreams (1%) were the most commonly reported AEs from this SOC in the DTG + RPV treatment group, and all other events from this SOC were reported in <1% of DTG + RPV subjects. The majority of the events were considered Grade 1 or 2. Of the subjects in the DTG + RPV group reporting any event from this SOC, 3 reported Grade 3 events and 2 reported Grade 4 events.

The incidence of insomnia was low and comparable in both treatment groups (DTG + RPV 3%; CAR 2%) (m2.7.4 Section 2.1.6.3). Nightmare and abnormal dreams were reported in 7 subjects (1%) in the DTG + RPV treatment group, with none in the CAR group. This is a listed event for both DTG and RPV. The incidence of anxiety was low and comparable in both treatment groups (DTG + RPV 2%, CAR 2%).

Although the incidence of depression and suicidal behaviors was higher in those with a previous history of anxiety or depression (12%) compared with those without a history (3%) in the DTG + RPV treatment group, the majority of patients with this history (100/114) did not report recurrences during the study (m2.7.4 Section 2.1.6.3).

The reporting rate for AEs relating to depression (PTs containing 'depression', 'depressed mood', 'depressive', 'hypomania', or 'bipolar') was higher in the DTG + RPV treatment group (4%) compared with the CAR treatment group (2%) (m2.7.4 Section 2.1.6.3). All events were single occurrences in both treatment groups.

There were 6 events considered drug-related in the DTG + RPV treatment group and none in the CAR group.

During the Early Switch Phase, 9 subjects in the DTG + RPV treatment group withdrew due to a psychiatric disorder (m2.7.4 Section 2.1.6.3). One subject with a past history of depression withdrew due to suicidal thoughts. Two subjects withdrew with depression; both of whom had a current or past history of the condition at Baseline. Four subjects withdrew due to anxiety. Two additional subjects in the DTG + RPV treatment group experienced an event during the Early Switch Phase, and withdrew in the Late Switch Phase. One subject with a past history of panic attacks and depression withdrew due to anxiety and panic attack and a second subject withdrew due to insomnia.

Drug-related AEs in the psychiatric disorders SOC were also reported more frequently in the DTG + RPV treatment group (DTG + RPV 5%; CAR <1%) (m2.7.4 Section 2.1.6.3). The majority of these drug-related events were Grade 1 with ≤1% of subjects having any Grade 2, 3, or 4 drug-related psychiatric disorders SOC events. In the DTG + RPV treatment group, 1 drug-related AE of anxiety was considered Grade 4, and 2 drug-related AEs of depression and 1 drug-related AE of suicidal ideation were considered Grade 3.

The number of subjects reporting AEs relating to suicidal behaviors (PTs containing 'suicide', 'suicidal', or 'intentional self-injury') was low and comparable across the treatment groups (DTG + RPV 4 [<1%]; CAR 3 [<1%]) (m2.7.4 Section 2.1.6.3). All events in the DTG + RPV group were single occurrences. Two subjects (1 in each treatment group) reported an event that was considered drug-related and led to withdrawal (Grade 3 suicidal ideation in a DTG + RPV subject with a past history of depression, and Grade 4 suicide attempt in a CAR subject); all events reported in the remaining 5 subjects were considered not related to study treatment and did not lead to withdrawal. Of these 5 remaining subjects, 1 subject reported a Grade 4 event (suicidal ideation in a DTG + RPV subject with a current history of depression), and all other events were Grade 1 or 2. Three of 4 subjects in the DTG + RPV group had a history of depression (2 current, 1 past). All events were reported as recovered or recovered with sequelae. None of the events resulted in completed suicide.

Three additional subjects in the DTG + RPV group reported symptoms that included suicidal ideation (m2.7.4 Section 2.1.6.3). These were identified by review of the PSRAE forms, post database freeze. The Investigator sites did not complete AE forms for these events, hence, these are not accounted for in the AE data listing or tables. One subject reported an AE of worsening depression, which led to withdrawal. However, this subject also had suicidal ideation described on the PSRAE form but this AE was not reported in the eCRF. Another subject reported a PSRAE of passive suicidality without a corresponding AE entered in the eCRF. The third subject reported a PSRAE of worsening of depressive disorders with 'suicidal tendencies'. For this subject a corresponding SAE of worsening of depressive disorder was entered in the eCRF, but did not mention 'suicidal tendencies'.

Events of suicidal ideation and behavior were reported via PSRAE forms (as well as on AE or SAE forms). Suicidality assessments were also administered via the eC-SSRS. Results are discussed in m2.7.4 Section 2.1.6.3.

5.3.6.4. Drug Resistance

Drug resistance is discussed in m2.7.2.4 Section 4.1.13.

5.3.6.5. Skin and Subcutaneous Disorders

Any preferred terms related to a rash due to drug were identified from DTG + RPV ISO. This included preferred terms containing 'rash', 'eruption', 'photosensitivity', or 'urticaria', such as rash erythematous, rash generalized, rash papular, rash pruritic, toxic skin eruption, photosensitivity and urticaria. There were no reports in the database for severe rash with terms that included Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme (m2.7.4 Section 2.1.6.5). Rash AESIs identified in the ISO were reported in 22 (4%) subjects in the DTG + RPV group and 7 (1%) subjects in the CAR group. There were no rash AESIs that were serious, Grade 3 to 4 or severe, lead to withdrawal, or fatal. Six of the rash AESI (all in the DTG + RPV group) were considered drug-related.

For events reported specifically from the skin and subcutaneous tissue disorders SOC, a higher proportion of subjects reported events in the DTG + RPV treatment group (DTG + RPV 13%; CAR 9%) (m2.7.4 Section 2.1.6.5). Except for the PT of "rash", which was reported at 2% in the DTG + RPV treatment group, all other event PTs in both treatment groups were reported at ≤1%. All events in the DTG + RPV treatment group were Grade 1 or 2.

Drug-related AEs in the skin and subcutaneous disorders SOC were reported in 2% of subjects in the DTG + RPV treatment group and no subjects in the CAR treatment group (m2.7.4 Section 2.1.6.5). Rash (4, <1%) and alopecia (2, <1%) were considered drug-related in more than 1 subject. All other drug-related skin events occurred in single subjects. There were no Grade 3 or 4 drug-related skin events.

5.3.6.6. Gastrointestinal Disorders

GI events were reported more frequently in the DTG + RPV treatment group (DTG + RPV 25%; CAR 16%) (m2.7.4 Section 2.1.6.6). The most commonly reported events in both treatment groups were diarrhea and dyspepsia. In the DTG + RPV group, there were 5 Grade 3 events reported by 4 subjects (peptic ulcer, abdominal pain upper, abdominal pain, gastroesophageal reflux disease, and gastrointestinal hemorrhage) and 1 Grade 4 event of acute pancreatitis. All other events in the DTG + RPV treatment group were Grade 1 or 2.

Drug-related GI disorders were also reported more frequently in the DTG + RPV treatment group (DTG + RPV 7%; CAR <1%) (m2.7.4 Section 2.1.6.6). The most commonly reported drug-related AEs in the DTG + RPV treatment group was diarrhea (2%). The majority of drug-related GI events were Grade 1. Of drug-related

events reported in the DTG + RPV treatment group, 8 events were Grade 2 (3 events of diarrhea, 2 events each of dyspepsia and abdominal distension, and 1 event of constipation). There was 1 Grade 4 event drug-related event reported in the DTG + RPV group of acute pancreatitis. All other drug-related events in the DTG + RPV were considered Grade 1.

There were 3 SAEs reported: acute pancreatitis, gastrointestinal hemorrhage, and GERD in the DTG + RPV group (m2.7.4 Section 2.1.6.6).

5.3.6.7. Renal Disorders

See Clinical laboratory results in Section 5.4.

5.3.6.8. Musculoskeletal and Connective Tissue Disorders

The incidence of events in the musculoskeletal and connective tissue disorders SOC was comparable between the 2 treatment groups (DTG + RPV 15%; CAR 16%) (m2.7.4 Section 2.1.6.8). No events of rhabdomyolysis were reported. The majority of events from this SOC were Grade 1 for both treatment groups. There was 1 Grade 3 events reported (hemarthrosis) in the DTG + RPV group; no Grade 4 events were reported from the musculoskeletal and connective tissue disorders SOC. Three drug-related events were reported from the DTG + RPV treatment group (arthralgia, muscle spasms, and musculoskeletal pain, all Grade 1).

5.3.6.9. Grade 3 to 4 Lipase Elevations

Adverse events and laboratory data related to lipase elevations and pancreatitis are discussed in m2.7.4 Section 2.1.4.

5.4. Clinical Laboratory Evaluations

5.4.1. Clinical Chemistry

Results of the clinical laboratory findings demonstrate that there are no laboratory signals of concern in subjects switching from their current ART regimen to receiving DTG + RPV treatment. No clinically relevant differences were observed overall in Grade 3 and Grade 4 post-baseline emergent toxicities between the DTG + RPV and CAR groups (m2.7.4 Section 3.1).

The majority of the post-baseline emergent clinical chemistry toxicities were Grade 1 or Grade 2 in intensity. Among the lipase elevations, there was a single asymptomatic event of pancreatitis that occurred in a subject in the DTG + RPV treatment group (see m2.7.4 Section 2.1.4 for a brief description).

5.4.1.1. Liver Chemistry Results

Seven subjects reported hepatobiliary AEs in the Early Switch Phase (DTG + RPV <1%; CAR <1%) (m2.7.4 Section 3.1.1). There was 1 case reported as DILI, which was reported as an SAE and considered related to DTG + RPV (m2.7.4 Section 2.1.4). One event of chronic cholecystitis in the DTG + RPV group was considered serious in a patient who also had non-serious biliary colic. All other events were not serious and were not considered related to study drug. There were no Grade 4 events. There were no hepatobiliary AEs reported with an onset during the Late Switch Phase.

There were 9 subjects with elevations of ALT >3 x ULN in the DTG + RPV group (Table 6). Six of the elevations were due to other causes; viral hepatitis (1), alcohol (3) and other drugs (2). Two of the remaining 3 subjects had mild elevations which returned to normal despite continuing treatment with DTG + RPV. One subject was diagnosed with DILI and this was the only subject who withdrew in the DTG + RPV group (m2.7.4 Section 3.1.1). There was 1 subject in the Late Switch Group with an elevation of ALT > 3 x ULN due to acute HCV.

Table 6 Summary of Subjects With ALT Greater Than or Equal to 3 x ULN During the Early Switch Phase, Pooled Data (Safety Population)

Hepatobiliary Criteria	DTG + RPV N=513 n (%)	CAR N=511 n (%)
ALT ≥3 x ULN to <5 x ULN	6 (1)	2 (<1)
ALT ≥5 x ULN to <10 x ULN	3 (<1)	2 (<1)
ALT ≥10 x ULN to <20 x ULN	0	0
ALT≥20 x ULN	0	1 (<1)

Data Source: 201636/201637 Table 3.613
Note: For ALT ≥3 x ULN to <5 x ULN, ≥5 x ULN to <10 x ULN, ≥10 x ULN to <20 x ULN, ≥20 x ULN, subjects are summarized based on the maximum value post Baseline.

5.4.1.2. Renal Laboratory Results

Prior studies with DTG and with RPV have shown that subjects receiving DTG or RPV had mean increases from Baseline in serum creatinine evident by Week 2 that remained stable while subjects remained on drug (m2.7.4 Section 3.1.2). In Studies 201636 and 201637, subjects in the DTG + RPV group had mean increases from Baseline in serum creatinine evident at Week 4 (the earliest time point assessed) that remained stable through Week 48. Consistent with this, the mean change from Baseline in estimated GFR from CKD-EPI equation showed a small decrease in the DTG + RPV group compared with little change in the CAR group.

In contrast to the results using creatinine, the change from Baseline in CKD-EPI GFR using Cystatin C showed no difference between the DTG + RPV and CAR treatment groups and little change from Baseline in either treatment group (m2.7.4 Section 3.1.2).

Additionally, change from Baseline in CKD-EPI eGFR was assessed using Cystatin C during the Early Switch Phase for subgroups of subjects who were or were not receiving TDF at Baseline (m2.7.4 Section 3.1.2). For subjects in both treatment groups, regardless of whether they were receiving TDF at Baseline, there was no change from Baseline to Week 48 in median cystatin C.

Ten (2%) subjects in the DTG + RPV group had Grade 1 maximum post-baseline emergent elevations in creatinine; there were no Grade 2 to Grade 4 elevations (m2.7.4 Section 3.1.2). Three (<1%) and 1 (<1%) subjects in the CAR group had Grade 1 and Grade 2, respectively, maximum post-baseline emergent elevations in creatinine; there were no Grade 3 to Grade 4 elevations.

5.4.1.3. Lipid Parameters

A small proportion of subjects in both treatment groups had treatment-emergent cholesterol and triglycerides toxicity of Grade 2 or higher at Week 48 (m2.7.4 Section 3.1.5). The differences in the changes in lipid profile through Week 48 between the groups were not clinically significant.

5.4.2. Hematology Parameters

Overall, there were few post-baseline toxicities. The maximum intensity of post-baseline emergent hematology toxicities was comparable across treatment groups (m2.7.4 Section 3.2).

5.5. Effects on Bone

5.5.1. Bone Mineral Density Assessments

Findings from Study 202094 (DEXA sub-study) are discussed in m2.7.4 Section 4.4.1.

Subjects who switched to a once daily 2-drug regimen of DTG + RPV demonstrated statistically significant increases in total hip BMD from Baseline to Week 48 (assessed by areal density) compared with subjects who continued on treatment with an ART regimen containing TDF (CAR) (m2.7.4 Section 4.4.1). This was demonstrated via an analysis of percent change from Baseline at Week 48 in total hip BMD, using an ANCOVA model adjusted for age, BMI, and BMD at Baseline. A statistically significant increase in BMD in the lumbar spine from Baseline to Week 48 was also observed in the DTG + RPV group compared with the CAR group.

5.5.2. Bone Biomarkers

In the DTG + RPV group, all bone turn over biomarkers (BSAP, P1NP, and osteocalcin) decreased from Baseline to Week 48 (m2.7.4 Section 4.4.2). The decrease in bone biomarkers observed for the DTG + RPV group was statistically significantly greater than the changes observed in the CAR group. Full data of the CTX bone biomarker was not available at the time of preparation of this submission.

5.6. Drug Interactions

Study LAI116181 (Table 1) demonstrated that there are no significant drug interactions between DTG and RPV, the 2 components of the FDC tablet. There are no shared major metabolism pathways between DTG and RPV. No common target organs were identified in DTG and RPV non-clinical studies. Any interactions that have been identified with DTG and RPV individually can be extrapolated to DTG/RPV FDC.

5.7. Special Patient Populations

No studies in special populations have been conducted for DTG/RPV FDC. Since DTG/RPV FDC is bioequivalent to co-administration of the SEs, conclusions from prior special population studies can be applied to DTG/RPV FDC (Section 3). The effects of DTG/RPV FDC are anticipated to be consistent with those observed for DTG and RPV.

Effects of renal and hepatic impairment were evaluated as part of the development programs for DTG and RPV.

5.7.1. Gender, Age, and Race

Data from studies with DTG and RPV SEs do not suggest any effect of age, gender, or race on the safety profile of DTG/RPV FDC (beyond what might be expected for each subgroup) (m2.7.4 Section 5.1.1). In the 201636 and 201637 pooled analysis, there were no significant differences noted in the number of AEs reported post-baseline between males (77%) and females (78%) in the DTG + RPV group. Events occurring in subjects <50 years (76%) and ≥50 years (80%) in the DTG + RPV group were similar. In the pooled studies, 29% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older (Section 4.5). Some difference was observed in the number of AEs reported between races in the DTG + RPV group (e.g., lower incidence in Asian subjects). However, the majority of subjects were white and there were relatively small numbers in the other groups.

5.7.2. Hepatitis B and/or C Virus Co-Infection

DTG/RPV FDC has not been studied in patients with hepatitis B virus co-infection (m2.7.4 Section 5.1.2). In studies with the SEs, DTG or RPV, a higher incidence of liver chemistry elevations were observed in patients co-infected with hepatitis B and/or C. In Studies 201636 and 201637, subjects were excluded if they had evidence of hepatitis B at Screening, had an anticipated need for hepatitis C therapy, or for use of interferon therapy. Thus, data on the use of this 2-drug regimen in hepatitis B or hepatitis C co-infected patients from these studies are limited.

5.7.3. Hepatic Impairment

No dose adjustment of DTG/RPV FDC is required in patients with mild or moderate hepatic impairment (Child-Pugh Grade A or B) (m2.7.4 Section 5.1.3). DTG/RPV FDC has not been studied in patients with severe hepatic impairment (Child-Pugh Grade C).

5.7.4. Renal Impairment

No dose adjustment of DTG/RPV FDC is required in patients with renal impairment (m2.7.4 Section 5.1.4).

5.8. Pregnancy and Lactation

Based on animal, clinical trial, and post-marketing data for DTG and RPV, DTG/RPV FDC is not expected to increase the risk of adverse developmental or reproductive outcomes in humans when used in accordance with the proposed dosing information.

As there have been no adequate and well controlled clinical studies of DTG and/or RPV in pregnant women, labeling will advise that DTG/RPV FDC should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Human pregnancy data are discussed in m2.7.4 Section 5.4.

Health experts recommend that, where possible, HIV infected women do not breast feed their infants in order to avoid transmission of HIV.

5.9. Withdrawal Effects, Abuse Potential, Overdose

Experience with overdose of DTG/RPV FDC, or the individual components (DTG and RPV) is limited. There is no specific treatment for overdose with DTG/RPV FDC. Patients should be treated supportively, with monitoring of vital signs and ECG (QT interval), as needed (m2.7.2 Section 2.4.4.1).

As DTG and RPV are both highly bound to plasma proteins, it is unlikely that the DTG/RPV FDC will be significantly removed by hemodialysis or peritoneal dialysis. Administration of activated charcoal may be used to aid in removal of unabsorbed active substance.

5.10. Post-Marketing

DTG/RPV FDC is not currently approved or marketed in any country.

Depression and suicidal behaviors were upgraded from an important potential risk to an important identified risk for DTG, and added to the DTG GDS/RSI as a labeled adverse reaction in January 2015. Myalgia and arthralgia were also added to the DTG GDS/RSI as a labeled adverse reaction in July 2016.

No other significant safety concerns or risks have been identified from marketing experience through to 16 January 2017 for DTG or RPV.

Data reported from publications describing over 400 patients using DTG and RPV together support the efficacy and safety profile observed in the Phase III trials.

5.11. Safety Conclusion

The 48 week safety data from Studies 201636 and 201637 support the proposition that DTG + RPV is a well-tolerated regimen for the maintenance of HV-1 suppression. This NRTI-sparing regimen has the potential to avoid short and long term toxicities seen with this class.

Key findings from the safety data for Studies 201636 and 201637 are as follows:

- Over 48 weeks, the safety data from the two identical, randomized, open-label Phase III studies of patients switching to DTG + RPV are consistent with current labelling and the known safety profile for the SEs. No new adverse drug reactions were observed.
- Greater proportions of subjects in DTG + RPV group compared with those in the CAR group reported AEs (77% vs. 71%), drug-related AEs (19% vs. 2%), and AEs leading to withdrawal (4% vs. <1%), which is expected when comparing a switch group to patients continuing their current tolerated treatment.
- There was no difference in the incidence of serious drug-related AEs, which was low for both treatment groups (<1% of subjects in each group).
- There was no evidence for an increased risk of rash with or without systemic symptoms with DTG + RPV compared with CAR. Serious rash was not observed in Studies 201636 and 201637, including no reports of Stevens Johnson syndrome, TEN, or erythema multiforme.
- The psychiatric AE profile for DTG + RPV was comparable to the known safety profile for the SEs. Psychiatric AEs leading to withdrawal, while the most common SOC with withdrawals, each occurred in less than 5 (<1%) subjects in the DTG + RPV group.
- Based on Week 48 data, there was no increased risk of renal toxicity or hepatic toxicity for DTG + RPV compared with CAR.
- There were no clinically significant differences in the changes in lipid profile between the 2 groups.

Additional key safety findings relevant to the DTG/RPV FDC program are as follows:

- The results of DEXA scans in Study 202094, supported by the bone biomarker data in Studies 201636 and 201637, suggest a potential benefit of improving bone health in switching from a TDF-containing 3-drug ART regimen to a regimen of DTG + RPV.
- The data reported in publications from over 400 patients using DTG and RPV together support the efficacy and safety profile observed in the Phase III trials (Studies 201636 and 201637).

6. BENEFITS AND RISKS CONCLUSIONS

Establishing the risk/benefit profile of an FDC includes an assessment of the safety/efficacy/tolerability of each individual component taken alone as well when used

in combination. DTG/RPV FDC is a 2-drug, NRTI-sparing regimen intended for the long-term treatment of HIV-1 infection. It is the combination of 2 well-established marketed products, DTG and RPV. The efficacy and safety profile of DTG has been described in the DTG clinical program, while the efficacy and safety profile of RPV has been has been described in the RPV clinical program. As found in the bioequivalence study (201676), there is no clinically significant difference in exposure of component drugs when they are dosed as an FDC. Therefore, conclusions from relevant DTG or RPV SE studies can be extrapolated to DTG/RPV FDC as appropriate. Based on the established efficacy, safety, tolerability, and combined resistance profiles of DTG SE and RPV SE and the Week 48 data from the 2 large pivotal Phase III clinical studies (201636, 201637), DTG + RPV is an effective, and well tolerated regimen for the maintenance of HIV-1 suppression. Safety in Studies 201636 and 201637 is consistent with the established safety profile for the SEs. The Phase III studies did not identify an increased risk of ART resistance selection with the use of this novel 2-drug regimen. The potential benefit of this 2-drug regimen is not downgraded by any newly identified risk associated with the use of these 2 agents.

6.1. Therapeutic Context

Currently, there are no approved 2-drug regimens to maintain suppression. Treatment simplification has long been a goal to increase treatment adherence and improve the quality of life for patients with HIV. The use of NRTI-sparing regimens for the long-term treatment of HIV infection has the potential to avoid known NRTI-associated adverse drug reactions and long-term toxicities.

6.1.1. HIV-1 Infection

In 2015, an estimated 36.7 million people worldwide were living with HIV/AIDS and 2.1 million people were newly infected with HIV [UNAIDS, 2016a]. Of the people living with HIV/AIDS in 2015, 17 million were on ARV therapy. In 2016, the number of people who have access to treatment has increased to 18.2 million [UNAIDS, 2016b]. Increasing access to treatment is contributing to a reduction in AIDS-related deaths among adults and children. AIDS-related deaths have decreased by 45%, from a peak of 2 million in 2005 to 1.1 million in 2015.

Where treatment is available, HIV infection has become a manageable chronic disease [UNAIDS, 2016b]. Better treatment coverage means that a growing number of people will be living with HIV into old age. Globally, 17% of adults living with HIV are 50 years or older. In high-income countries, 31% of adults living with HIV are 50 years or older. As people living with HIV age, they are more susceptible to the adverse effects of antiretroviral therapy and must increasingly manage long-term side-effects. They are also more likely to take antiretroviral medication in combination with other medications and to experience age-related diseases as comorbidities.

6.1.2. Current Therapies and Unmet Medical Need

A study by the Antiretroviral Therapy Cohort Collaboration [ART-CC, 2013] found that of more than 21,000 patients in a European and North American cohort on their first cART regimen (either PI- or NNRTI-based), 51% modified or interrupted their first cART regimen during a median of 28 months of follow-up with one third of interruptions occurring within the first 6 months of starting therapy. Forty percent of all treatment interruptions were due to the secondary side effects or toxicities of cART, 17% were due to the desire for simplification of the regimen and 14% were due to patient choice. These observations have led to numerous "switch" ART studies, designed to understand the efficacy, safety, and tolerability of switching patients from one regimen to another.

Fixed-dose combination therapy is preferred by many patients and has well-recognized benefits. These include the simplification of therapy by combining different products in fixed proportions into a single tablet with the potential to increase patient adherence due to it being a simpler regimen. This also avoids the risk of "partial adherence," where patients take some, but not all, of their medicines. Better adherence with full treatment regimens can decrease the likelihood of virologic failure and subsequent development of resistance. While some FDC options are now available, the opportunity to develop new FDCs to better address toxicities while concurrently suppressing the emergence of resistance remains.

Potential benefit exists from evaluating new FDCs of existing agents—with a focus on utilizing agents with better safety and that possess a higher barrier to resistance, while minimizing the number of components, and developing more convenient dosing options (e.g., once-daily administration, reduced pill burden, smaller pill size), while retaining efficacy. Study LAI116482 (LATTE) is an ongoing Phase IIb dose-ranging study (3 oral-dose regimens of the INSTI cabotegravir 10 mg, 30 mg, or 60 mg) evaluating the utility of a 2-drug, 2-class combination of cabotegravir + RPV given as a once-daily oral regimen following induction of virologic suppression using oral cabotegravir plus 2 NRTIs. Data from LAI116482 provided proof of principle for RPV combined with an INSTI as an effective 2-drug regimen for the maintenance of virologic suppression [Margolis, 2015]. Additionally, cabotegravir has similar virologic characteristics to DTG and, based on available data, has a similar antiviral activity, safety and tolerability profile to DTG, which further supports the clinical investigation of a regimen including DTG + RPV as a 2-drug combination for the treatment of HIV-1 infection. DTG + RPV is being evaluated in the 2 Phase III studies (201636 and 201637) as described in Table 1.

NRTI-based therapies, while highly effective and largely well-tolerated, have associated long-term toxicities, including lactic acidosis risks, bone and kidney changes [Carr, 2003]. As the population with HIV ages, new treatment options with fewer long-term toxicities are needed. Hence, the development of new safe and efficacious drugs continues, with individual profiles being evaluated within the context of combination treatment regimens.

Data available to date suggest that DTG is a drug that provides good efficacy with a high barrier to the development of resistance in INSTI-naïve subjects and is generally well tolerated [DTG IB, GSK Document Number RM2007/00683/10]. In addition, RPV

represents a favorable therapeutic option when considering the efficacy, safety, and tolerability as well as the convenience of once daily dosing with the potential for FDCs [RPV IB, 2017]. RPV has been assessed in simplification regimens including: 2 NRTIs + RPV in SPIRIT and an INSTI + RPV in LAI116482, both of which maintained virologic suppression [Palella, 2014; Margolis, 2015].

Similar efficacy was expected for the DTG/RPV FDC based on the activity of both DTG and RPV as individual agents, and is supported by the lack of antagonism when the anti-HIV activity for DTG + RPV in combination was tested in vitro [GSK Document Number 2015N229965_00]. These data are further supported by the lack of a drug-drug interaction between the approved doses of DTG (50 mg) and RPV (25 mg) (LAI116181) that are being developed as combination therapy for this HIV-1 infected, virologically suppressed patient population.

6.2. Benefits of DTG/RPV FDC in the Treatment of HIV-1 Infection

New therapeutic options that combine potency, tolerability and ease of use are needed for all sectors of the HIV population, including treatment-experienced adults. 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 small tablets; adherence benefits are important given that HIV is a lifelong, incurable infection.

DTG/RPV FDC is a 2-drug, NRTI-sparing regimen intended for the long-term treatment of HIV-1 infection. Based on the established efficacy, safety, tolerability, and combined resistance profiles of DTG and RPV and the 48 week data from the 2 large pivotal Phase III clinical studies (201636, 201637), DTG + RPV is an effective, and well tolerated regimen for the maintenance of HIV-1 suppression.

DTG/RPV FDC has distinct advantages over many of the current widely-used therapies as follows:

- Convenience of DTG and RPV in a small sized single tablet, which may help improve overall treatment adherence;
- Simplified 2-drug regimen with a known tolerability profile. The pivotal Phase III studies demonstrate that the SE tolerability profiles are confirmed for the FDC.
- No increased risk of ART resistance selection with the use of this novel 2-drug regimen identified in Studies 201636 and 201637;
- Targets HIV replication at the early and late stage of the virus life cycle resulting in good maintenance of viral suppression with a low risk of virologic failure;
- Once-daily dosing, without the need for a pharmacokinetic booster, which may significantly decrease possible drug interactions with concomitant drugs;
- Patients taking DTG/RPV FDC are predicted to have less risk of specific toxicities such as bone disorders from TDF, as was seen in the DEXA sub-study, and less risk from HSR than ABC.

- DTG and RPV have a generally favorable drug interaction profile with few clinically relevant interactions that require a dose adjustment, dose separation, or contraindication. Only the most significant CYP3A4 inducers, metal cations dosed in close proximity (DTG), and drugs affecting gastric pH (RPV) need management.
- As seen in Studies 201636 and 201637, subjects could be successfully "switched" to DTG + RPV, from a variety of ARV drug regimens, including enzyme inducing NNRTI-based regimens. Plasma concentrations of DTG and RPV during the immediate post-NNRTI switch period were sufficient to maintain virologic response.
- Demonstrated success in enrolled female subjects (22%) and subjects ≥50 years old (28%) (groups that have often been under-represented in clinical studies).
- Avoidance of long term exposure to the NRTI class of ART, and therefore may avoid known NRTI-associated adverse drug reactions, long-term toxicities, and NRTI-class related resistance. As a patient ages, avoiding drug classes that have been identified as potentially aggravating natural aging issues, such as cardiovascular risk, renal function decreases, and loss of bone mass, may be desirable.

The individual efficacy and safety profiles of DTG and RPV have been evaluated in the respective clinical programs, and supported a favorable risk-benefit profile.

6.3. Risks Associated with DTG/RPV FDC in the Treatment of HIV-1 Infection

Clinical studies have shown that there are no clinically significant interactions between DTG and RPV. There are no shared metabolism pathways between the components of DTG/RPV FDC, and no common target organs were identified in respective non-clinical studies. As such, there is no pharmacologic data that would predict increased safety risk for DTG/RPV FDC beyond that identified for the DTG and RPV SEs. The pivotal Phase III studies (201636, 201637) demonstrate that the SE tolerability profiles are confirmed for the FDC and there were no new AEs observed.

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

- As expected due to open label and treatment switch design elements, there was an imbalance between the treatment groups in incidence of AEs for the Week 48 analysis in Studies 201636 and 201637. A higher proportion of subjects who switched to DTG + RPV reported at least 1 AE overall. The current ART treatment group was stable on medication for at least 6 months prior to study entry; therefore, subjects were expected to tolerate continued treatment well without significant adverse effects. Conversely, it was anticipated that some subjects who initiated treatment with DTG + RPV might experience new AEs in line with the AE profile of DTG and RPV. These findings are consistent with those observed in the TRIUMEQ™ switch study (STRIIVING, 201147) [Trottier, 2017] and Complera/Eviplera switch study (SPIRIT, GS-US-264-0106) [Palella, 2014].
- Incidence of elevated liver chemistries in subjects treated with DTG/RPV FDC, including cases of hypersensitivity with liver involvement are predicted to be low.

There is no evidence of increased risk of hepatotoxicity from the DTG + RPV FDC over and above that of the SEs.

- There were no cases of hypersensitivity considered related to the DTG + RPV combination. HSR is an uncommon but manageable risk for DTG. From analysis of data from the DTG SE and DTG + RPV development program, the risk of hypersensitivity reaction with the DTG/RPV FDC is not expected to be any different from that observed with DTG.
- The incidence of insomnia in the DTG + RPV clinical program is less than that observed for ING114467 (SINGLE) [Walmsley, 2013] and in line with other Phase III/IIIb studies for DTG.
- No additional risk of depression or suicidal behaviors was observed in the DTG + RPV clinical program.
- As expected based on prior history of the SEs, no instances of DAIDS Grade 3, Grade 4, or serious skin reactions (including Stevens Johnson syndrome, Toxic Epidermal Necrolysis, or erythema multiforme), were seen with DTG + RPV or are expected with DTG/RPV FDC.
- Mild to moderate rash is an expected adverse reaction for DTG/RPV FDC. From the DTG + RPV data, episodes rarely required interruptions or discontinuations of therapy. From analysis of data from the DTG + RPV clinical development program, neither an additive nor synergistic effect on the risk of rash is expected when DTG and RPV are used in combination.
- Resistance may develop to any antiretroviral regimen, particularly in the setting of incomplete adherence to therapy. However, the risk of developing drug resistance in patients receiving DTG/RPV FDC is expected to be low since patients starting treatment will be virally suppressed, and taking only one component (monotherapy risk) would not be a factor for the FDC.

The safety profile seen for DTG + RPV in Studies 201636 and 201637 is consistent with current labelling and the established safety profile for DTG and RPV. There is no predicted additive or synergistic effect on the risk of hepatic disorders, psychiatric AEs, depression, or suicide in patients taking the DTG/RPV FDC tablet beyond that expected for the SEs. Data reported from publications describing over 400 patients using DTG and RPV together support the efficacy and safety profile observed in the Phase III trials.

6.4. Benefit-Risk Assessment

The individual efficacy and safety profiles of DTG and RPV have been evaluated in the SE clinical programs, and supported a favorable risk-benefit profile for their respective indications.

DTG + RPV demonstrated a high level of efficacy and was non-inferior in both of the individual studies (Studies 201636 and 201637), and in the pooled analyses in maintaining HIV-1 suppression, compared with staying on CAR, given as standard triple regimen at Week 48.

The 2-drug regimen of DTG + RPV was not found to increase risk of virological failure in the individual studies and the pooled study population, nor increase the finding of resistance development.

There are no expected additive or synergistic effects on the safety profile in patients taking DTG/RPV FDC beyond that expected for the SEs. The pivotal Phase III studies (201636, 201637) demonstrate that the SE tolerability profiles are confirmed for the FDC. The potential benefit of this 2-drug regimen is not downgraded by any newly identified risk associated with the use of these 2 agents.

As expected, there was an imbalance between the treatment groups in incidence of AEs for the Week 48 analysis. No clinically relevant differences were observed in laboratory abnormalities, both chemistry and hematology, between the DTG + RPV and current ART groups. The safety profile seen for DTG + RPV in Studies 201636 and 201637 is consistent with current labelling and the established safety profile for DTG and RPV. No new AEs were observed in Studies 201636 and 201637.

DTG/RPV FDC compared well with CAR in efficacy and tolerability. This NRTI sparing regimen has the potential to avoid long term exposure to this class of ART, and thereby possibly avoid NRTI-class related resistance, and longer term toxicities. As a small sized, once-daily tablet regimen, with a known tolerability profile and good maintenance of viral suppression with no increased risk of resistance, DTG/RPV FDC offers patients a novel 2-drug treatment option that was shown to be non-inferior to the current standard of care, 3-drug regimens.

There are no additive or synergistic effects expected on the safety profile in patients taking DTG/RPV FDC beyond those observed for the SEs and no new ADRs were identified in Studies 201636 and 201637.

6.5. Appendix

A descriptive approach was used to conduct the benefit-risk assessment. Therefore, no quantitative methods and results are presented.

7. REFERENCES

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APPENDIX – EXPLANATIONS FOR EMPTY MODULES

The following provides a brief justification for the absence of modules in Module 5.

Module	Title	Justification for Empty Module
5.1	Table of contents	eCTD Submitted
5.3.1.1	Bioavailability (BA) Study Reports	The absolute bioavailability of DTG + RPV has not been established. Comparative BA and BE study reports can be found in m5.3.1.2.
5.3.1.3	In Vitro - In Vivo Correlation Study Reports	No IVIVC studies were conducted for the FDC or the separate agents. The formulation development is supported by relative BA and BE studies. The in vitro dissolution data are presented in m2.7.1.
5.3.2.1	Plasma Protein Binding Study Reports	No plasma protein binding studies were conducted using DTG/RPV; however, plasma protein binding studies for DTG or RPV, including human samples can be found in m4.2.2.3.
5.3.2.3	Reports of Studies Using Other Human Biomaterials	Reports of studies using other human biomaterials are in m4.2.
5.3.3.2	Patient PK and Initial Tolerability Study Reports	There are no studies conducted with DTG/RPV FDC that would apply to this module. Data are available in the modules for separate entities.
5.3.3.5	Population PK Study Reports	No population PK reports are included. The pharmacokinetics of DTG and RPV were evaluated by non-population PK methodology.
5.3.5.2	Study Reports of Uncontrolled Clinical Studies	All studies conducted with DTG/RPV FDC were controlled studies, hence there are no reports of uncontrolled studies.
5.3.7	Case Report Forms and Individual Patient Listings	These will be provided upon request.