CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210192Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210192
Priority or Standard	Priority
Submit Date(s)	June 1, 2017
Received Date(s)	June 1, 2017
PDUFA Goal Date	December 1, 2017
Division/Office	DAVP/OAP
Review Completion Date	See DARRTS electronic signature page
Established Name	dolutegravir/rilpivirine
(Proposed) Trade Name	JULUCA
Pharmacologic Class	Dolutegravir is an integrase strand-transfer inhibitor (INSTI), and rilpivirine is a non-nucleoside reverse transcriptase inhibitors (NNRTI)
Applicant	ViiV
Formulation(s)	FDC Tablet
Dosing Regimen	dolutegravir 50 mg/rilpivirine 25 mg
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	JULUCA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of JULUCA.

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ARV	antiretroviral
BMD	Bone mineral density
BPCA	Best Pharmaceuticals for Children Act
cART	combination antiretroviral therapy
CCR5	C-C chemokine receptor type 5
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DAIDS	Division of AIDS
DAVP	Division of Antiviral Products
DBRUP	Division of Bone Reproductive and Urologic Products
DPV	Division of Pharmacovigilance
DMC	data monitoring committee
DTG	dolutegravir
ECG	electrocardiogram
eCTD	electronic common technical document
ES	Early Switch
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	fixed dose combination
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
HAART	Highly Active Antiretroviral therapy
HIV-1	human immunodeficiency virus type-1

ICH	International Conference on Harmonization
IND	Investigational New Drug
INSTI	integrase strand transfer inhibitors
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
ITT-E	intent-to-treat exposed
LS	late switch
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleos(t)ide reverse transcriptase inhibitor
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	protease inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RPV	rilpivirine
RT	reverse transcriptase
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event
TEADR	treatment emergent adverse reaction
US PI	US prescribing information
WHO	World Health Organization

1 Executive Summary Division Level Concurrence

1.1. Product Introduction

Juluca is a fixed dose combination (FDC) drug product containing dolutegravir (DTG) and rilpivirine (RPV). The individual drug products are approved for the treatment of HIV-1 infection in combination with other antiretroviral (ARV) drug products. DTG is an integrase strand transfer inhibitor (INSTI) of human immunodeficiency virus type-1 (HIV-1). DTG inhibits viral replication by blocking the integrase enzyme responsible for insertion of viral genome into host cell DNA. RPV is a nonnucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. RPV binds directly to reverse transcriptase (RT) and blocks the DNA polymerase activities by causing a disruption of the enzyme's catalytic site. In addition to a relative BA study, a BE study was conducted to establish the bioequivalence of DTG/RPV FDC product to the individual drug products.

Established name:	Dolutegravir, rilpivirine
Trade name:	Juluca
Chemical class:	Non-new molecular entity (non-NME)
Pharmacologic class:	Fixed dose combination (FDC) product containing an integrase strand transfer inhibitor and a non-nucleoside reverse transcriptase inhibitor
Proposed indication:	Juluca is indicated for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) (b) (4) (b) (4)
Dosage form:	Tablet (DTG 50mg/RPV 25mg)
Dose and regimen:	One tablet once daily

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness required by law as defined in 21 CFR 314.126(a)(b), to support approval of Juluca for the treatment of HIV infection (see Section 7.3 for further detail). Juluca is an FDC product containing DTG and RPV. Non-inferiority was met between Juluca and 3-drug regimens containing either a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an INSTI in combination with two nucleoside (tide) reverse transcriptase inhibitors (NRTIs) in adults who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least six months with no history of treatment failure and no known substitutions associated

with resistance to DTG or RPV. The efficacy of DTG + RPV was demonstrated in two identical 48-week, open-label, randomized, active-controlled, non-inferiority trials, SWORD-1 (201636; NCT02429791) and SWORD-2 (201637; NCT02422797). At Week 48, the NI margin based on the Division's preferred primary endpoint for switch trials (proportion of subjects who were virologic failures (HIV-1 RNA $\geq$ 50 copies/mL)) was met. The pre-specified NI margin was 4%. At Week 48, the proportion of subjects who were virologic failures was 0.6% and 1% in the DTG+RPV and CAR treatment groups, respectively [adjusted treatment difference and 95% CI: -0.6 (-1.7%, 0.6%)]. Additionally, in the pooled analysis, the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 95% in the DTG+RPV treatment group and the current antiretroviral regimen (CAR) group [adjusted treatment difference and 95% CI: -0.2% (-3.0%, 2.5%)].

In addition to a relative BA study, a BE study was conducted establishing the bioequivalence of Juluca to the individual drug products, DTG and RPV. Therefore, the two trials conducted using the individual drug products supports the approval of Juluca, an FDC product containing DTG and RPV.

1.3 Overall Conclusions and Recommendation

Approval of Juluca is recommended as a complete ARV regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of virologic failure or no known substitutions associated with resistance to either DTG or RPV. This recommendation is based on the findings from two, identical Phase 3, open-label, randomized active-controlled trials, SWORD-1 and SWORD-2. The results from the trials support an acceptable risk-benefit assessment for use DTG/RPV as a two-drug complete ARV regimen.

The pre-specified non-inferiority margin of 4% based on HIV RNA $\geq$ 50 copies/mL was met. At Week 48, in the pooled analyses from SWORD-1 and SWORD-2, the proportion of subjects with HIV RNA $\geq$ 50 copies/mL was 0.6% and 1% in the DTG+RPV and CAR treatment groups, respectively [adjusted treatment difference and 95% CI: -0.6 (-1.7%, 0.6%)]. Additionally, overall 95% of subjects in both treatment groups maintained viral suppression through 48 weeks of treatment. The proportion of subjects with HIV RNA <50 copies at Week 48 was 95% in the DTG+RPV treatment group and CAR treatment group [adjusted treatment difference and 95% CI: -0.2% (-3.0%, 2.5%)].

The overall safety profile from the pooled analyses demonstrated an acceptable safety profile No new safety findings were apparent from the pooled analyses. The adverse reactions observed during SWORD-1 and SWORD-2 were generally similar to those observed during the development programs for DTG and RPV. Based on the pooled 48-weeks data analysis for SWORD-1 and SWORD-2, subjects who switched to DTG+RPV at baseline experienced adverse

reactions more frequency than subjects who stayed on their CAR (19% vs. 2%). More subjects in the DTG+RPV treatment group also discontinued due to adverse events compared to CAR treatment group (4% vs. <1%). However, the proportion of subjects with serious adverse events was similar between the two treatment groups. Of note, a higher incidence of adverse reactions in the DTG+RPV treatment group was expected because subjects randomized to the DTG+ RPV treatment group were initiating a new regimen and thus will experience new adverse reactions or tolerability issues. Whereas subjects randomized to continue CAR are less likely to experience new adverse reactions because they have been on their current regimen for at least 6 months prior to enrollment. Therefore, an increase in overall reported adverse reactions soon after switching to DTG+RPV regimen does not necessarily mean that DTG+RPV is a less tolerated regimen.

The proposed label, with modifications as proposed by the review team, should allow for the safe and effective use of Juluca in the intended population for the treatment of HIV-1 infection.

2 Therapeutic Context

2.1. Analysis of Condition

According to the WHO, approximately 37 million people were living with HIV globally in 2015, including 1.8 million children who are less than 15 years of age. As reported by the CDC, by the end of 2014, the number of persons living in the United States with diagnosed HIV infection was 955,081. In 2015, the number of new HIV diagnoses in the United States was 39,513. Currently, effective treatment of HIV-1 infection for treatment-naïve or treatment-experienced patients without history of virologic failure comprises of combination antiretroviral therapy with at least 3 antiretroviral (ARV) medications, two of which belong in the nucleos(t)ide reverse transcriptase inhibitor (NRTI) class. The third agent is selected from an integrase strand transfer inhibitors (INSTI), protease inhibitors (PI), or non-nucleoside reverse transcriptase inhibitors (NNRTI) class.

Treatment of HIV infection has dramatically improved since the mid-1990s, after the introduction of use of highly active antiretroviral drugs therapy (HAART). Despite such progress, there is a continued need for development of new ARV drug products, new fixed dose combination (FDC) products, and new regimens because of the ongoing epidemic in certain parts of the world or the need for better tolerated regimens. The introduction of FDC drug products has allowed for simpler ARV regimens, increasing the likelihood of adherence and thereby improving treatment outcomes. Availability of new regimens such as FDC products has also allowed patients to be able to switch if they are not tolerating their current regimens or have 'pill fatigue' due to multiple pill regimens. For example, according to a publication by the Antiretroviral Therapy Cohort Collaboration (2013), among the 21,000+ patients in a European and North American cohort who are on their first combination antiretroviral therapy (cART)

regimen, more than half modified or interrupted their first cART regimen either due to adverse events or toxicities of cART, desire for simplification of the regimen, or due to patient choice. These observations suggest that there is a need for continued development of new products and/or regimens.

2.2. Analysis of Current Treatment Options

Currently 27 drugs are approved for the treatment of HIV infection in the adult populations (excluding fixed dose combination products). As shown in

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Table 1, approved drugs belong to six mechanistic classes namely, NRTI, NNRTI, PI, INSTI, CCR5 antagonist, and fusion/entry inhibitor. The current standard of care for patients with HIV-1 infection who are treatment-naïve or without significant history of virologic failure or resistance is a 3-drug regimen containing INSTI, PI or NNRTI, plus 2 NRTIs.

Juluca is the first FDC to receive approval recommendation as complete regimen only requiring two drugs for the treatment of HIV-1 in virologically suppressed adults. Juluca is an effective two drug NRTI-sparing regimen and differs from the current standard of care which typically includes two NRTIs plus a PI, NNRTI or INSTI.

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Table 1 Currently Approved ARV Drugs for the Treatment of HIV Infection

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx EC®
	Zalcitabine (ddC)	Hivid®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir disoproxil fumarate (TDF)	Viread®
	Tenofovir alafenamide (TAF)[1]	
	Emtricitabine (FTC)	Emtriva®
NNRTI	Nevirapine (NVP)	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine (ETR)	Intelence®
	Rilpivirine (RPV)	Edurant®
PI	Indinavir (IDV)	Crixivan®
	Nelfinavir	Viracept®
	Saquinavir, (hard gel, soft gel)	Invirase®, Fortavase®
	Fosamprenavir (FPV)	Lexiva®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Atazanavir (ATV)	Reyataz®
	Darunavir (DRV)	Prezista®
	Tipranavir	Aptivus®
Integrase Inhibitor	Raltegravir (RAL)	Isentress®
	Elvitegravir[2]	
	Dolutegravir (DTG)	Tivicay®
CCR5 receptor antagonist	Maraviroc (MVC)	Selzentry®
Fusion/entry Inhibitor	Enfuvirtide (T-20)	Fuzeon®
Pharmacokinetic Enhancers[3]	Ritonavir (r)	Norvir®
	Cobicistat (cobi)[4]	

*Please refer to the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents for discussions on the safety and efficacy evidence considered for recommending preferred regimens in treatment-naïve patients.
[1]TAF is approved for the treatment of HIV infection as part of FDC products - Descovy (FTC/TAF), Odefsey (FTC/RPV/TAF), and Genvoya (elvitegravir/cobicistat/FTC/TAF). The single agent TAF (Vemlidy) is indicted for the treatment of chronic Hepatitis B.
[2] Elvitegravir is approved as part of FDC product only- Stribild (elvitegravir/cobicistat/FTC/TDF), Genvoya (elvitegravir/cobicistat/FTC/TAF).
[3] Pharmacokinetic enhancers do not have direct antiviral activity
[4] Cobicistat is approved as part of FDC products- Genvoya, Prezcobix (darunavir/cobi) and Evotaz (atazanavir/cobi)

Per the Department of Health and Human Services Guidelines for Use of Antiretroviral Agens in Adults and Adolescents Living with HIV the following is recommended, alternative and other antiretroviral options for treatment-naïve patients.

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI + 2 NRTIs:

- DTG/ABC/3TC[a] **(AI)**—if HLA-B*5701 negative
- DTG + tenofovir[b]/FTC[a] (**AI** for both TAF/FTC and TDF/FTC)
- EVG/c/tenofovir[b]/FTC (**AI** for both TAF/FTC and TDF/FTC)
- RAL[c] + tenofovir[b]/FTC[a] (**AI** for TDF/FTC, **AII** for TAF/FTC)

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred

Boosted PI + 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) + tenofovir[b]/FTC[a] (**AI** for DRV/r and **AII** for DRV/c)
- (ATV/c or ATV/r) + tenofovir[b]/FTC[a] **(BI)**
- (DRV/c or DRV/r) + ABC/3TC[a] **—if HLA-B*5701–negative (BII)**
- (ATV/c or ATV/r) + ABC/3TC[a] **—if HLA-B*5701–negative and HIV RNA <100,000 copies/mL** (**CI** for ATV/r and **CIII** for ATV/c)

NNRTI + 2 NRTIs:

- EFV + tenofovir[b]/FTC[a] (**BI** for EFV/TDF/FTC and **BII** for EFV + TAF/FTC)
- RPV/tenofovir[b]/FTC[a] **(BI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**

INSTI + 2 NRTIs:

- RAL[c] + ABC/3TC[a] **(CII)—if HLA-B*5701–negative and HIV RNA < 100,000 copies/mL**

Recommended Initial Regimens for Most People with HIV
Regimens to Consider when ABC, TAF, and TDF Cannot be Used:[d] • DRV/r + RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm³** • LPV/r + 3TC[a] (BID)[e] **(CI)**

[a] 3TC may be substituted for FTC, or vice versa, if a non–fixed-dose NRTI combination is desired.
[b] TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.
[c] RAL can be given as 400 mg BID or 1200 mg (two 600-mg tablets) once daily.
[d] Several other NRTI-limiting treatment strategies are under investigation. See the section titled Selected Strategies That Are Under Evaluation and Not Yet Recommended below for discussion regarding these regimens.
[e] LPV/r plus 3TC is the only boosted PI plus 3TC regimen with published 48-week data in a randomized controlled trial in ART-naive patients. Limitations of LPV/r plus 3TC include twice-daily dosing, high pill burden, and greater rates of gastrointestinal side effects than other PIs

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Juluca is not marketed in the United States.

Edurant (rilpivirine; a NNRTI) tablet, 25 mg received FDA approval on May 20, 2011 and is currently indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients with HIV-1 RNA less than or equal to 100, 000 copies/mL.

Tivicay (dolutegravir; an INSTI) tablet, 50 mg received FDA approval on August 12, 2013 and is currently indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 30 kg.

3.2. Summary of Pre-submission/Submission Regulatory Activity

IND 123306 for GSK336579 (dolutegravir and rilpivirine) FDC tablet was originally submitted by ViiV Healthcare as a Pre-IND in July, 2014. At the time the Sponsor requested advice on their proposed plan to develop dolutegravir and rilpivirine FDC tablet as a complete regimen for the treatment of HIV-1 infection in adult patients who are virologically suppressed (b) (4) DAVP provided advice on their discipline specific questions, and on the pivotal bioequivalence study which DAVP recommended be conducted in both the

fed and fasted states. In addition, the Sponsor was advised to demonstrate durability of the regimen over a minimum of 48-week period, with possibility of additional week 96 data being requested. In addition, for the pooled analyses, the Agency and the Sponsor agreed (IND123306: End of Phase 2 Responses of 09 January 2015) that a NI margin of -8% would be used to support the noninferiority of DTG +RPV FDC tablet with respect to CAR. DAVP reminded the Sponsor of the Division's preferred endpoint for switch trials per the Guidance for Industry. A noninferiority margin of 4% should be met based on HIV RNA $\geq$ 50 copies/mL. DAVP will use this endpoint and noninferiority margin when assessing efficacy. DAVP will also review the proportion of subjects who maintain HIV RNA < 50 copies/mL though Week 48. DAVP also agreed with the Sponsor that they could continue FDC formulation development under IND 75382 (dolutegravir), and once an appropriate formulation was developed they could submit an original IND (123306) under which they would conduct their pivotal BE and other relevant studies.

In March, 2016 the Sponsor submitted a new IND to initiate the relative BE study. The purpose of the BE study 201767 was to demonstrate that the exposures from the FDC product are similar to the individual products. In addition, under IND 75382 with cross-reference to IND 123306, the Sponsor conducted two identical global multicenter, randomized parallel group, non-inferiority studies (201636 and 201637), evaluating the efficacy, safety and tolerability of switching to dolutegravir plus rilpivirine from current INSTI-, NNRTI-, or PI-based regimens in adults who were virologically suppressed.

In February 2017, the Sponsor requested a pre-NDA meeting to discuss the content and format of a new drug application (NDA) for the FDC tablet. The Sponsor also notified the Agency of their intent to utilize a Rare Pediatric Disease Priority Review Voucher for a priority review of their NDA application. In advance of the meeting, Preliminary Comments were sent to the Sponsor on March 17, 2017 and was followed by a teleconference on March 22, 2017. In the Preliminary Comments, DAVP agreed to receiving more complete resistance data on one subject within 30 days of the NDA submission, and agreed to the Sponsor's proposed timeline for submitting the required Safety Update Report.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

FDA's Division of Scientific Investigations (DSI) performed clinical site inspections of five clinical trial sites enrolling subjects in the phase 3 trials. The DSI inspections of medical records did not raise concern regarding data integrity and data from these sites were determined as acceptable. Please refer to the DSI clinical inspection summary for NDA 210192 for details. Bioanalytical site inspections for the RBA/BE studies were also conducted by the Division of

New Drug Bioequivalence Evaluation in the Office of Study Integrity and Surveillance. A routine inspection of (b) (4) was conducted. No significant deficiencies were observed and no Form FDA 483 was issued. No significant outstanding manufacturing or facility risks were identified. The manufacturing facilities were found acceptable. Please refer to Product Quality, Facilities review for further details.

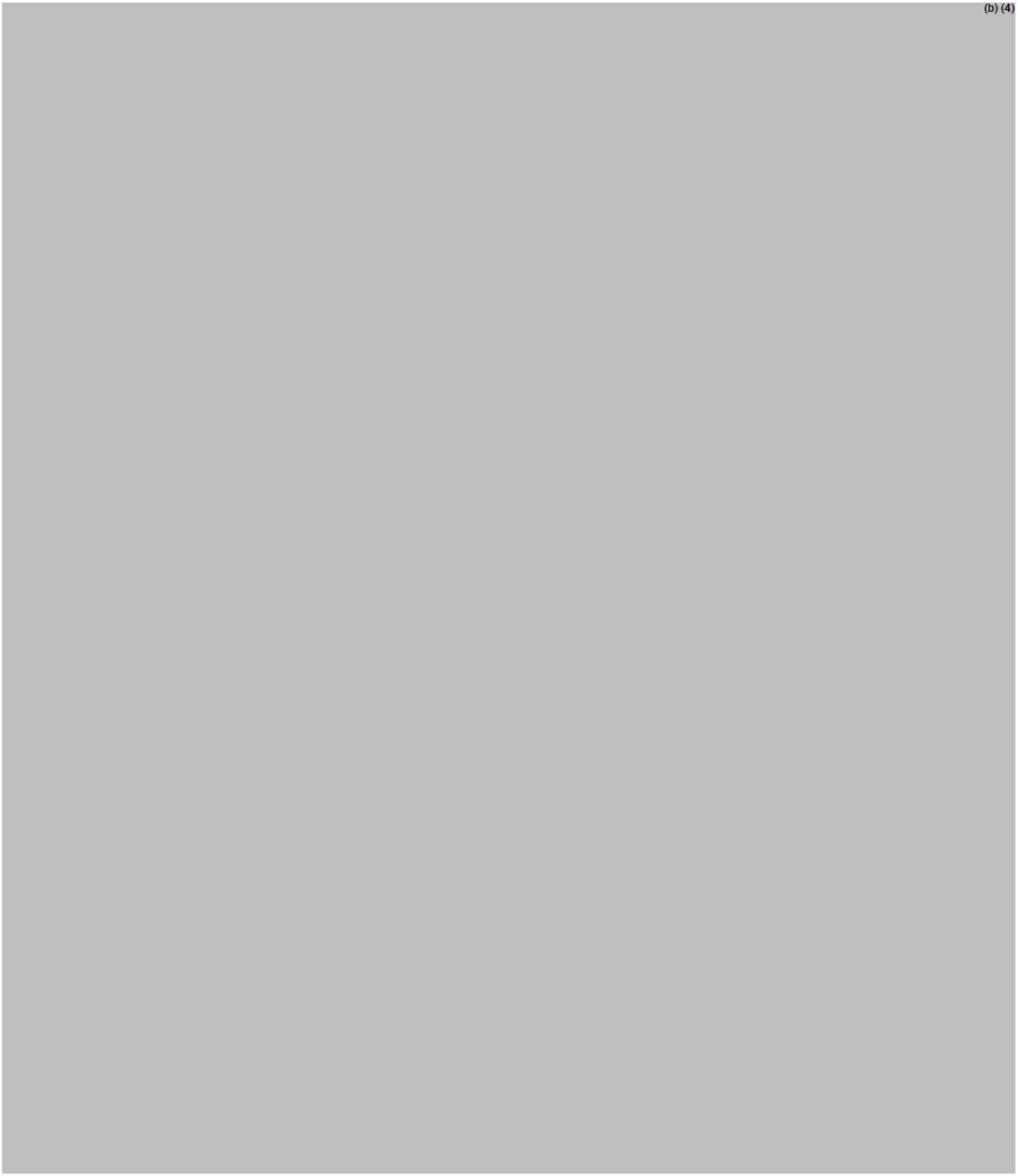
4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

DTG/RPV fixed-dose combination tablets are an immediate-release oral dosage form containing 52.6 mg of dolutegravir sodium (equivalent to 50 mg DTG) and 27.5 mg of rilpivirine hydrochloride (equivalent to 25 mg RPV). The tablets are pink, film coated, oval (approximately 14 x 7 mm), and biconvex with 'SV J3T' debossed on one face. (b) (4) The quantitative composition of the tablets is listed in the sponsor's table below. See FDA product quality review for additional details.

Table 2 Quantitative Composition of JULUCA™ (DTG/RPV) Tablets

(b) (4)



5 Nonclinical Pharmacology/Toxicology

Prior approvals for DTG and RPV included comprehensive nonclinical packages. In agreement with ICH Guidance M3 (R2), nonclinical combination studies were not conducted with DTG/RPV, except for a combination pharmacokinetic study in dogs, to determine any potential effects of co-administration.

Systemic Exposure of Dolutegravir and Rilpivirine Following Oral Administration of Fixed-Dose Combination Tablet Formulations in the Beagle Dog Under Fed and Fasted Conditions (15EDS002 or 2015N239161)

To compare the relative bioavailability of DTG and RPV when administered as a fixed-dose combination, male beagle dogs (n=3) were administered each dose orally during fed or fasting using a 5-way randomized crossover design. Each dog received

- Control (A dosing regimen that included 2 individual tablets co-dosed under fasting conditions: Tivicay lot 132376073 [Dolutegravir/GSK1349572, 50mg] and Edurant lot DCL5401/GSK COMET Lot 132378251 [Rilpivirine/GSK1329758, 25mg]),
- Formulation C (b) (4) and
- Formulation (b) (4)

with a minimum 10-day washout period. Due to facility constraints, 3 additional dogs received control under fed conditions. As the study was done non-GLP and had specific objectives, general safety was not described. It does not appear that the dogs had any significant adverse events during the study. The sponsor's tables below contain plasma pharmacokinetic parameters for DTG and RPV, respectively. While there does not appear to be an effect of a fixed dose formulation on exposure compared to a dual regimen, results indicated a food effect: an approximate 3 to 9-fold increase in exposure of DTG and an approximate 4 to 19-fold increase in exposure of RPV.

Table 3 Summary of Plasma DTG Pharmacokinetic Parameters Following Administration of DTG/RPV Formulations

Mean Plasma Pharmacokinetic Parameters [Range]						
Analyte	**Dose (mg)**	**Formulation (TX) [a]**	**T_{max} [b] (h)**	**C_{max} (ng/mL)**	**AUC_{0-t} (ng.h/mL)**	**% Relative Bioavailbility [c]**
Dolutegravir	50	A, Fasted	1.0 [0.5 – 3.0]	473 [303 – 572]	1690 [1480 – 2030]	
Dolutegravir	50	A, Fed	2.0 [1.0 – 5.0]	3160 [2740 – 3420]	10800 [9500 – 12600]	642
Dolutegravir	50	C, Fasted	1.0 [0.5 – 1.0]	411 [327 – 517]	1200 [764 – 1490]	
Dolutegravir	50	C, Fed	1.0 [1.0 – 1.0]	3600 [2830 – 4220]	9140 [6760 – 11600]	758
Dolutegravir	50	D, Fasted	1.0 [1.0 – 3.0]	825 [327 – 1460]	2860 [1320 – 5010]	
Dolutegravir	50	D, Fed	1.0 [0.5 – 2.0]	3440 [3110 – 3750]	10500 [8770 – 13200]	368

a. Values are n=3
b. Values are mean [range] except for T_{max} which is shown as median [range].
c. % Relative bioavailability calculated as mean AUC_{Fed}/AUC_{Fasted} x 100

Table 4 Summary of Plasma RPV Pharmacokinetic Parameters Following Administration of DTG/RPV Formulations

Mean Plasma Pharmacokinetic Parameters [Range]						
Analyte	**Dose (mg)**	**Formulation (TX) [a]**	**T_{max} [b] (h)**	**C_{max} (ng/mL)**	**AUC_{0-t} (ng.h/mL)**	**% Relative Bioavailbility [c]**
Rilpivirine	**25**	A, Fasted	2.0 [1.0 – 2.0]	37.0 [10.2 – 54.3]	1040 [176 – 1610]	
Rilpivirine	**25**	A, Fed	4.0 [3.0 – 4.0]	395 [361 – 439]	18200 [14200 – 23300]	1740
Rilpivirine	**25**	C, Fasted	1.0 [0.5 – 2.0]	21.0 [8.5 – 36.2]	450 [131 – 636]	
Rilpivirine	**25**	C, Fed	1.0 [1.0 – 1.0]	320 [262 – 365]	8720 [5620 – 12100]	1940
Rilpivirine	**25**	D, Fasted	1.0 [1.0 – 2.0]	61.6 [15.9 – 147]	2860 [464 – 3010]	
Rilpivirine	**25**	D, Fed	2.0 [1.0 – 2.0]	420 [325 – 493]	12200 [8830 – 18600]	906

a. Values are n=3
b. Values are mean [range] except for T_{max} which is shown as median [range].
c. % Relative bioavailability calculated as mean AUC_{Fed}/AUC_{Fasted} x 100

Recommendation: The nonclinical package supports approval of JULUCA. Similar findings of increased exposure with food were observed in clinical trials, see **Clinical Pharmacology**.

6 Clinical Pharmacology

The Applicant submitted the following clinical pharmacology data to support the approval of JULUCA.

1. Bioequivalence trial to compare the DTG and RPV pharmacokinetics of the formulations used in Phase 3 trials (single entity products of DTG and RPV) and the to-be-marketed formulation (fixed dose combination product)
2. Pilot food effect and relative bioavailability study
3. Analysis using sparse PK samples collected in Phase 3 trials
   - Comparison to historical data
   - Exposure-response relationship for efficacy and safety
   - Residual induction effects of efavirenz and nevirapine on DTG and RPV during the initial switching phase

The application is approvable from a clinical pharmacology perspective. The key study design, results, and review issues for each study are summarized in following sections.

1. Pivotal relative bioavailability trial (Study 201676)

This was an open-label, randomized, 2-period, 2-treatment, crossover trial to evaluate the relative bioavailability of single entity products of DTG and RPV (used in SWORD-1 and SWORD-2 trials) and the to-be-marketed formulation, a fixed dose combination tablet containing 50 mg DTG and 25 mg RPV in 113 healthy adult subjects.

The single entity products and the final to-be-marketed formulation were bioequivalent under moderate fat conditions. The test to reference ratios of geometric means with corresponding 90% CI for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the predefined range, 80-125%. Overall, the study design, results, and conclusion are acceptable from a clinical pharmacology perspective. The results are summarized in **Table 5**.

Table 5 Summary of Statistical Analysis of DTG and RPV PK Parameters of Test and Reference Products

	DTG (n=113)			RPV (n=113)		
	Test	Reference	Ratio	Test	Reference	Ratio
C_{max} (µg/mL)	3.65 (3.53-3.77)	3.47 (3.36-3.60)	1.05 (1.02-1.08)	0.093 (0.087-0.101)	0.083 (0.078-0.089)	1.12 (1.05-1.21)
AUC_t (µg/mL·hr)	63.6 (60.7-66.6)	61.3 (58.5-64.2)	1.04 (1.01-1.07)	3.06 (2.84-3.30)	2.77 (2.56-3.99)	1.11 (1.04-1.18)
AUC_{inf} (µg/mL·hr)	65.0 (62.1-68.0)	62.7 (59.8-65.6)	1.04 (1.01-1.06)	3.25 (3.02-3.51)	2.93 (2.71-3.17)	1.11 (1.05-1.17)

Test: JULUCA FDC; Reference: single entity products (DTG 50 mg + RPV 25 mg)
For C_{max} and AUC values, data are expressed as geometric mean (95% CI)
For the ratio of test to reference PK parameters, data are expressed as ratio (90% CI)
Data source: Applicant's CSR. The reviewer's reanalysis confirmed the bioequivalence of the two formulations

2. Pilot food effects and relative bioavailability study (study 201674)

This was a Phase I, 2-part food effect and relative bioavailability study of different FDCs of DTG and RPV (AS, AM, AQ, AU and AK formulations) and single entity products of DTG 50 mg and RPV 25 mg in fasted and fed healthy subjects. Of note, the final to-be-marketed formulation, the AW formulation, was not evaluated in this trial. The sponsor stated that the AM formulation is identical to the AW formulation (b) (4) Therefore, this review is focused on the food effect and relative bioavailability of the AM formulation only and food effect on the AS, AQ, AU and AK formulations are not discussed here.

The PK parameters of DTG and RPV were compared between the single entity products and the AM formulation under high fat conditions (Part 1) and fasted conditions (Part 2). In addition, the PK parameters of DTG and RPV were compared between fasted and moderate-fat conditions following the administration of a single dose FDC (**Table 6**).

The following conclusions were made from the results of this study.

1. Under high fat conditions, C_{max} and AUC values of DTG and RPV were comparable between single entity products and the AM formulation.
2. Under fasting conditions, C_{max} and AUC values of DTG and RPV were comparable between single entity products and the AM formulation.
3. The AUC_{inf} of DTG and RPV is increased by approximately 86% and 57%, respectively, under moderate fat conditions as compared to fasted conditions following the administration of the AM formulation.
4. Based on cross-cohort comparison conducted in different subjects, there is no significant difference in RPV and DTG exposures under high fat conditions as compared to moderate fat conditions.

Table 6 Summary of DTG and RPV PK Parameters Under Fasting and Fed Conditions

Prandial conditions	PK parameters	DTG		RPV	
		Single entity	FDC	Single entity	FDC
Fasting (n=12)	C_{max} (µg/mL)	2.20 (50%)	1.94 (67%)	0.049 (75%)	0.050 (77%)
	AUC_{inf} (µg/mL·hr)	39.7 (46%)	34.6 (53%)	2.18 (65%)	2.23 (71%)
Moderate fat (n=12)	C_{max} (µg/mL)	N/A	3.38 (21%)	N/A	0.095 (33%)
	AUC_{inf} (µg/mL·hr)	N/A	64.6 (22%)	N/A	3.51 (43%)
High fat (n=12*)	C_{max} (µg/mL)	3.33 (21%)	3.37 (19%)	0.094 (28%)	0.099 (32%)
	AUC_{inf} (µg/mL·hr)	56.1 (24%)	61.8 (28%)	3.43 (49%)	3.74 (39%)

Data source: reviewer's analysis, CSR 201674- Other Data Listings
Data are expressed as geometric mean (%CV)
Fasting and moderate fat conditions were evaluated in Part 2 in the same subjects while high fat condition was evaluated in part 1.
*:N=11 for RPV; Subject 118 data were excluded from the analysis because > 40% of AUC was extrapolated.
FDC = AM formulation
N/A = Not assessed

3. Pharmacokinetic data collected in SWORD-1 and SWORD-2

A. Comparison to historical data

In SWORD-1 and SWORD-2, two separate predose PK samples were collected out of the following four time points: Weeks 4, 24, 48, or at the Withdrawal visit in HIV patients. The predose concentrations of DTG and RPV observed in SWORD-1 and SWORD-2 were comparable to historical data listed in EDURANT and TIVICAY USPIs (**Table 7**). The slightly higher DTG exposure observed in SWORD-1 and SWORD-2 is possibly due to food effects; DTG was administered under fed conditions only in SWORD-1 and SWORD-2 while it was administered without regard to food in the original clinical trials supporting TIVICAY labeling.

Table 7 Pre-Dose Concentrations Observed in SWORD-1 and SWORD-2

	SWORD-1 and SWORD-2	Individual product's USPI
DTG C_0	1.41 µg/mL	1.11 µg/mL
RPV C_0	80.1 ng/mL	80 ng/mL

Data expressed as geometric mean (CV%)
Data source: reviewer's analysis - PK dataset of CSR 201636 and 201637

B. Exposure-response relationship for efficacy

Exposure-response relationship between predose concentrations of DTG and RPV and efficacy (% responders by Snapshot at Week 48) was explored. The proportion of responders was 92% and above across the predose concentration quartiles and no exposure-response relationship was observed for either DTG or RPV (**Figure 1**).

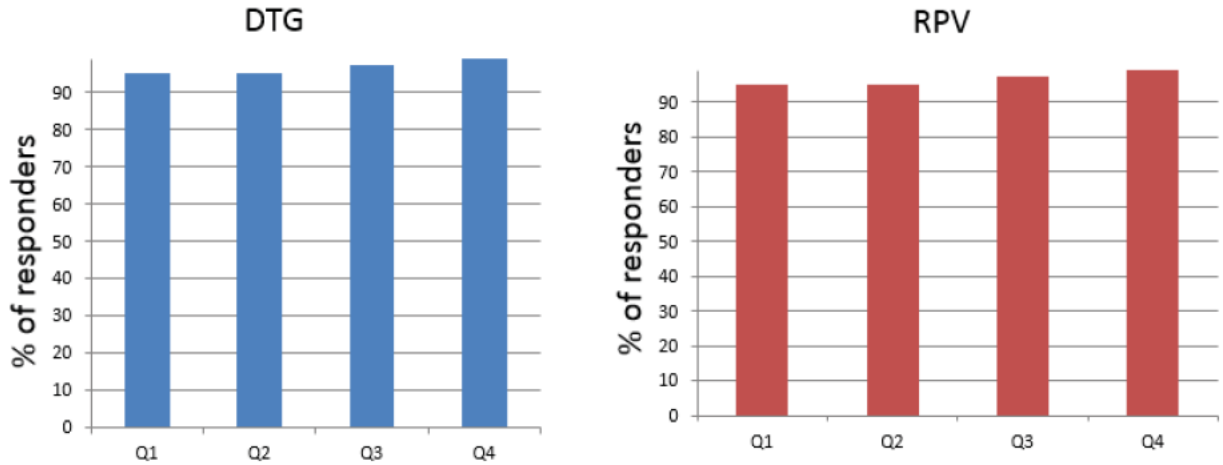


Figure 1 Percent of Snapshot Virologic Response at Week 48 by DTG and RPV Pre-Dose Concentration Quartile in SWORD-1 and SWORD-2

Data source: reviewer's analysis - PK dataset of CSR 201636 and 201637
DTG predose concentrations (range, median): Q1 (0.19-0.96 µg/mL, 0.78 µg/mL); Q2 (0.96-1.4 µg/mL, 1.2 µg/mL); Q3 (1.4-2.2 µg/mL, 1.7 µg/mL); Q4 (2.1-5.5 µg/mL, 2.7 µg/mL)
RPV predose concentrations (range, median): Q1 (19-61 ng/mL, 50 ng/mL); Q2 (61-80 ng/mL, 70 ng/mL); Q3 (80-107 ng/mL, 91 ng/mL); Q4 (107-615, 134 ng/mL)

In addition, predose concentrations were evaluated in 5 subjects who met the virologic failure criteria (b) (6). In those patients, predose concentrations of DTG and RPV were not lower than the mean predose concentrations of DTG and RPV observed in SWORD-1 and SWORD-2. However, the interpretation of this finding is limited as concentrations were measured only at Week 4, 24, or withdrawal visits, thus it may not capture overall adherence or drug concentrations throughout the study period (**Table 8**).

Table 8 Pre-Dose Concentrations of DTG and RPV in Patients Who Met Virologic Failure Criteria

Subject ID	Week 4	Week 24	Withdrawal	Reference
(b) (6)	**DTG: 2.4 µg/mL RPV: 102 ng/mL**	**DTG: 2.3 µg/mL RPV: 110 ng/mL**	At Week 24	Geometric mean C_0 in SWORD-1 and SWORD-2 **DTG: 1.4 µg/mL RPV: 80 ng/mL**
	DTG:2.3 µg/mL RPV: 71 ng/mL	**DTG: 2.6 µg/mL RPV: 81 ng/mL**	At Week 36	
	NA	NA	At Week 64 **DTG: 3.0 ng/mL RPV: 169 ng/mL**	
	NA	NA	At Week 64	
	NA	NA	At Week 36	

Data source: reviewer's analysis - PK dataset of CSR 201636 and 201637
*: Late phase switch
#: PK samples were collected at 10-12 hours post dose in both Week 4 and 24.
Week 4: DTG 7.6 µg/mL and RPV 170 ng/mL at 10 hours post dose
Week 24: DTG 5.7 µg/mL and RPV 218 ng/mL at 12 hours post dose

C. Exposure-response relationship for safety

The exposure-response relationship between predose concentrations and safety endpoints were explored. No meaningful associations between DTG or RPV exposures and safety parameters were observed for common adverse events (back pain, diarrhea, headache, nasopharyngitis, and upper respiratory infection) and laboratory parameters (serum creatinine, GFR, urine albumin/creatinine, ALT, bilirubin, LDL, and HDL).

D. Residual induction effects of efavirenz and nevirapine on the pharmacokinetics of DTG and RPV.

DTG and RPV are substrates of CYP3A and their concentrations are significantly decreased by coadministration of CYP3A inducers such as rifampin or efavirenz. DTG and RPV concentrations are expected to be lower in the first couple of weeks in patients who switched from regimens containing metabolic inducers (e.g., nevirapine, efavirenz) to DTG and RPV. This is due to the slow kinetics of CYP3A enzyme degradation after the discontinuation of inducers. The residual induction effects can last for several weeks even if inducers are no longer detected in plasma.

In SWORD-1 and SWORD-2, a total of 242 subjects were switched from inducer-containing regimens (efavirenz, nevirapine or etravirine) to DTG/RPV. Among these subjects, approximately 40 patients provided additional pre-dose samples at Week 2 and Week 8 to determine of the effects of residual induction on DTG and RPV concentrations.

Residual induction effects were observed in patients who switched from inducer-containing regimens to DTG/RPV at Week 2 in SWORD-1 and SWORD-2 (**Table 9**); DTG and RPV C_0 concentrations were lower than C_0 concentrations by 46% and 25%, respectively, compared to those observed at Week 24. The residual effects became minimal by Week 8. In addition, at Week 4, DTG and RPV predose concentrations were comparable between patients who switched from inducers (NNRTIs) and non-inducers (non-NNRTIs), as summarized in **Table 10**.

Overall, lower DTG and RPV concentrations during the initial switch phase are not considered clinically relevant; in SWORD-1 and SWORD-2, 2 out of 242 patients who switched from an inducer-containing regimen and 3 out of 271 patients who switched from a non-inducer containing regimen met the virologic failure criteria.

It should be noted that this conclusion is specific to the setting of switching to DTG/RPV from an existing antiretroviral regimen that contains a CYP3A inducer in already virologically suppressed HIV patients. Depending on the exact CYP3A inducer (i.e., others not studied in this trial) and whether patients are virologically suppressed or not, residual induction effects may become clinically relevant.

Table 9 Pre-Dose Concentrations of DTG and RPV in Subjects Who Switched from Efavirenz or Nevirapine and Who Provided Extra Sampling

	Week 2 N=35	Week 4 N=41	Week 8 N=45	Week 24 N=48
DTG (µg/mL)	0.69 (0.56-0.84)	0.92 (0.75-1.12)	1.24 (0.99-1.53)	1.31 (1.05-1.63)
RPV (ng/mL)	53.9 (45.0-64.5)	66.8 (57.8-77.2)	69.3 (58.8-81.5)	76.2 (66.7-87.1)

Data are expressed as geometric mean (90% CI)
Data source: reviewer's analysis - PK dataset of CSR 201636 and 201637

Table 10 Pre-Dose Concentrations of DTG and RPV at Week 4 by Prior Regimen Types

	NNRTI N=149	Non-NNRTI N=157
DTG (µg/mL)	1.19 (1.07-1.33)	1.33 (1.21-1.46)
RPV (ng/mL)	68.9 (63.5-74.7)	75.9 (68.3-81.5)

Data are expressed as geometric mean (90% CI)
Data source: reviewer's analysis - PK dataset of CSR 201636 and 201637

7 Statistical and Clinical Evaluation of Efficacy

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 11 summarizes the clinical trials conducted in support of approval for Juluca.

- Two pivotal clinical trials were conducted to evaluate the safety and efficacy of dolutegravir plus rilpivirine as a complete regimen for the treatment of HIV-1 infection. SWORD-1 and SWORD-2 are on-going, identical, Phase 3, randomized, open-label, clinical trials conducted with the individual drug products, DTG and RPV.

- A sub-study (DEXA) study was conducted to evaluate changes in bone mineral density (BMD) when subjects switched ARV regimen from TDF-containing regimen to DTG+RPV. Please refer to the clinical safety review section for additional details. Please also refer to review by Dr. Stephen Voss from the Division of Bone Reproductive and Urologic Products (DBRUP)

- A BE study was conducted to establish the bioequivalence of the FDC product, Juluca, to the individual drug products. A relative oral bioavailability (BA) trial was also conducted to evaluate effect of food on exposure.

- The sponsor also conducted a drug-drug-interaction (DDI) study to demonstrate that DTG and RPV can be co-administered together.

Table 11 Summary of Clinical Trials Conducted in Support of Juluca

Study	Study Design	Population	Treatment details
201636 (SWORD-1, NCT02429791) Status: Ongoing; 48 week CSR completed	Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1 infected ART-experienced subjects	Treatment groups: DTG 50 mg + RPV 25 mg once daily Current antiretroviral regimen (CAR): 2 NRTIs + INSTI, NNRTI, or PI
201637 (SWORD-2, NCT02422797) 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 CAR: 2 NRTIs + INSTI, NNRTI, or PI
202094 (DEXA Sub-study) 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 TFV-containing ART regimen CAR: 2 NRTIs + INSTI, NNRTI, or PI
201676 (Pivotal BE) 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

201674 (Relative BA and food effect) 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
LAI116181 (DTG + RPV DDI) 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

Data Source: Clinical Overview Table 1

7.1.2. Review Strategy

Data Sources

The Applicant electronically submitted the study reports, data sets, and literature references. Data were submitted in Standard Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) formats. The Applicant additionally provided the software code used for analyzing the primary and secondary endpoints. All data sources are located at \\CDSESUB1\EVSPROD\NDA210192\0000.

Data and Analysis Quality

The quality of the submitted data for the SWORD trials was generally sufficient for review. The primary and secondary efficacy results from the submitted datasets, including results of Week 48 virologic failure and virologic success endpoints were reproducible. Furthermore, the analyses conducted by the Applicant appeared generally consistent with the pre-specified statistical analysis plan.

According to the applicant, the SWORD trials were conducted in conformance with ICH Good Clinical Practice standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The Applicant documented quality assurance measures and noted that no serious breaches with GCP were identified. The reviewer's assessment of the data quality and documentation of GCP did not find any cause for concern.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. SWORD-1 and SWORD-2

Trial Design and Endpoints

Trial Design

The Applicant submitted two identically designed open-label, multicenter, global, phase 3, non-inferiority studies (SWORD-1 and SWORD-2) to evaluate the efficacy and safety of switching from a 3-drug current antiretroviral regimen to the investigational 2-drug combining DTG and RPV. The two trials were designed to demonstrate the non-inferior antiviral activity of switching to DTG+RPV once daily compared to continuation of CAR over 48 weeks in HIV-1 infected ART (antiretroviral therapy)-experienced subjects who were virologically suppressed for at least 12 months and had no history of virologic failure. Note that CAR contained 2 NRTIs plus either an INSTI, NNRTI, or PI. The studies are ongoing, and the planned duration is 148 weeks.

The Applicant provided the following rationale for the open-label design:

> "A double-dummy design could not be undertaken given the diversity of the comparator regimens, and the logistical challenges of providing blinding for each regimen, and the marked increase in pill burden that would result from this blinding. This marked increase in pill burden could both substantially hinder compliance, and discourage subject enrollment."

To minimize potential bias resulting from the open-label design, the applicant devised a study blinding agreement that was to be adhered to by the study team. The staff was not to receive summaries of the data prior to the planned Week 48 analysis.

Five hundred and ten subjects in SWORD-1 and 518 in SWORD-2 were randomized 1:1 to each treatment group. Randomization was stratified by baseline third agent class (INSTI, NNRTI, or PI) and age group (< or ≥50 years old), and planned participation in the DEXA sub-study. The applicant is conducting the sub-study to evaluate change from baseline in bone mineral density following the switch from a triple ART regimen. The DEXA sub-study recruited subjects who were receiving ART regimens which included TDF at the time of randomization to receive treatment in one of the SWORD studies.

In SWORD-1, a total of 66 investigational centers in 13 countries randomized one or more subjects: 1 center in Argentina, 2 in Australia, 4 in Belgium, 6 in Canada, 5 in France, 5 in Germany, 3 in Italy, 2 in Netherlands, 5 in Russian Federation, 14 in Spain, 3 in Taiwan, 2 in UK and 14 in US. In SWORD-2, a total of 60 investigational centers in 11 countries randomized one or more subjects: 13 in Argentina, 3 in Australia, 7 in Canada, 6 in France, 5 in German, 2 in Italy, 5 in Spain, 4 in Taiwan, 4 in Russian Federation, 1 in the UK and 13 in the US.

Both trials consisted of 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. The study Schematic for both studies is provided in the following figure.

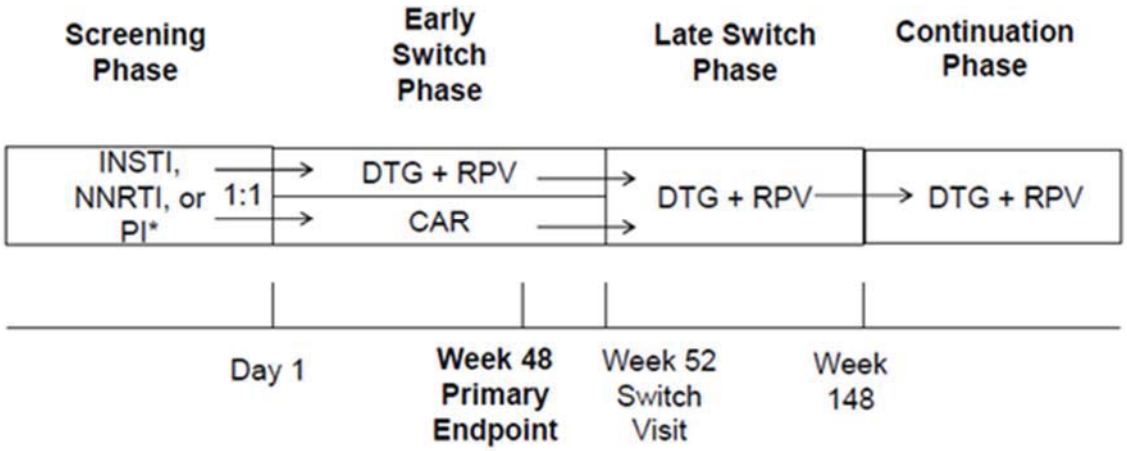


Figure 2 Study Schematic

Source: Applicant's Clinical Study Report for SWORD-1, page 44

Post-baseline study visits and assessments (complete physical examinations, urine collection for lab procedures, blood samples collection for laboratory analyses including HIV-1 RNA levels, CD4+ cell counts, etc.), occurred at Weeks 2, 4, 8, 12, 16, 24, 36, 48, 52 (late switch), 56, 64, 76, 88, 100, and every 12 weeks following Week 100 after which subjects continued treatment with visits every 12 weeks until week 148.

Primary endpoint:

The pre-specified primary endpoint in both studies was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 using the Snapshot algorithm.

The Applicant noted that after the protocols were approved, the Agency updated their guidance on the choice of the primary endpoint and associated non-inferiority margin for switch trials. The Agency recommended the snapshot virologic failure response rates at Week 48 to be the primary endpoint for the switch trials. Therefore, in this submission, the Applicant included the FDA recommended primary endpoint as a secondary endpoint.

Secondary Efficacy Endpoints:

The following secondary endpoints were of focus in this review because they were either closely related to the primary endpoint or involved a key HIV marker:

- Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 24 using the Snapshot algorithm;
- Snapshot virological failures at week 48;
- Change from Baseline in CD4+ lymphocyte count at Weeks 24 and 48.

Statistical Analysis Plan

Analysis Populations:

The statistical analysis plan defined the following analysis populations and described their use in efficacy, secondary analysis, and safety summaries:

- ITT (Intent to Treat) Population:
  The ITT population consisted of all randomized subjects. Subjects were assessed according to their randomized treatment even if no study treatment was taken or the wrong treatment was received.

  This population fully preserves the randomization which ensures that the treatment groups are comparable statistically. Sensitivity analyses in this population were conducted by the reviewer to ensure consistency with the primary analysis.

- ITT-E (ITT-Exposed) population:
  The ITT-E population consisted of all randomly assigned subjects who received at least one dose of study drug. Subjects were assessed according to their randomized treatment, regardless of the treatment received. Efficacy analyses were conducted based on the ITT-E population.

- Safety Population:
  The safety population consisted of all subjects who received at least one dose of study drug. Subjects were assessed according to the actual treatment received. This population was used for safety analyses.

- Per Protocol (PP) population:
  The PP population included subjects in the ITT-E population except for major protocol violators: e.g. violations which could have affected the assessment of antiviral activity or where study drug compliance was known to be less than 90%. Sensitivity analysis were conducted in this population.

Sample size estimation

The Applicant computed the sample size assuming a true 87% response rate in each arm, a non-inferiority margin of -10%, and a 2.5% one-sided significance level. Under these assumptions, each study required 238 subjects per treatment arm which ensured 90% power to demonstrate non-inferiority for the primary endpoint. Under the same assumptions, the pooled data from SWORD-1 and SWORD-2 provided >90% power to show non-inferiority for the primary endpoint using a non-inferiority margin of -8% at the significance level 0.025.

Rationale for non-inferiority margin

Primary endpoint:

The non-inferiority margin (NI) for the primary endpoint was based on a clinical justification, as NI margin justification would involve two already approved products. The goal of the trial was to show that the new regimen was not much worse than the current regimen. The Applicant opined that -10% was a reasonable non-inferiority margin to demonstrate adequate preservation of treatment effect in a virologically suppressed population. The -10% margin selection is consistent with the current HIV-1 treatment guidance. In addition, for the pooled analyses, a NI margin of -8% was used to support the noninferiority of DTG +RPV FDC tablet with respect to CAR.

Secondary endpoint
As mentioned earlier that the Applicant included snapshot virologic failure response rates at Week 48 as a secondary endpoint although the Agency recommended the snapshot virologic failure response rates at Week 48 as the primary endpoint for the switch trials.

The Applicant used a NI margin of 4% for comparing the snapshot failure response rates at Week 48 between the DTG + RPV and CAR groups. The proposed 4% margin is recommended by the FDA Guidance on HIV-1 infection dated November 2017.

Efficacy analyses:

For the primary comparison between the treatment groups at Week 48, adjusted estimates of the difference in the proportion of subjects with viral load <50 copies per/mL were presented with the 2-sided confidence intervals (CIs). The analysis was stratified by the Baseline third agent class (INSTI, NNRTI, PI) and age group (< or ≥50 years old) using Cochran-Mantel Haenszel (CMH) weights.

For each study, non-inferiority was concluded if the lower bound of a two-sided 95% CI for the difference in response rates between the 2 treatment groups was greater than -10%. A margin of -8% was utilized for the pooled analysis.

Note that the secondary endpoint comparing the snapshot virological failure response rates between the DTG + RPV and CAR groups at Week 48 was assessed using a NI margin of 4%. The assessments included adjusted estimates of the difference in the proportion of subjects with viral load ≥50 copies per/mL with the 2-sided confidence intervals (CIs). The analysis was also stratified by the Baseline third agent class (INSTI, NNRTI, PI) and age group (< or ≥50 years old) using Cochran-Mantel Haenszel (CMH) weights.

Interim analyses:

An independent data monitoring committee (IDMC) reviewed clinical efficacy data from both studies approximately 9 months after the first subject first visit with the intent of having approximately 50% of subjects reaching Week 24. A futility rule based on a Bayesian posterior predictive probability approach was applied to assess the probability that DTG + RPV demonstrated non-inferiority with the CAR arm. The Applicant remained blinded to this analysis. In addition, the number of subjects meeting clinical virologic withdraw (CVW) criteria were monitored and an inadequate response triggered an IDMC data review. The Applicant noted that the trial did not stop before Week 48.

Protocol Amendments

There were two protocol amendments reported by the Applicant. They are described as follows:

- Amendment No. 1 (26 February 2015) was implemented prior to enrollment of any subjects in the study and included the following: additional PK visits for all subjects in the Late Switch Phase (added Weeks 56, 76, 100, or Withdrawal), added PK visits (Weeks 2, 4, and 8) for the first 20 subjects in the NNRTI Subset who switched from EFV or NVP in the Early Switch Phase, and the addition of stratification by planned participation in the 202094 sub-study. Minor revisions to inclusion and exclusion criteria, revision to the description of IDMC monitoring of CVW Criteria, revision to guidance regarding prohibited medications, revision to the definition of study completion, revisions to Suicidal Risk Monitoring section and edits to the Time and Events Table were also included.

- Amendment No. 2 (8 June 2015) was implemented following study initiation and included the following edits: added reasons for switch for PI-class aligned with other ART class switches, clarification of Exclusion Criterion 10 in relation to evidence of HBV infection, revisions to stratified analysis of the primary endpoint, revisions to Virologic Withdrawal Criteria, and minor clarifications and corrections of typographical errors. The risk mitigation strategy around rash and the requirement to discontinue study drug following observation of Grade 3 or 4 rash were revised and clarified

Inclusion/Exclusion Criteria

Inclusion Criteria
The key inclusion criteria for the SWORD studies, as defined by the Applicant, included the following:

- HIV-1 infected men or women ≥18 years of age

- Must have been on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening
- Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability and/or safety concerns or access to medications, or convenience/simplification
- Acceptable stable cART regimens prior to Screening included 2 NRTIs plus:
    - INSTI (either the initial or second cART regimen)
    - NNRTI (either the initial or second cART regimen)
    - Boosted PI (or ATV unboosted) (must have been initial cART regimen; one within class switch permitted for tolerability)
- Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12-month window, and one within 6 months prior to Screening
- Plasma HIV-1 RNA <50 c/mL at Screening
- Females of childbearing potential must have had a negative pregnancy test at both Screening and Day 1 and agreed to protocol-defined contraception to avoid pregnancy
- Subject was willing and able to understand requirements of study participation and provide signed and dated written informed consent prior to Screening
- Subjects enrolled in France: a subject was eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category

Exclusion Criteria:
The key exclusion criteria for the SWORD studies, as defined by the Applicant, included the following:

Exclusionary Criteria prior to Screening or Day 1

- Within 6 months prior to Screening and after confirmed suppression to <50 c/mL on current ART regimen, any plasma HIV-1 RNA measurement ≥50 copies/mL;
- Within the 6 to 12month window prior to Screening and after confirmed suppression to <50 c/mL, any plasma HIV-1 RNA measurement >200 c/mL;
- Within the 6 to12 month window prior to Screening and after confirmed suppression to <50 c/mL, 2 or more plasma HIV-1 RNA measurements ≥50 c/mL;
- Any drug holiday during the window between initiating first HIV ART and 6 months prior to Screening, except for brief periods (less than 1 month) where all ART was stopped due to tolerability and/or safety concerns;
- Any switch to a second line regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA measurement ≥400 c/mL after initial suppression to <50 c/mL while on first line HIV therapy regimen);

Exclusionary medical conditions (key criteria)

- Women who were pregnant, breastfeeding or planning to become pregnant or breastfeed during the study
- Any evidence of an active CDC Category C disease. Exceptions included cutaneous Kaposi's sarcoma not requiring systemic therapy and historic CD4+ lymphocyte counts of <200 cells/mm3
- Subjects with any degree of hepatic impairment
- Subjects positive for HBV surface antigen at Screening, or with an anticipated need for HCV therapy during the study
- Subjects who in the investigator's judgment posed a significant suicidality risk

Exclusionary Treatments prior to Screening or Day 1 (key criteria)

- Use of medications which are associated with Torsades de Pointes. (See SPM for a list of relevant medications)
- A history of use of any regimen consisting of only single NNRTI therapy (even if only for peri-partum treatment), or only single or dual NRTI therapy prior to starting cART
- Current or prior history of ETR use
- Current use of TPV/RTV or FPV/RTV

Exclusionary Laboratory Values or Clinical Assessments at Screening (key criteria)

- Evidence of viral resistance based on the presence of any resistance-associated major PI, INSTI, NRTI, or NNRTI mutation and INSTI resistance associated substitution R263K in any available prior resistance genotype assay results
- Any verified Grade 4 laboratory abnormality, with the exception of Grade 4 lipid abnormalities. A single repeat test was allowed during the Screening period to verify a result
- Alanine aminotransferase≥5 x ULN, or ALT ≥3 x ULN and bilirubin ≥1.5 x ULN (with >35% direct bilirubin)
- QTc interval (Bazett) >450 msec or QTc (Bazett) >480 msec for subjects with bundle branch block. The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB)

7.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant states the clinical trials were conducted in accordance with the Declaration of Helsinki. The trials followed the guidelines as outlined the International Conference on Harmonization of Good Clinical Practices (GCP). According to the Applicant, GCP noncompliance issues were not identified in either phase 3 trials. The phase 3 trials were conducted according to FDA requirements, under IND 123306, with cross references to INDs 75382 (DTG) and 67699 (RPV) and NDAs 204790 (DTG) and 202022 (RPV). Additionally, FDA site inspections did not reveal evidence of GCP non-compliance at the inspected sites.

Financial Disclosure

See Section 15.2 for details on the financial disclosure.

Summaries of Analysis Populations, Subject Disposition, Demographics and Baseline Disease Characteristics

Summaries of Analysis Populations

Summaries of Analysis Populations in Study SWORD-1, SWORD-2 and pooled studies are provided in **Table 12**.

Table 12 Summary of Analysis Populations for Studies SWORD-1, SWORD-2, and Pooled Data

Study Population	SWORD-1		SWORD-2		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
ITT	254	256	262	256	516	512
ITT-E	252	256	261	255	513	511
Safety	252	256	261	255	513	511
PP	226	239	231	238	457	477

Source: Statistical reviewer's table

As shown in Table 12 , the numbers of subjects included in the ITT, ITT-E and safety populations were similar across treatment groups for the individual studies and for the pooled analyses population.

For the PP population, there were imbalances across treatment groups for SWORD-1 and for the pooled analyses. Note that for the PP population, in SWORD-1, there were 26 protocol violations (out of 252 subjects) in DTG+RPV group whereas there were 17 protocol violations (out of 256 subjects) in CAR group. Thus, the proportion of protocol violations was similar (DTG+RTV vs. CAR: 10% vs. 7%; (Fisher's exact P-value 0.15) across the treatment groups in SWORD-1. In SWORD 2, there were 30 protocol violations (out of 261 subjects) in DTG+RPV group whereas there were 17 protocol violations (out of 255 patients) in CAR group. The proportion of protocol violations was similar (Fisher's exact P-value 0.07) between DTG+RPV group (11%) and CAR group (7%) in SWORD-2. For the pooled analysis population, there were 56 protocol violations (out of 513 subjects) in DTG+RTV group and 34 protocol violations in CAR group (out of 511 subjects) in CAR group. The proportion of protocol violations was significantly different (Fisher's exact P-value 0.02) between DTG+RPV group (11%) and CAR group (7%). However, these differences did not affect the overall trial results.

Note that on October 23, 2017, the Applicant reported that in the original submission (June 1, 2017) overall 24 subjects in the CAR group (13 subjects in SWORD-1 and 11 subjects in SWORD-2) were wrongly classified as taking prohibitive medications. These 24 CAR subjects were

excluded in the original submission and were added to the PP population in the October 23, 2017 submission. These discrepancies within the PP population did not affect the outcome or conclusions.

Subject Disposition

Summaries of subject disposition for Studies SWORD-1, SWORD-2 and the Pooled Data (ITT-E Population) are provided in the following **Table 13.**

In SWORD-1, a total of 252 and 256 subjects were randomized and treated with DTG + RPV and CAR respectively. Similar proportions of subjects in each treatment group withdrew from the study (DTG + RPV: 5%; CAR: 7%). The most common reasons for withdrawal were withdrew consent (DTG + RPV: 1%; CAR: 3%) and AE (DTG + RPV: 2%; CAR: <1%). Three subjects were withdrawn from the study due to investigator's assessment of lack of efficacy. Among those, 1 subject in DTG + RPV group and 1 in the CAR group were withdrawn from the study due to confirmed virologic withdrawal (CVW). The remaining one subject in the DTG+RPV group was not withdrawn for CVW.

In SWORD-2, a total of 261 and 255 subjects were randomized and treated with DTG + RPV and CAR respectively. The same number of subjects in each treatment group withdrew from the study (6%). The most common reasons for withdrawal were AEs (DTG + RPV: 4%; CAR: <1%) and withdrew consent (DTG + RPV: <1%; CAR: 3%). Three subjects (1 subject in DTG+RPV group and 2 subjects in CAR group) were withdrawn from the study due to investigator's assessment of lack of efficacy. Among those, 1 subject in DTG + RPV group and 1 in the CAR group were withdrawn from the study due to CVW. The remaining one subject in the CAR group was not withdrawn for CVW.

For both studies combined, a total of 513 subjects were randomized and treated by DTG + RPV and 511 subjects remained on their CAR. Similar proportions of subjects in each treatment group withdrew from the study. The most common reason for withdrawal was adverse events. Less than 1% of subjects from both groups were withdrawn from the study due to investigator's assessment of lack of efficacy.

This differences in the protocol violations are likely partially due to the differential handling of prohibited medications of the patients who took prohibited medication for the DTG+RPV, whereas patients who took the same concomitant medication in the CAR are not considered prohibited.

Table 13 Summary of Subject Disposition for Studies SWORD-1, SWORD-2 and Pooled Studies (ITT-E Population) ongoing at Week 52

Number of subjects, n (%)	SWORD-1		SWORD-2		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252)	(N=256)	(N=261)	(N=255)	(N=513)	(N=511)
Randomized and treated	252	256	261	255	513	511
Ongoing*	239 (95)	238 (93)	245 (94)	239 (94)	484 (94)	477 (93)
Premature Withdrawal	13 (5)	18 (7)	16 (6)	16 (6)	29 (6)	34 (7)
Primary reason for withdrawal						
Adverse event	6 (2)	2 (<1)	11 (4)	1 (<1)	17 (3)	3 (<1)
Investigator discretion	0	2 (<1)	0	1 (<1)	0	3 (<1)
Lack of efficacy	2 (1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)	3 (<1)
Lost to Follow-up	1 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)
Protocol deviation	1 (<1)	4 (2)	0	3 (1)	1 (<1)	7 (1)
Reached protocol defined stopping criteria	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Withdrew consent	3 (1)	7 (3)	2 (<1)	7 (3)	5 (<1)	14 (3)

Source: Statistical reviewer's table/Applicant's CSR Table 4, page 80 for SWORD-1 and Table 3, page 78 for SWORD-2
*Note: 'Ongoing' includes all subjects who completed the Early Switch Phase and entered the Late Switch Phase.

Demographic Characteristics

Demographic characteristics were well balanced across treatment groups in both SWORD studies. In SWORD-1, 23% of subjects in the DTG + RPV group and 20% of subjects in the CAR group were women, and 27% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. In SWORD-2, 24% of subjects in the DTG + RPV group and 22% of subjects in the CAR group were women, and 30% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. The majority of subjects were white in both studies.

Table 14 provides a summary of the demographic characteristics for the individual and pooled studies. Demographic characteristics were well balanced across treatment groups in both

SWORD studies. In SWORD-1, 23% of subjects in the DTG + RPV group and 20% of subjects in the CAR group were women, and 27% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. In SWORD-2, 24% of subjects in the DTG + RPV group and 22% of subjects in the CAR group were women, and 30% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. The majority of subjects were white in both studies.

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Table 14 Summary of Demographic Characteristics for SWORD-1, SWORD-2 and Pooled Studies (ITT-E Population)

	SWORD-1		SWORD-2		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Age (years), median (range)	43.0 (23-78)	43.0 (22-76)	43.0 (21-79)	43.0 (22-69)	43.0 (21-79)	43.0 (22-76)
Age group (y), n (%)						
<35	53 (21)	60 (23)	64 (25)	55 (22)	117 (23)	115 (23)
35-<50	130 (52)	125 (49)	119 (46)	129 (51)	249 (49)	254 (50)
≥50	69 (27)	71 (28)	78 (30)	71 (28)	147 (29)	142 (28)
Sex, n (%)						
Female	58 (23)	51 (20)	62 (24)	57 (22)	120 (23)	108 (21)
Male	194 (77)	205 (80)	199 (76)	198 (78)	393 (77)	403 (79)
Ethnicity, n (%)						
Hispanic/Latino	30 (12)	34 (13)	37 (14)	48 (19)	67 (13)	82 (16)
Not Hispanic/Latino	222 (88)	222 (87)	224 (86)	207 (81)	446 (87)	429 (84)
Race, n (%)						
American Indian or Alaska Native	3 (1)	6 (2)	11 (4)	8 (3)	14 (3)	14 (3)
Asian	25 (10)	34 (13)	13 (5)	16 (6)	38 (7)	50 (10)
Central/South Asian Heritage	0	0	0	1 (<1)	0	1 (<1)
Japanese/East Asian Heritage/South East Asian Heritage	25 (10)	34 (13)	13 (5)	15 (6)	38 (7)	49 (10)
Black/African American	24 (10)	27 (11)	13 (5)	20 (8)	37 (7)	47 (9)
Native Hawaiian or other Pacific Islander	1 (<1)	0	1 (<1)	0	2 (<1)	0

White	198 (79)	188 (73)	223 (85)	210 (82)	421 (82)	398 (78)
White & African American/African Heritage	0	0	0	1 (<1)	0	1 (<1)
White and American Indian or Alaska Native	0	1 (<1)	0	0	0	1 (<1)
Asian and African American/African Heritage	1 (<1)	0	0	0	1 (<1)	0

Source: Statistical reviewer's table/Applicant's CSR Table 6, page 83 for SWORD-1 and Table 6, page 81 for SWORD-2

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 15 provides a summary of the baseline characteristics for the individual and pooled studies. Baseline characteristics were well balanced across the treatment groups. Overall, in SWORD-1, most subjects had negative test results at screening for HCV infection (DTG + RPV: 94%; CAR: 92%) and were in CDC Class A (DTG + RPV: 81%; CAR: 77%). Overall, in SWORD-2, most subjects had negative test results at screening for HCV infection (DTG + RPV: 95%; CAR: 92%) and were in CDC Class A (DTG + RPV: 75%; CAR: 73%).

Table 15 Summary of Baseline Characteristics for Studies SWORD-1, SWORD-2, and Pooled Studies (ITT-E Population)

	SWORD-1		SWORD-2		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	N=252	N=256	N=261	N=255	N=513	N=511
Baseline HIV-1 RNA (c/mL)						
<50 copies/mL	247 (98)	253 (99)	259 (99)	251 (98)	506 (99)	504 (99)
≥50 copies/mL	5 (2)	3 (1)	2 (1)	4 (2)	7 (1)	7 (1)
Baseline CD4+ (cells/mm3)						
Median	611	638	609	628	611	638
Min., Max.	37, 1521	95, 1523	114, 1774	108,1671	37, 1774	95, 1671
Hepatitis B & C co-infection						
B only	0	1 (<1)	0	1 (<1)	0	2 (<1)
C only	15 (6)	19 (7)	13 (5)	21 (8)	28 (5)	40 (8)
B and C	0	0	0	0	0	0
Borderline C only	0	0	1 (<1)	0	1 (<1)	0
Neither	237 (94)	236 (92)	247 (95)	233 (91)	484 (94)	469 (92)
CDC Category						
A: Asymptomatic or Lymphadenopathy or Acute HIV	203 (81)	198 (77)	197 (75)	187 (73)	400 (78)	385 (75)
B: Symptomatic, not AIDS	20 (8)	35 (14)	35 (13)	33 (13)	55 (11)	68 (13)

C: AIDS	29 (12)	23 (9)	29 (11)	34 (13)	58 (11)	57 (11)
Missing	0	0	0	1 (<1)	0	1 (<1)

Source: Reviewer's table /Applicant's CSR Table 7, page 84 forSWORD-1 and Table 7, page 82 for SWORD-2

Protocol Violations/Deviations

As summarized above, the intent-to-treat (ITT) population for SWORD-1 and SWORD-2 includes all subjects who were randomized and the ITT-E population are randomized subjects who received at least one dose of study drug(s). The ITT-E population was used to conduct the efficacy analysis. The per-protocol population (PP) was defined as subjects who did not have protocol deviations. Subjects with protocol deviations were thus excluded from PP analysis.

The Applicant references the ICH E3 guidance, for identifying protocol deviations for inclusion in the CSR. Important deviations were defined as deviations that may have 'compromised subject rights, safety, or well-being or impacted the scientific integrity of the study'. For example, deviations from important inclusion or exclusion criteria and administration of prohibited medication were considered significant protocol deviations.

Overall, the proportion of subjects with protocol deviation leading to exclusion from the PP was 56 (11%) in DTG+RPV treatment group and 34 (7%) in the CAR treatment group. The most common *important* protocol deviations were 'not meeting eligibility criteria' and 'administration of prohibited medication'. Overall 25 DTG + RPV- and 31 CAR treated-subjects received protocol prohibited medications. In the DTG+RPV treatment group, 12 subjects violated the inclusion criterion that required at least one documented HIV RNA <50 copies/mL prior to enrollment. In the CAR treatment group, 5 subjects did not meet the inclusion criterion that required subjects to be on uninterrupted CAR for at least 6 months before screening; additionally, 7 subjects in the CAR treatment group were enrolled despite meeting the criterion that excluded subjects with "a drug holiday…6 months prior to Screening except for brief periods (less than 1 month) where all ART was stopped due to tolerability/safety concerns".

Additionally, summarized below by the statistical reviewer are the major protocol deviations which could have affected the assessment of antiviral activity or where study drug compliance was known to be less than 90%.

In SWORD-1, there were 26 subjects with protocol violations (out of 252 subjects) in the DTG+RPV group whereas there were 17 subjects with protocol violations (out of 256 subjects) in the CAR group. The proportion of protocol violations was similar (Fisher's exact P-value:0.15) between DTG+RPV group (10%) and CAR group (7%) in SWORD-1.

In SWORD 2, there were 30 subjects with protocol violations (out of 261 subjects in the DTG+RPV group whereas there were 17 protocol subjects with violations (out of 255 patients) in the CAR group. The proportion of protocol violations was not significantly different (Fisher's exact P-value:0.07) between DTG+RPV group (11%) and CAR group (7%) in SWORD-2.

For the pooled analyses, there were 56 subjects with protocol violations (out of 513 subjects in the DTG+RTV group and 34 subjects with protocol violations in the CAR group (out of 511 subjects) in the CAR group. The proportion of protocol violations is significantly (Fisher's exact P-value: 0.02) higher in the DTG+RPV group (11%) than the CAR group (7%) in pooled analyses. However, these differences did not affect the overall trial results.

Treatment Compliance and Concomitant Medications

Treatment Compliance

Per protocol, investigators were to remind subjects about the importance of treatment adherence. Study drug accountability was recorded through multiple methods, including patients' reporting, Visual Analogue Scale and pill accountability each time a subject received a refill of medication supply. Although the study drug accountability information was collected in the subjects site records, the data was not recorded in the CRF; therefore the information was not reviewed for independent verification. However, missed doses were recorded as protocol deviations after consideration of the pill count and speaking with the subject. Data on missed doses was submitted as part of the protocol deviation data.

Concomitant Medications and Non-Drug Therapies

The Applicant reported that subjects were advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential drug-drug interactions between such treatments and the study drugs. The use of concomitant medications is described below. Overall, the most commonly prescribed concomitant medication were anti-pyretic, NSAIDS, and antibiotics. Omeprazole was the most commonly used prohibited medication.

ARVs Use at Screening

The trial design allowed for subjects to be on PI-, NNRTI-, or INSTI- based regimen in combination with 2 NRTIs. As summarized in **Table 16**, the most common third agent class was NNRTI (54% in each treatment group); efavirenz was the most commonly used NNRTI in both treatment groups. Rilpivirine was prescribed in 6% and 8% of DTG+RPV and CAR treatment groups, respectively. The INSTI class was the least frequently prescribed third agent - 20% and 19% in the DTG+RPV and CAR treatment groups, respectively. DTG was prescribed in 6% of each treatment group. At screening all subjects received NRTIs in their regimen.

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Table 16 Summary of ARV use at Screening for SWORD-1 and SWORD-2

	SWORD-1		SWORD-2		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	N=252	N=256	N=261	N=255	N=513	N=511
Any ARV, n(%)	**252 (100)**	**256 (100)**	**261 (100)**	**255 (100)**	**513 (100)**	**511 (100)**
Any NRTI	**252 (100)**	**256 (100)**	**261 (100)**	**255 (100)**	**513 (100)**	**511 (100)**
Tenofovir	184 (73)	172 (67)	190 (73)	187 (73)	374 (73)	359 (70)
Emtricitabine	166 (66)	156 (61)	186 (71)	185 (73)	352 (69)	341 (67)
Lamivudine	85 (34)	100 (39)	75 (29)	70 (27)	160 (31)	170 (33)
Abacavir	56 (22)	66 (26)	48 (18)	55 (22)	104 (20)	121 (24)
Zidovudine	11 (4)	17 (7)	21 (8)	10 (4)	32 (6)	27 (5)
Didanosine	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)
Phosphazide*	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Stavudine	1 (<1)	0	0	0	1 (<1)	0
Any NNRTI	131 (52)	134 (52)	144 (55)	144 (56)	275 (54)	278 (54)
Efavirenz	83 (33)	86 (34)	102 (39)	103 (40)	185 (36)	189 (37)
Nevirapine	29 (12)	31 (12)	27 (10)	18 (7)	56 (11)	49 (10)
Rilpivirine	18 (7)	17 (7)	15 (6)	22 (9)	33 (6)	39 (8)
Etravirine	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Any PI	75 (30)	74 (29)	58 (22)	62 (24)	133 (26)	136 (27)
Darunavir/rit^	31 (12)	19 (7)	27 (10)	21 (8)	58 (11)	40 (8)
Atazanavir/rit	24 (10)	23 (9)	15 (6)	18 (7)	39 (8)	41 (8)
Lopinavir	7 (3)	7 (3)	10 (4)	18 (7)	17 (3)	25 (5)
Ritonavir	7 (3)	7 (3)	10 (4)	20 (8)	17 (3)	27 (5)
Atazanavir	10 (4)	22 (9)	4 (2)	4 (2)	14 (3)	26 (5)
Lopinavir/rit	10 (4)	10 (4)	10 (4)	18 (7)	20 (4)	28 (5)
Darunavir	0	0	1 (<1)	0	1 (<1)	0
Fosamprenavir/rit	0	0	1 (<1)	0	1 (<1)	0
Nelfinavir	0	0	0	1 (<1)	0	1 (<1)
Any INSTI	46 (18)	48 (19)	59 (23)	49 (19)	105 (20)	97 (19)
Raltegravir	13 (5)	22 (9)	30 (11)	22 (9)	43 (8)	44 (9)

Dolutegravir	16 (6)	17 (7)	17 (7)	16 (6)	33 (6)	33 (6)
Elvitegravir	17 (7)	9 (4)	12 (5)	11 (4)	29 (6)	20 (4)

Source Concomitant Medications Datasets
*****Phosphazide (Nikavir) is a reverse transcriptase inhibitor from Russia
^ ritonavir

Efficacy Results- Primary Endpoint
This section focuses on the results of efficacy analyses. The applicant's analysis methods used for the primary and secondary efficacy endpoints were pre-specified in the protocol, and the reviewer's results were comparable to the Applicants analyses.

Because the two studies were identically designed and similarly conducted, the efficacy analysis based on the pooled data was also done. Therefore, the results will be presented individually and pooled, whenever applicable.
Note that although the Applicant's primary analysis focused on HIV RNA < 50 copies/mL, the Agency considers HIV RNA > 50 copies/mL more appropriate for switch trials in virologically suppressed patients. As noted earlier, the Agency views proportion of patients with HIV-RNA greater than or equal to the lower limit of quantification at 48 weeks as the primary efficacy endpoint. The virological failure response rates between the DTG + RPV and CAR groups will be discussed under the secondary endpoint.

The review below summarizes the efficacy results as presented in the protocol per the prespecified primary analysis of HIV RNA < 50 copies/mL at Week 48.

Primary Endpoint
The Applicant conducted the primary analysis to evaluate the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 using the FDA snapshot algorithm. The reviewer's results were identical to the Applicant's results. The overall results for the individual trials are summarized in **Table 17**. **Table 18** summarizes the primary efficacy analysis outcome and provides the FDA snapshot algorithm subcategories.

In SWORD-1, 95% of subjects in the DTG + RPV group and 96% of subjects in the CAR group achieved plasma HIV-1 RNA <50 copies/mL at Week 48. The adjusted 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 (-4.3%) was greater than -10%.

In SWORD-2, 94% of subjects in both the DTG + RPV and CAR groups achieved plasma HIV-1 RNA <50 copies/mL at Week 48. The adjusted analysis demonstrated that DTG + RPV was non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.9%) was greater than -10%.

In the pooled analysis, an approximately equal proportion of subjects in the DTG + RPV group (95%) achieved the primary efficacy endpoint compared with the CAR group (95%). The

adjusted analysis demonstrated that DTG + RPV was non-inferior to CAR at Week 48 as the lower bound of the 95% CI for the adjusted treatment difference (-3.0%) was greater than -8%.

The ITT analyses classifying untreated subjects as failures resulted in similar conclusion as the ITT-E analyses.

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Table 17 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 – Snapshot Analysis for Studies SWORD-1, SWORD-2, and Pooled Studies (ITT-E Population)

Treatment	Number Responded/ Total Assessed	Adjusted Difference in Proportion, % (95% CI)
SWORD-1		
DTG + RPV	240 / 252 (95%)	-0.6 (-4.3, 3.0)
CAR	245 / 256 (96%)	
SWORD-2		
DTG + RPV	246 / 261 (94%)	0.2 (-3.9, 4.2)
CAR	240 / 255 (94%)	
POOLED		
DTG + RPV	486 / 513 (95%)	-0.2 (-3.0, 2.5)
CAR	485 / 511 (95%)	

Source: Statistical reviewer's table/ Applicant's CSR Table 15, page 93 for SWORD-1 and Table 15, page 92 for SWORD-2

Table 18 Virologic Outcome at Week 48 for SWORD-1 and SWORD-2

Outcome n (%)	SWORD-1		SWORD-2	
	DTG+ RPV N=252	CAR N=256	DTG+RPV N= 261	CAR N=255
HIV RNA <50 copies/mL*	**240 (95)**	**245 (96)**	**246(94)**	**240(94)**
HIV RNA ≥50 copies/mL	**2 (<1)**	**1 (<1)**	**1 (<1)**	**4 (2)**
Data in window not below threshold (50 copies/ml)	0	1 (<1)	0	1 (<1)
Discontinued for lack of efficacy	2 (<1)	0	0	2 (<1)
Discontinued for other reason while not below threshold	0	1 (<1)	1 (<1)	0
Change in ARV	0	0	0	1(<1)
No Virologic Data	**10 (4)**	**9 (4)**	**14 (5)**	**11 (4)**
Discontinued due to AE or Death	5 (2)	2 (<1)	12 (5)	1 (<1)
Discontinued study for Other Reasons	5 (2)	7 (3)	2 (<1)	9 (4)
Missing data during window but on study	0	0	0	1 (<1)

Data Source: FDA Viral Load Analysis Dataset

Efficacy Results-Virologic Failure at Week 48

Although the Applicant's primary analysis focused on HIV RNA < 50 copies/mL, FDA considers HIV RNA > 50 copies/mL to be more appropriate and informative for switch trial designs in virologically suppressed patients, as summarized by the Guidance for Industry 'Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment'. **Table 19** summarizes the Week 48 outcome based on proportion of subjects with HIV RNA ≥ 50 copies/mL. The proportion of subjects who were classified as Snapshot virologic failures at

Week 48 is summarized in Table 19. The results indicated that the combined use of DTG + RPV was non-inferior to CAR based on the snapshot algorithm for virologic failure within a non-inferiority margin of 4% in both SWORD studies.

Table 19 Analysis of Proportion of Subjects Classified as Virologic Failures at Week 48 – Snapshot Analysis for Studies SWORD-1, SWORD-1, and Pooled Studies (ITT-E Population)

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

Source: Statistical reviewer's table/ Applicant's (Dated 09/01/2017) Table 2.181 (SWORD-1), Table 2.182 (SWORD-2) and Table 2.183 (Pooled),

Sensitivity Analyses- Proportion of Subjects Classified as Virologic Failures at Week 48

As summarized in **Table 18**, in SWORD-1, there were 5 subjects in the DTG+RPV group and 7 patents in the CAR group who discontinued the study due to other reasons. Additionally, in SWORD-2, 2 subjects in the in SWORD-2, 2 patients in the DTG + RPV group and 9 in the CAR group discontinued the study due to other reasons. Subjects who discontinued due to other reasons (such as physician decision, withdraw consent, or lost to follow-up) were regarded as failures in the primary analysis. Due to the nature of the trial design, i.e. open-label, the potential for imbalanced and bias discontinuation rate to favor DTG+RPV treatment group was considered. Therefore, sensitivity analyses were conducted to assess if discontinuation due to 'other reasons' influenced the overall efficacy outcome.

The statistical reviewer conducted sensitivity analyses imputing the control group subjects who discontinued due to other reasons as successes instead of failures. The results of the sensitivity analysis are shown in **Table 20**. Noninferiority of DTG + RPV to CAR was demonstrated in both studies because the lower bound of the 95% CI for the treatment difference was greater than -10%.

Table 20 Sensitivity Analyses by Imputing Discontinued Due to Other Reasons as Success in the CAR Group Virologic Outcome at Week 48 for SWORD-1 and SWORD-2

	Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion% (95% CI)
SWORD-1 (7 imputed in CAR group as successes)	CAR	240 / 252 (95)	-3.2 (-6.2, -0.02)
	DTG + RPV	252 / 256 (98)	
SWORD-2 (9 imputed in CAR group as successes)	CAR	246 / 261 (94)	-3.4 (-6.8, 0.00)
	DTG + RPV	249 / 255 (98)	

Source: Statistical reviewer's table

Efficacy- Other important secondary endpoints

The reviewer conducted secondary efficacy analyses including a snapshot analysis at Week 24, and changes in CD4 counts from baseline at Week 24 and Week 48.

Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 24 (Snapshot Analysis)

In SWORD-1, at Week 24, a similar proportion of subjects in the DTG + RPV group (98%) achieved virologic success compared with the CAR group (96%). In SWORD-2, a similar proportion of subjects in the DTG + RPV group (97%) achieved virologic success compared with the CAR group (98%). As expected, the pooled analysis also resulted in a high proportion of subjects of subjects achieving virologic success for both weeks. The results are provided in **Table 21**.

Table 21 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 24– Snapshot Analysis for Studies SWORD-1, and SWORD-2(ITT-E Population)

Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion, % (95% CI)	Adjusted Difference in Proportion, % (95% CI)
SWORD-1			
DTG + RPV	246 / 252 (98)	1.1 (-1.8, 4.1)	1.0 (-1.9, 4.0)
CAR	247 / 256 (96)		
SWORD-2			
DTG + RPV	252 / 261 (97)	-1.1 (-4.0, 1.8)	1.1 (-4.0, 1.8)
CAR	249 / 255 (98)		
POOLED			
DTG + RPV	496 / 511 (97)	0.0 (-2.1, 2.1)	-0.0 (-2.1,2.0)
CAR	498 / 513 (97)		

Source: Statistical reviewer's table

Change from Baseline in CD4+ Lymphocyte Count

The change from Baseline in CD4+ Lymphocyte count along with interquartile range (IQR=Third quartile, first quartile) is summarized in
Table 22**.** In SWORD-1, SWORD-2 and the pooled studies, CD4+ cell counts were maintained overall in both treatment groups.

Table 22 Summary of Change from Baseline in CD4+ Lymphocyte Count (cells/mm3) by Visit in Study SWORD-1, SWORD-2 and Pooled Studies (ITT-E Population)

SWORD-1	DTG + RPV (N=252)	CAR (N=256)
Median (IQR)		
Baseline	611.5 (442, 800)	638.0 (459.5, 846.0)
Week 24	22.0 (-67.0, 103.0)	33.0 (-45.0, 129.0)
Week 48	25.0 (-68, 119)	35.0 (-37.0, 104.0)
SWORD-2	**DTG + RPV (N=261)**	**CAR (N=255)**
Median (IQR)		
Baseline	609.0 (467.0, 814.0)	628.0 (481.0, 824.0)
Week 24	30.0 (-44.0, 140)	29.5 (-48.0, 123.0)
Week 48	29.0 (-47.0, 108.0)	13.0 (-59.0, 108.0)
POOLED	**DTG + RPV (N=513)**	**CAR (N=511)**
Median (IQR)		
Baseline	611.0 (459, 809)	638.0 (470.0, 829.0)
Week 24	26.5 (-58.0, 126.0)	31.0 (-48.0, 126.0)
Week 48	28.0 (-55.0, 112.5)	22.0 (-46.0, 108.0)

Source: Statistical reviewer's table

Subgroup Analyses

Subgroup Analyses by Demographics- Gender, Age and Race

The Applicant has provided subgroup analyses by age-group, gender and race for the primary endpoint. The weighted least squares chi-squared statistic was used to test for one- way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Tests of homogeneity for the primary endpoint were assessed at the one-sided 10% level of significance.

The SWORD studies were not powered for testing the noninferiority of DTG+RPV to CAR in the subgroups. In addition, there was potentially inflation of the type I error rate because of testing multiple null hypotheses. For these reasons, confidence intervals for treatment differences in subgroups were not considered to be inferential.

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Plasma HIV-1 RNA <50 copies/mL at Week 48 by Age Subgroups (Snapshot Analysis)

Table 23 summarizes the proportion of Subjects with plasma HIV-1 RNA <50 copies/mL at Week 48, by age subgroups in SWORD-1, SWORD-2 and Pooled data. The success rates across age subgroup categories were comparable in SWORD-1, SWORD-2 and pooled data. There were no interactions between the two treatment groups and age-group as assessed by homogeneity test for the primary endpoint suggesting that there was not a differential treatment effect among age groups.

Table 23 Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 by Age Subgroups in SWORD-1, SWORD-2 and Pooled data -Snapshot Analysis (ITT-E Population)

Study	Age	Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion% (95% CI)
SWORD-1	<50	CAR	185	178/185 (96)	1.1 (-2.6, 4.7)
		DTG + RPV	183	178/183 (97)	
	≥50	CAR	71	67 / 71 (94)	-4.5 (-13.4, 4.4)
		DTG + RPV	69	62 / 69 (90)	
SWORD-2	<50	CAR	184	170/184 (92)	1.6 (-3.6, 6.7)
		DTG + RPV	183	172/183 (94)	
	≥50	CAR	71	70 / 71 (99)	-3.7 (-9.3, 1.9)
		DTG + RPV	78	74 / 78 (95)	
POOLED	<50	CAR	369	348/369 (94)	1.3 (-1.8, 4.5)
		DTG + RPV	366	350/366 (96)	
	≥50	CAR	142	137/142 (96)	-4.0 (-9.2, 1.3)
		DTG + RPV	147	136/147 (93)	

Source: Statistical reviewer's table/ Applicant's CSR Table 25, page 101 for SWORD-1 and Table 25, page 100 for SWORD-2

Plasma HIV-1 RNA <50 copies/mL at Week 48 by Gender Subgroups (Snapshot Analysis)

A summary of proportion of responders at Week 48 by gender is provided in

Table 24. Success rates across gender subgroup categories were comparable in SWORD-1, SWORD-2 and pooled data. There were no interactions between the two treatment groups and gender-group in both studies as assessed by homogeneity test.

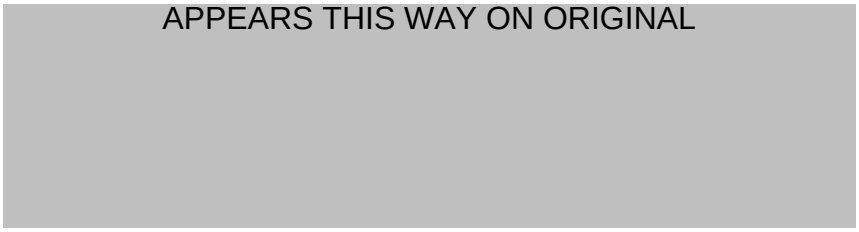

Table 24 Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 by Gender Subgroups in SWORD-1, SWORD-2 and Pooled Studies -Snapshot Analysis (ITT-E Population)

Study	Sex	Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion% (95% CI)
SWORD-1	Female	CAR	46 / 51 (90)	1.2 (-9.7, 12.1)
		DTG + RPV	53 / 58 (91)	
	Male	CAR	199 / 205 (97)	-0.7 (-4.2, 2.8)
		DTG + RPV	187 / 194 (96)	
SWORD-2	Female	CAR	52 / 57 (91)	2.3 (-7.2, 11.9)
		DTG + RPV	58 / 62 (94)	
	Male	CAR	188 / 198 (95)	-0.5 (-4.9, 3.9)
		DTG + RPV	188 / 199 (94)	
POOLED	Female	CAR	98 / 108 (91)	1.8 (-5.5, 9.0)
		DTG + RPV	111 / 120 (93)	
	Male	CAR	387 / 403 (96)	-0.6 (-3.4, 2.2)
		DTG + RPV	375 / 393 (95)	

Source: Statistical reviewer's table/ Applicant's CSR Table 27, page 104 for SWORD-1 and Table 28, page 104 for SWORD-2

Race Subgroup Analyses

Subgroup analyses by race are provided below in **Table 25.** The results show that success rates across race subgroup categories (White, African American/African Heritage and other) are comparable in SWORD-1, SWORD-2 and pooled data. Note that the reviewer's results varied slightly from those of the Applicant's because of misclassifications; however, the conclusions were the same. For example, in SWORD-1, the reviewer classified 1 mixed race subjects in the CAR group as the other race whereas the Applicant classified the subjects as white. Similarly, in SWORD-2, the reviewer classified 1 mixed subject in CAR group as the other race whereas the Applicant classified this subject as white. The Applicant did not provide subgroup analyses for other races. The reviewer conducted subgroup analyses by combining other races.

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Table 25 Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 by Race-Snapshot Analysis (ITT-E Population)

	Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion% (95% CI)
SWORD-1			
White	CAR	179/188 (95)	-0.8(-5.2,3.7)
	DTG + RPV	187/198 (94)	
African American/African Heritage	CAR	25 / 27 (93)	3.2(-9.7, 16.2)
	DTG + RPV	23 / 24(96)	
Other	CAR	41 / 41 (100)	N/A
	DTG + RPV	30 / 30 (100)	
SWORD-2			
White	CAR	199/210 (95)	-1.5 (-6.0, 3.0)
	DTG + RPV	208/223 (93)	
African American/African Heritage	CAR	19 / 20 (95)	4.8 (-4.4,13.9)
	DTG + RPV	13 / 13(100)	
Other	CAR	22 / 25(88)	12.0 (-1.0, 25.0)
	DTG + RPV	25/25(100)	
POOLED			
White	CAR	378/398 (95)	-1.2%, (-4.3, 2.0)
	DTG + RPV	395/421(94)	
African American/ African Heritage	CAR	44 / 47 (94)	3.0(-3.7, 12.0)
	DTG + RPV	36 /3 7 (97)	
Other	CAR	63 / 66 (95)	5.0 (-4.8, 9.6)
	DTG + RPV	55 / 55 (100.0)	

Source: Statistical reviewer's table

Subgroup Analyses by Baseline Characteristics- Baseline Third agent and CD4+ Cell Count

Baseline Third Agent:

The reviewer computed treatment differences by Baseline third agent class. In both treatment groups, the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 was similar in each of the baseline third agent class groups (**Table 26**). The test for homogeneity of the treatment difference across baseline third agent class was not statistically significant.

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Table 26 Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 in SWORD-1 , SWORD-2 and Pooled Studies by Baseline Third Agent - Snapshot Analysis (ITT-E Population)

STUDY	Third agent	Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion (95% CI)
SWORD-1	PI	CAR	68 / 74 (92)	2.8 (-5.3, 10.8)
		DTG + RPV	71 / 75 (95)	
	NNRTI	CAR	131/134 (98)	-3.1 (-7.7, 1.5)
		DTG + RPV	124/131 (95)	
	INSTI	CAR	46 / 48 (96)	2.0 (-5.1, 9.0)
		DTG + RPV	45 / 46 (98)	
SWORD-2	PI	CAR	60 / 62 (97)	-5.4 (-13.9,3.1)
		DTG + RPV	53 / 58 (91)	
	NNRTI	CAR	134/144 (93)	3.5 (-1.6, 8.6)
		DTG + RPV	139/144 (97)	
	INSTI	CAR	46 / 49 (94)	-2.4 (-12.1,7.4)
		DTG + RPV	54 / 59 (92)	
POOLED	PI	CAR	128/136 (94)	-0.9 (-6.7, 4.9)
		DTG + RPV	124/133 (93)	
	NNRTI	CAR	265/278 (95)	0.3 (-3.1, 3.8)
		DTG + RPV	263/275 (96)	
	INSTI	CAR	92 / 97 (95)	-0.6 (-6.8, 5.7)
		DTG + RPV	99 /105 (94)	

Source: Statistical reviewer's Table/Applicant's CSR Table 24, page 99 for SWORD-1 and Table 24, page 98 for SWORD-2

CD4+ Lymphocyte Count Subgroup

The reviewer computed the proportions of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 by baseline CD4+ lymphocyte count group endpoint. The results are summarized in the following **Table 27**. The efficacy rates were comparable between the two groups in the SWORD studies, except when the sample sizes were less than 25. In the pooled analyses, the efficacy rates were comparable between the two groups.

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Table 27 Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 by CD4+ Lymphocyte Count, Snapshot Analysis (ITT-E Population)

Treatment	Number Responded/ Total Assessed	Difference in Proportion, % (95% CI)
SWORD-1		
<200 cells/mm^3		
DTG + RPV	5 / 6 (83)	16.7 (-44.4, 77.8)
CAR	2 / 3 (67)	
200 - <350		
DTG + RPV	18 / 22 (82)	-14.0 (-32.0, 4.0)
CAR	23 / 24 (96)	
350 - <500		
DTG + RPV	55 / 57 (96)	-3.5 (-8.3, 1.3)
CAR	47 /4 7 (100)	
≥500		
DTG + RPV	162/167 (97)	2.0 (-2.1, 6.0)
CAR	173/182 (95)	
Treatment	**Number Responded/ Total Assessed**	**Difference in Proportion, % (95% CI)**
SWORD-2		
<200		
DTG + RPV	5 / 5 (100)	NA
CAR	5 / 5 (100)	
200 - <350		
DTG + RPV	23 / 25 (92)	12.0 (-8.5, 32.5)
CAR	16 / 20 (80)	
350 - <500		
DTG + RPV	50/50 (100)	8.0 (0.5, 15.5)
CAR	46 /5 0 (92)	
≥500		
DTG + RPV	168/181 (93)	-3.3 (-8.0, 1.4)
CAR	173/180 (96)	
Treatment	**Number Responded/ Total Assessed**	**Difference in Proportion, % (95% CI)**
POOLED		
<200		
DTG + RPV	10 / 11 (91)	3.4 (-25.1, 31.9)
CAR	7 / 8 (88)	
200 - <350		
DTG + RPV	41 / 47 (87)	-1.4 (-14.8, 12.0)
CAR	39 / 44 (89)	
350 - <500		

DTG + RPV	105/107 (98)	2.3 (-2.5, 7.0)
CAR	93/97 (96)	
≥500		
DTG + RPV	330/348 (95)	--0.8 (-3.9, 2.4)
CAR	346/362 (96)	

Source: Statistical reviewer's table/Applicant's CSR Table 28, page 105 for SWORD-1 and Table 29, page 105 for SWORD-2

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Please refer to the multiple analyses conducted for SWORD-1 and SWORD-2 and summarized under section 7.2 (Review of Relevant Individual Trials Used to Support Efficacy). Because the two trials were identical, the analyses were pooled to present the overall outcome for the two trials. For each analysis table presented in section 7.2, a column was added to present the results for the pooled analysis.

7.3.2. Integrated Assessment of Effectiveness

In SWORD-1 and SWORD-2, the combined dolutegravir and rilpivirine regimen achieved non-inferior viral suppression at 48 weeks compared with a three-drug regimen. The treatment effect was further supported by comparable results across groups for demographic and baseline subgroups.

7.4. Conclusions and Recommendations

The primary efficacy endpoint for the SWORD trials was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm. An important primary endpoint for switch trials is also the proportion of subjects with HIV RNA ≥ 50 copies/mL using the Snapshot algorithm. Based on the review of the submitted data, DTG+RPV was non-inferior to the continuation of CAR in virologically suppressed, HIV-1-infected adults. At Week 48, the NI margin based on the Division's preferred primary endpoint for switch trials (proportion of subjects who were virologic failures (HIV-1 RNA $\underline{\geq}$ 50 copies/mL) was met. The pre-specified NI margin was 4%. At Week 48, the proportion of subjects who were virologic failures was 0.6% and 1% in the DTG+RPV and CAR treatment groups, respectively [adjusted treatment difference and 95% CI: -0.6 (-1.7%, 0.6%)]. Additionally, in the pooled analysis, the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 95% in the DTG+RPV treatment group and the current antiretroviral regimen (CAR) group [adjusted treatment difference and 95% CI: -0.2% (-3.0%, 2.5%)]. Therefore, approval of this NDA is recommended.

8 Virology

8.1 Nonclinical Virology

Please refer to the Microbiology reviews of NDA202022 S002 for complete nonclinical virology review of rilpivirine and to NDA204790 SDN000 for complete nonclinical virology review of dolutegravir.

8.1.1 Mechanism of Action

Dolutegravir (DTG) inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for formation of the provirus. Strand transfer biochemical assays using purified recombinant HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. It non-competitively inhibits the viral encoded reverse transcriptase and thereby disrupts viral replication. Using a primer extension-based scintillation proximity assay, the median inhibitory activity (IC_{50}) of HIV-1 RT by rilpivirine was 42 nM.

8.1.2 Antiviral Activity in Cell Culture

Dolutegravir EC_{50} values were 0.51 nM and 0.53 nM against HIV-1 strain BaL or HIV-1 strain NL432, respectively, in PBMCs. MT-4 cells infected with HIV-1 strain IIIB and incubated with dolutegravir for 4 or 5 days resulted in EC_{50} values of 0.71 nM and 2.1 nM. Dolutegravir exhibits antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from the clinical isolates. Dolutegravir demonstrates antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G and 3 group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values ranged from 0.09 nM to 0.61 nM when tested against 3 HIV-2 clinical isolates in PBMC assays.

Rilpivirine had antiviral activity against wildtype laboratory strain HIV-1IIIB in the MT4 T-cell line with a median EC_{50} value of 0.73 nM and a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM. Rilpivirine was less active against group O primary isolates with EC_{50} values ranging from 2.9 to 8.5 nM and demonstrated limited activity in cell culture against HIV-2 with a median EC_{50} value of 5220 nM (range 2510 to 10830 nM).

8.1.3 Cell Culture Resistance

Dolutegravir-resistant viruses were selected in cell culture starting from wild-type HIV-1 strain IIIB and had a 4-fold maximum fold decrease in susceptibility for the passaged resistant virus

populations with substitutions S153F and S153Y in integrase. Passage of the wild-type HIV-1 strain NL432 in the presence of dolutegravir selected for E92Q (passage population virus fold change = 3.1) and G193E (passage population virus fold-change = 3.2) substitutions. Additional passage of wild-type clade B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T. Passage of mutant viruses with the Q148R or H substitutions selected for additional substitutions in integrase including L74M, E92Q, T97A, E138K, G140S, M154I, and N155H.

The susceptibility of DTG was tested against 60 integrase inhibitor-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 integrase inhibitor-resistant site-directed mutant HIV-2 viruses. Single INSTI substitutions T66K, I151L and S153Y conferred a >2-fold decrease in DTG susceptibility (range 2.3- to 3.6-fold). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148H and substitutions at E138/G140/Q148 showed a >2-fold decrease in DTG susceptibility (range 2.5 to 21). In HIV-2 mutants, substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in DTG susceptibility and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in DTG susceptibility, respectively.

Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1. The frequently observed amino acid substitutions that emerged in cell culture selection experiments and conferred decreased susceptibility to rilpivirine included: L100I, K101E and P, V106I and A, V108I, E138K and G, Q, R, V179F and I, Y181C and I, V189I, G190E, H221Y, F227C and M230I and L.

8.2 Clinical Virology

8.2.1 Methodology

In the SWORD studies, a HIV-1 RNA viral load value of ≥50 copies/mL mandated repeat assessment of viral load. The subjects who had 2 consecutive viral loads ≥50 copies/mL, with the second one being >200 copies/mL (the second being the confirmatory virology sample) were analyzed for resistance. The study allowed any subjects with a second virology sample of ≥50 and <200 copies/mL to be evaluated for possible mitigating circumstances that could have led to low-level viral load increases. If they failed to suppress to <50 copies/mL on a third viral load test, or, if there was no mitigating reason for the repeated increase to >50 copies/mL, then the subject met virologic withdrawal criteria.

8.2.2 Clinical Virology Analyses of Efficacy

There were 5 subjects in Study 201636 and 4 subjects in Study 201637 assessed for virologic failure.

SWORD-1 (Study 201636)

Subject (b) (6):

- This subject (randomized to DTG + RPV treatment arm) had a viral load of 88 copies/mL at Week 24 followed by confirmation time point viral load of 466 copies/mL.
- Resistance testing of the Virologic Withdrawal confirmation time point showed integrase substitution G193E with no change in DTG susceptibility; fold change compared with wild-type (FC) = 1.02.
- At Baseline, G193E was detected in exploratory HIV-1 DNA archive sequencing assay. No phenotypic data are generated in this assay.
- Subject withdrew from study with a decreased HIV-1 RNA of 162 copies/mL.
- Resistance testing was carried out at the Week 24 confirmation time point as the viral load at the Week 24 Virologic Withdrawal time point (88 copies/mL) was below resistance testing cutoff.

Subject (b) (6)

- This subject (randomized to CAR treatment arm and receiving Truvada+darunavir/r) had a viral load of 712 copies/mL at Week 48 followed by confirmation time point viral load of 323 copies/mL.
- No RT-, PRO- or INSTI-associated major IAS resistance substitutions were detected at the virologic withdrawal time point.
- Subject withdrew from study with a decreased viral load of 232 copies/mL.

Subject (b) (6)

- This subject (randomized to DTG + RPV treatment group) had an elevated viral load at Week 36 of 55 copies/mL. At subsequent confirmation time point subject had a viral load of 73 copies/mL.
- Resistance testing was not performed on the Week 36 time point sample as the viral load (55 copies/mL) was below testing cutoff.
- Subject withdrew from study with viral load <50 copies/mL.

Subject (b) (6)

- This subject (randomized to CAR treatment arm and receiving TIVICAY+KIVEXA through Week 48) had a viral load of 833 copies/mL at Week 64 followed by confirmation time point viral load of 1174 copies/mL.
- The subject withdrew from study with viral load <50 copies/mL. Resistance testing was not reported in time for the Week 48 analysis.

Subject 2 (b) (6)

- Subject 1072 (randomized to CAR treatment arm and receiving ABC+3TC+ATV through Week 48) at Week 64 with sequential viral loads of 79 copies/mL and

162 copies/mL.
- Resistance testing was not performed on the Week 64 virologic withdrawal time point sample due to low viral load (79 copies/mL).

SWORD-2 (Study 201637)

Subject (b) (6)
- This subject (randomized to CAR group and receiving DTG + KIVEXA) had a Day 1 viral load of 83 copies/mL, and suppressed to <50 copies/mL until Week 24 with a viral load of 86 copies/mL and a confirmatory viral load of 217 copies/mL at Week 24 retest.
- Resistance testing was not performed on the Week 24 time point sample as the viral load (86 copies/mL) was below testing cutoff.
- Subject withdrew from the study with viral load <50 copies/mL.

Subject (b) (6)
- This subject (randomized to DTG + RPV group) had a viral load of 1,059,771 copies/mL at Week 36. Following resumption of DTG+RPV, the subject had a subsequent 3-$\log_{10}$ decline in viral load with viral load of 1,018 copies/mL.
- At the virologic withdrawal time point, a K101K/E substitution mixture was detected in RT with no decreased susceptibility to RPV.
- Integrase resistance testing showed I84L and F181F/Y substitutions at Week 36.
- The K101E substitution in RT was not detected alone or as a mixture at Baseline by the DNA archive assay.
- Subject withdrew from study with viral load <50 copies/mL.

Subject (b) (6)
- This subject (randomized to CAR group and receiving Atripla) had elevated viral load of 853 copies/mL at Week 4, followed sequentially by viral loads of 89 copies/mL, 86 copies/mL, and 60 copies/mL.
- Resistance testing of the first sample of the Week 4 time point showed polymorphic integrase substitution V151I with no change in DTG susceptibility (fold change compared with wild-type fold change = 0.89). No RT and PRO substitution was observed and the subject was susceptible to all drugs accessed.
- At Baseline, V151I was detected with the HIV-1 DNA archive assay. No phenotypic data are generated in this assay.
- Subject withdrew from study with viral load <50 copies/mL.

Subject (b) (6)
- This subject (randomized to CAR group and receiving Stribild) had elevated viral load of 74 copies/mL at Week 8, followed sequentially by viral loads of 78 copies/mL at Week 12, and then 55 copies/mL.
- The PI-identified URTI as the potential cause of the initial elevated viral load, with

subsequent viral load elevations potentially due to multiple vaccines the subject received between Week 8 and Week 12. After resolution of the intercurrent illness and immunization, and on further discussion between the PI and the Medical Monitor, the subject was allowed to stay on study.

- Resistance testing was not performed on the Week 12 timepoint sample as the viral load is below testing cutoff.
- At Week 24 subject viral load was suppressed to <50 copies/mL and the subject remained on study.

After assessment of the above data, 4 subjects were concluded to have confirmed virologic failure (b) (6). Thus, in the pooled studies (SWORD-1 and 2), 2 subjects in each treatment arm met the confirmed virologic withdrawal criteria at any time during through Week 48.

8.2.3. Resistance Analyses

Table 28 shows the resistance data from the 4 virologic failure subjects in the SWORD studies.

Table 28 Virologic Failure Subjects from Studies 201636 and 201637 with Resistance Data

PID	Arm	Timepoint	Viral Load	INSTI Substitutions	NNRTI Substitutions	Phenotype
(b) (6)	DTG RPV	Week 24	466 copies/mL	V72I M154M/I/L **G193E**	K104K/R V189V/I G196E	DTG 1.02 RPV 0.01
	CAR [DRV/r FTC TDF]	Week 48	712 copies/mL	V72I	G196E	DRV 0.66 FTC1.08 TDF 1.02
	CAR [EFV FTC TDF]	Week 4	853 copies/mL	V72V/I V151I M154I	K104R	EFV 1.04 FTC 0.96 TDF 0.92
	DTG RPV	Week 36	1059 copies/mL	I84L F181F/Y	**K101K/E**	DTG 1.64 RPV 1.21

itutions are resistance-associated substitutions.
PID = Patient Identification

8.3 Conclusions and Recommendations

In the pooled SWORD-1 and SWORD-2 studies, 2 virologic failure subjects in each treatment arm met confirmed virologic withdrawal (CVW) criteria at any time through Week 48. The 2 virologic failure subjects in the dolutegravir/rilpivirine arms had detectable resistance substitutions at rebound. One subject had the NNRTI-resistance-associated substitution K101K/E with no decreased susceptibility to rilpivirine (fold-change = 1.2) at Week 36. This

subject had identified non-adherence but resumed dolutegravir plus rilpivirine and had less than 50 copies per mL at the withdrawal visit. The other subject had the dolutegravir resistance substitution G193E, but no detectable phenotypic resistance (fold-change = 1.02) at Week 24. No resistance-associated substitutions were observed in the 2 subjects in the comparative current antiretroviral regimen arms.

This NDA for a fixed-dose combination (FDC) of dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), an non-nucleotide reverse transcriptase inhibitor (NNRTI) is approvable with respect to virology for the treatment of HIV-1 in adults who are virologically suppressed (<50 copies/mL) without known or suspected resistance to either DTG or RPV.

The following modifications to Section 12.4 of the product label are recommended:

Virologically Suppressed Subjects:
In the pooled SWORD-1 and SWORD-2 trials, 2 subjects in each treatment arm had confirmed virologic failure at any time through Week 48. The 2 subjects in the dolutegravir/rilpivirine arms had detectable resistance substitutions at rebound. One subject had the NNRTI-resistance-associated substitution K101K/E with no decreased susceptibility to rilpivirine (fold-change = 1.2) at Week 36, had no INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir (fold-change less than 2), and had HIV-1 RNA less than 50 copies per mL at the withdrawal visit. The other subject had the dolutegravir resistance-associated substitution G193E at baseline (by exploratory HIV DNA archive sequencing) and Week 24 (by conventional sequencing) without decreased susceptibility to dolutegravir (fold-change = 1.02) at Week 24. No resistance-associated substitutions were observed for the other 2 subjects in the comparative current antiretroviral regimen arms.

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9 Review of Safety

9.1. Overview of Safety

The benefits-risks assessment for DTG/RPV FDC was established through 1) two Phase 3 safety and efficacy trials using the individual drug products, 2) a drug-drug-interaction (DDI) study for DTG plus RPV, and 3) a relative oral bioavailability study and a bioequivalence study confirming that the FDC is equivalent to the co-administration of the individual drug products, DTG plus RPV.

Severe hypersensitivity reactions, liver chemistry abnormalities, renal (elevation is serum creatinine) and psychiatric events were the primary safety issues identified for DTG during the original NDA review. No exposure-response or dose-response correlations were observed with regards to safety outcomes. Similarly, depressive disorders, hepatotoxicity, rash and hypersensitivity, and renal events (elevation is serum creatinine) were the primary safety signal described for RPV at the time of the original NDA review. Again, no exposure-response or dose-response correlations were observed.

Please refer to the respective individual drug products NDA reviews (204790, DTG; 202022, RPV) and Prescribing Information for details on the safety profile of each drug product.

9.1.1. Safety Review Approach

Data from two identical switch trials (SWORD-1 and SWORD-2) were reviewed to support safety for DTG 50 mg plus RPV 25mg QD. The phase 3 trials only differed by country or clinical trial sites locations. Because the two trials were identical, an integrated assessment of safety was conducted.

SWORD-1 and SWORD-2 are ongoing, randomized, open-label, 148-week studies, to evaluate the non-inferiority of switching to DTG 50 mg plus RPV 25 mg once daily compared to continuation of current INSTI-, NNRTI-, or PI- based ARV regimen in HIV-1-infected adults who are virologically suppressed (HIV-1 RNA <50 c/mL). The trial is divided into an Early Switch (ES) Phase and Late Switch (LS) Phase. After screening and randomization, subjects enter the ES phase to either switch their current regimen to DTG plus RPV or continue their current antiretroviral regimen (CAR). The Late Switch Phase started at Week 52 (i.e., the visit where the CAR group switches to DTG + RPV). The data for the randomized comparative assessment is thus derived from the Early Switch Phase, up to the cut-off date (22 November 2016). Additional key safety evaluations were conducted (e.g., SAEs, Grade 2-4 AEs, adverse events of special interest (AESI), withdrawals) for subjects who continued on the study to enter the Late Switch Phase and had available data for analyses.

Additionally, the 60-day Safety Update Report including SAEs, pregnancies, and AEs leading to

discontinuation from 23 November 2016 to 30 June 2017 was reviewed.

The adverse events were categorized by the Applicant using MedDRA standardized criteria. Causality assigned by the investigator was reviewed. Because the safety profiles for DTG and RPV are already well described, adverse events of special interest (AESI) were identified using the pre-existing characterization for the individual drug products.

9.1.2. Review of the Safety Database

Overall Exposure

A total of 513 subjects were exposed to at least one DTG + RPV dose in the clinical trials during the Early Switch (ES) Phase and up to the NDA data cut-off date. The median time of exposure to DTG + RPV was 364 days (52 weeks) for the individual trials and the pooled data. Please refer to **Table 29** for summary of exposure.

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Table 29 Summary of Extent of Exposure during the Early Switch Phase in Studies 201636, 201637, and Pooled Data (Safety Population)

	POOLED	
	DTG + RPV (N=513)	CAR (N=511)
Exposure (Weeks) n (%)		
<2 weeks	3 (<1)	1 (<1)
2 to <4 weeks	1 (<1)	1 (<1)
4 to <8 weeks	2 (<1)	3 (<1)
8 to <12 weeks	2 (<1)	2 (<1)
12 to <16 weeks	3 (<1)	1 (<1)
16 to <20 weeks	2 (<1)	0
20 to <24 weeks	1 (<1)	1 (<1)
24 to <28 weeks	2 (<1)	2 (<1)
28 to <32 weeks	3 (<1)	3 (<1)
32 to <36 weeks	3 (<1)	2 (<1)
36 to <40 weeks	3 (<1)	3 (<1)
40 to <44 weeks	2 (<1)	1 (<1)
44 to <48 weeks	2 (<1)	2 (<1)
48 to <52 weeks	1 (<1)	196 (38)
≥52 weeks[b]	483 (94)	293 (57)
Exposure (Days)		
Mean (SD)	352.4 (52.85)	355.5 (45.55)
Median (IQR)	364.0 (364.0 -364.0)	364.0 (362.0 -365.0)
Duration of dosing in cumulative subject years[a]	495.0	497.4

Data Source: Summary Clinical Safety Table 5
a. Cumulative sum across subjects of (treatment stop date - treatment start date + 1) divided by 365.25
b. For CAR subjects, exposure in the Early Switch Phase is calculated to the day prior to switching to DTG + RPV or to withdrawal where withdrawal took place sooner. For DTG + RPV subjects, exposure in the Early Switch Phase is calculated as 52 weeks (364 days) or to withdrawal if withdrawal took place sooner.

Relevant characteristics of the safety population

Please refer to **Demographic** characteristics were well balanced across treatment groups in both SWORD studies. In SWORD-1, 23% of subjects in the DTG + RPV group and 20% of subjects in the CAR group were women, and 27% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. In SWORD-2, 24% of subjects in the DTG + RPV group and 22% of subjects in the CAR group were women, and 30% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. The majority of subjects were white in both studies.

Table 14 which describes the demographics for the subjects enrolled in the two Phase 3 clinical trials. The safety of DTG and RPV based on race, gender, hepatic- and renal- function were previously characterized during the original or supplemental NDA reviews. Please refer to the reviews of the respective NDAs for details and to section 9.1.6 of this review for safety analyses based on race, gender and age. Efficacy outcomes by race and gender were also evaluated during this NDA review. Please refer to the efficacy section (7.2) **Table 13**, **Table 14**, and **Table 15** for details. Caution should be exercised when interpreting the results for the aforementioned subgroups as the trials were not powered for subpopulation-specific analysis. Of note, the study was designed to target enrollment of approximately 15% women and 15% older adults (> 50 years old). The trial met its target and enrolled >20% women (DTG + RPV 23%, CAR 21%), and > 15% older subjects (DTG + RPV group 29%, CAR group 28%).

Adequacy of the safety database

SWORD-1 and SWORD-2 provided sufficient safety data to allow for the assessment of the safety of DTG and RPV when administered together in HIV-1 infected adults. A total of 513 subjects were exposed to DTG plus RPV during the clinical trials. Additionally, each drug product has also been previously reviewed and the respective safety profiles are well characterized.

Therefore, the data available to date are sufficient to support the safe use of Juluca in patients who are currently on suppressive (HIV RNA <50 copies/mL) ARV regimen and have no history of virologic failure or resistance to the components of Juluca, (b) (4)

9.1.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Please also refer to section 4.1 for details. No issues regarding data integrity or submission quality were observed.

Categorization of Adverse Events

The Applicant provided accurate definitions for adverse events (AEs), severity of AEs and serious AEs (SAEs) in the Phase 3 protocols. While AEs refer to any adverse events without regards to causality, adverse drug reaction (ADR) is a term that describes events considered to be treatment-related; causality was assigned by the investigators. For the purpose of this review, the terms AE(s) and ADR(s) refer to events that occurred during treatment with study drugs. Therefore, AE(s) and ADR(s) are synonymous with treatment-emergent AE(s) and ADR(s), respectively.

Note that adverse reaction (AR) is used in the Prescribing Information to describe ADR. Therefore, ADR and AR are synonymous.

MedDRA dictionary was utilized for coding adverse events and the Applicant's translation of 'verbatim terms' to 'preferred terms' was accurate. Adverse events were further categorized by MedDRA High-Level Group Terms (HLGT), and System Organ Class (SOC). Additional grouping of terms was utilized during the review to identify select adverse events of interest. The DAIDS Table for Toxicity was used for grading adverse events. Adverse events were also followed to account for outcomes (e.g. resolved, ongoing/not-resolved).

Routine Clinical Tests

Routine clinical evaluations for safety included medical history for assessment of symptoms of adverse events, vital sign measurements (Baseline) and physical examinations for assessment of signs of adverse events, laboratory evaluations and ECG (Screening). In the phase 3 trials, key evaluations were performed at Baseline, Weeks 2, 4, 8, 12, 24, 24, 36, and 48 during the ES phase and at Week 52 (Switch Visit). During the LS Phase, the visits were scheduled at Week 56, 64, 76, 88, 100 then every 12 weeks until Week 148. Follow-up visits were scheduled for subjects who discontinued treatment prematurely due to adverse events.

9.1.4. Safety Results

Deaths

Two deaths were reported during the ES phase. One subject in the DTG + RPV group died due Kaposi's sarcoma; another subject in the CAR group died due to malignant lung neoplasm. Neither event was considered related to study treatment by the investigator. The investigator assessment is reasonable. Brief summaries for each of the cases are provided below:

- Subject (b) (6) was a 35-year old white male who switched from DRV, RTV, TDF/FTC based-regimen. The subject was randomly assigned to switch to DTG + RPV at Baseline (b) (6). The subject's CDC classification at Baseline was Category C (AIDS) and his HIV RNA was < 50 copies/mL. His HIV RNA was <40 copies/mL at all visits through his last visit at Week 24. His CD4 count was 289 cells/mm^3 at Week 24. Adverse events reported during the 24-weeks of treatment included respiratory tract infection and oral candidiasis. The subject experienced a fatal AE of Kaposi's sarcoma on Day 207, which was considered not related to study treatment by the Investigator.

- Subject (b) (6) was a 53-year old white male, with a baseline regimen of DRV, RTV, TDF/FTC; he was randomized to CAR and continued this regimen. The subject had a history of lung cancer. During the clinical trial, the subject presented with pain in the back. An MRI revealed neoplasms in the lungs. The subject died in (b) (6); an

autopsy reported cause of death as lung cancer.

One additional death was identified during the 60-day Safety Update Report.

- Subject (b) (6) was a 36-year old male. He was diagnosed with grade 3 plasmablastic lymphoma, 28 days after starting DTG + RPV. His CD4 cell count was low throughout the trial. He was asymptomatic until the Week 4 appointment, when he presented with weight loss (12kg) and adenopathy. Plasmablastic lymphoma was subsequently diagnosed. The patient was withdrawn from the trial. Despite chemotherapy, subject succumbed to the lymphoma.

Serious Adverse Events

As summarized in **Table 30**Table 30**,** during the ES phase, 27 (5%) and 21(4%) of DTG + RPV- and CAR- treated subjects experienced SAE, respectively.

Table 30 SAEs during Early Switch Phase Reported in at Least One Subject from DTG+RPV Group

SAE, by preferred term	DTG + RPV N=513	CAR N=511
Any subject with SAE	27(5%)	21(4%)
Pneumonia	3 (0.6%)	0 (0.0%)
Acute kidney injury	1 (0.2%)	0 (0.0%)
Depression	1 (0.2%)	0 (0.0%)
Suicide attempt	1 (0.2%)	1 (0.2%)
Panic attack	1 (0.2%)	0 (0.0%)
Vertigo	1 (0.2%)	0 (0.0%)
Drug-induced liver injury	1 (0.2%)	0 (0.0%)
Pancreatitis acute	1 (0.2%)	0 (0.0%)
Eosinophilic pneumonia acute	1 (0.2%)	0 (0.0%)
Abscess limb	1 (0.2%)	0 (0.0%)
Alcohol poisoning	1 (0.2%)	0 (0.0%)
Cholecystitis chronic	1 (0.2%)	0 (0.0%)
Facial bones fracture	1 (0.2%)	0 (0.0%)
Gastroenteritis	1 (0.2%)	0 (0.0%)
Gastrointestinal haemorrhage	1 (0.2%)	0 (0.0%)
Gastrooesophageal reflux disease	1 (0.2%)	0 (0.0%)
Haemarthrosis	1 (0.2%)	0 (0.0%)
Headache	1 (0.2%)	0 (0.0%)
Hodgkin's disease mixed cellularity stage unspecified	1 (0.2%)	0 (0.0%)
Kaposi's sarcoma	1 (0.2%)	0 (0.0%)
Lymphogranuloma venereum	1 (0.2%)	0 (0.0%)
Orchitis	1 (0.2%)	0 (0.0%)

Periorbital cellulitis	1 (0.2%)	0 (0.0%)
Plasmablastic lymphoma	1 (0.2%)	0 (0.0%)
Pulmonary sepsis	1 (0.2%)	0 (0.0%)
Renal colic	1 (0.2%)	0 (0.0%)
Rotavirus infection	1 (0.2%)	0 (0.0%)
Tibia fracture	1 (0.2%)	0 (0.0%)
Wrist fracture	1 (0.2%)	0 (0.0%)

Data Source: FDA Adverse Events Analysis Dataset

Of the reported SAEs, 4(<1%) and 1(<1%) of the DTG +RPV- and CAR-treated subjects had drug-related SAEs, further summarized below. Of note, depression, including suicide attempt and drug-induced liver injury are included in product labeling for both DTG and RPV. Therefore, summaries of these events are not included below. SAE summary (suicide attempt) for the CAR treatment group is also not provided below.

- **Subject** (b) (6) **(SAE - Pancreatitis acute)** is a 31-year-old male with a past medical history of alcohol intake. The subject had a Baseline lipase value of 173 U/L (normal range of 7-60). Apparently, the subject had 'significantly higher' than usual intake of alcohol and fatty food intake 1 week prior to the SAE. At the Week 24 visit (Day 174), the subject was asymptomatic but had a Grade 4 increase in lipase (to 1153 U/L per local site or 228 U/L once converted for normal range of 7 - 60]). The subject's lipase was 2200 U/L the following day and described slight abdominal pain for which he was hospitalized. The subject was treated with glucose + dextrose. DTG and RPV were discontinued. There were no findings from an abdominal CT examination, and lipase values normalized post discontinuation; lipase remained in the normal range and the SAE of pancreatitis acute was considered recovered/resolved 3 days after hospitalization (lipase 218 U/L). Based on review of this case, the reviewer concurs with the assessment of the Investigator that this case could be related to study drugs, however the case is confounded by the temporally related history of heavy alcohol and fatty food consumption.

Of note, a post-marketing safety assessment was conducted to evaluate the relationship between use of DTG and pancreatitis. Based on the assessment, no clear relationship was identified. The recommendation at this time is to continue routine pharmacovigilance monitoring. Given the current case is confounded with heavy intake of alcohol and fatty food, no new labeling recommendations are made at this time to include pancreatitis as an ADR.

- **Subject** (b) (6) **(SAE – Eosinophilic pneumonia acute)** is a 54-year-old female who received her first dose of study treatment in (b) (6), but had been taking DTG since (b) (6) Concomitant products included azithromycin, fluticasone propionate, salmeterol xinafoate, prednisone, cefuroxime, ranitidine, and flurazepam. Approximately 195 days after first dose of study drug (DTG + RPV), the subject was hospitalized with Grade 3 acute eosinophilic pneumonia and treated. Thoracic CT was suggestive of infectious involvement. A bronchoalveolar lavage (BAL) showed an

> inflammatory smear with polymorphonuclear neutrophil predominance (65%) and macrophages (35%); negative for malignant cells. A blood C-reactive protein was 20.37 mg/dL (normal range: 0.00, 0.5) and peripheral eosinophil count was '1400 ul' (normal range: 0.00 -0.4). An infectious cause was eliminated from the differential diagnosis and treatment with steroids was started, after which clinical and radiological improvement was observed. The outcome of the acute eosinophilic pneumonia was not recovered/not resolved but the subject was discharged from the hospital and continued on corticosteroid treatment. DTG and RPV were discontinued.

Though no eosinophils were observed in the BAL, the event was considered possibly related to study drugs because no infectious cause was identified and there was evidence of an increase in the peripheral eosinophil count. In additional, the subject improved after initialization of steroid therapy.

At the time of the data cut-off date, 960 subjects had some safety data beyond the Week 48 visit and included 483 (94%) from the DTG+RPV treatment arm and 477 (93%) from the CAR treatment arm who switched to DTG+RPV at the Week 52 visit. Overall, no new safety trends were identified. Of the subjects who were in the DTG+ RPV treatment group starting from Baseline ('early switchers'), 157 (31%) experienced at least 1 AE post Week 48. Of the subjects who switched to DTG+RPV at the Week 52 visit ('late switchers'), 171 (34%) experienced at least 1 AE after entering the LS Phase. The majority of the events were mild or moderate. Five (1%) among those who initiated DTG+RPV at Baseline and 7 (1%) among the 'late switchers' reported grade 3 or 4 AEs. Few subjects (2% and 1% among the 'early' and 'late switchers', respectively) experienced SAEs and only 6 (1 from early and 5 from late switchers) subjects discontinued due to AEs.

Overall, based on the review of the available safety data from the LS Phase, the safety profile of DTG+RPV generally remained the same. Similarly, no new safety findings were identified from the SAEs reported during the 60-day SUR.

In summary, based on the review of the SAEs data, no new language is proposed for the JULUCA label. Inclusion of the safety information, as prescribed in the labels for Tivicay and Edurant is adequate to describe the safety profile for JULUCA.

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 21(4%) in the DTG+RPV treatment group and 3(1%) in the CAR treatment group discontinued treatment due to adverse events, as summarized in **Table 31**. Within the DTG+RPV treatment group, no AE leading to discontinuation was reported in more than one subject, except for depression (or depressive disorders, in general), insomnia, anxiety, abdominal distention, and dyspepsia.

Depressive disorders (including suicidal behaviors) are AEs already labeled as ADRs in both DTG and RPV Prescribing Information. Of note, no increase in the overall incidence of the depression

was noted when DTG and RPV were administered in combination.

Insomnia has also been previously observed with DTG and is a labeled ADR. Anxiety was also recently identified to be associated with use of DTG-containing regimens during the postmarketing review for Triumeq, in accordance with the requirement under section 505(r) [section 915 of FDAAA]. The Prescribing Information for all DTG-containing labels, including Juluca, will include anxiety as an ADR.

'Abdominal distension' and 'dyspepsia' are not described as ADR in either DTG or RPV Prescribing Information; however, similar PT terms such as abdominal pain, abdominal discomfort and flatulence are included in DTG label and abdominal discomfort is included in the RPV label.

In summary, the adverse event terms leading to discontinuation *and* reported in more than 1 subject are already adequately covered in the labels, thus there is no need for introduction of new terms in the Juluca label.

Table 31 Summary of Adverse Events Leading to Discontinuation

Standardized AE preferred term	DTG + RPV N=516	CAR N=512
Any subject who discontinued due to an AE	21 (4%)	3 (1%)
Anxiety	4 (1%)	0 (0%)
Depression	3 (1%)	0 (0%)
Insomnia	2 (0.2%)	0 (0%)
Abdominal distension	2 (0.2%)	0 (0%)
Dyspepsia	2 (0.2%)	0 (0%)
Depressed mood	1 (0.2%)	0 (0%)
Suicidal ideation	1 (0.2%)	0 (0%)
Panic attack	1 (0/2%)	0 (0%)
Headache	1 (0.2%)	0 (0%)
Drug-induced liver injury	1 (0.2%)	0 (0%)
Pancreatitis acute	1 (0.2%)	0 (0%)
Eosinophilic pneumonia acute	1 (0.2%)	0 (0%)
Gastrointestinal haemorrhage	1 (0.2%)	0 (0%)
Peptic ulcer	1 (0.2%)	0 (0%)
Hodgkin's disease mixed cellularity	1 (0.2%)	0 (0%)
Kaposi's sarcoma	1 (0.2%)	0 (0%)
Plasmablastic lymphoma	1 (0.2%)	0 (0%)
Tremor	1 (0.2%)	0 (0%)
Breast cancer	0 (0%)	1 (0.2%)
Lung neoplasm malignant	0 (0%)	1 (0.2%)
Suicide attempt	0 (0%)	1 (0.2%)

Data Source: FDA Adverse Events Analysis Dataset

During the LS Phase, an additional 6 subjects discontinued due to adverse events (1 randomized to DTG + RPV at Baseline and 5 who switched to DTG + RPV at Week 52). In summary, the reported events do not change the overall safety profile of DTG+RPV.

In brief, one subject randomized to DTG+RPV at Baseline experienced anal squamous cell carcinoma with accompanying abscess and metastases to lymph nodes. The event was Grade 3 and not considered to be related to study drug. The adverse events described for the remaining 5 subjects are as follows: Hodgkin's disease (n=1), blood glucose and transaminases increased (n=1); pain in extremity, diarrhea abdominal distension, constipation (n=1); abulia, aphasia, chest discomfort, confessional state, disturbance in attention (n=1); abortion induced (n=1).

Significant Adverse Events

Other Medically Serious Events

Evaluation of reported AEs according to CDER's list of Designated Medical Events (DME) was performed to identify subjects who experienced one of the following: acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis or anaphylactoid reaction, aplastic anemia, blindness, bone marrow depression, deafness, disseminated intravascular coagulation, hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens-Johnson syndrome, torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation. **Table 32** summarizes the AEs considered DME that occurred during the ES Phase.

Table 32 Summary of Designated Medical Events

Standardized AE preferred term	DTG+ RPV N=513	CAR N=511
Any subject with DME	9 (1.8%)	4 (0.8%)
Acute kidney injury	1 (0.2%)	0 (0.0%)
Deafness unilateral	1 (0.2%)	0 (0.0%)
Myoclonus	0 (0.0%)	1 (0.2%)
Pancreatitis acute	1 (0.2%)	0 (0.0%)
Renal failure	1 (0.2%)	0 (0.0%)
Renal impairment	1 (0.2%)	0 (0.0%)
Toxic skin eruption	0 (0.0%)	1 (0.2%)
Retinal detachment	0 (0.0%)	1 (0.2%)
Vision blurred	2 (0.4%)	0 (0.0%)
Visual acuity reduced	1 (0.2%)	0 (0.0%)
Visual field defect	1 (0.2%)	0 (0.0%)
Visual impairment	0 (0.0%)	1 (0.2%)

Data Source: FDA Adverse Events Analysis Dataset

Most AEs qualifying as a DME are discussed as part of safety events of interest in the subsequent section, described as 'Submission Specific Primary Safety Concerns'. Specifically, renal-, psychiatric- nervous system- and skin- related events are discussed in their respective sections. Pancreatitis was discussed under 'Serious Adverse Events' section. The few remaining AEs not covered elsewhere in this review are summarized below.

Eye-Disorders

Overall, among DTG+RPV treated subjects, there were 4 subjects from the ES phase and 1 additional subject from the LS Phase who experienced eye-disorders, including vision blurred (n=2), visual acuity reduced (n=1), visual field defect and (n=2). One subject from the CAR treatment group experienced visual impairment. None of the events were considered serious; none were Grade 3 or 4 and none led to treatment discontinuation. One subject experienced a treatment related Grade 2 AE (vision blurred). Of note, a consult was initiated with the Office of Safety and Epidemiology after identification of a literature case reporting occurrence of optic neuropathy in associated with elvitegravir (an approved INSTI)/cobicistat use. FAERS database and published medical literature was reviewed by OSE for an association between use of INSTI and optic neuropathy and other ocular events. Based on the review of the available data, OSE concluded that there is insufficient evidence to draw casual association between use of INSTIs and optic neuropathy or other related ocular events. Routine pharmacovigilance monitoring will continue.

Deafness

Assessment of the adverse event 'deafness, unilateral' did not suggest that the event was related to DTG+RPV. The event was Grade 1, non-serious, and not considered treatment related. The subject was able to continue on study medications. An additional subject reported bilateral deafness during the LS Phase. This subject switched to DTG+RPV at Week 52. The event was grade 1, non-serious, not treatment-related and did not lead to treatment discontinuation.

No additional DME were identified during the LS Phase.

Treatment Emergent Adverse Events and Adverse Reactions

The primary goal of the safety review for DTG+RPV was to assess any new safety signals associated with co-administration of DTG and RPV, including the potential for additive toxicities for certain adverse reactions previously recognized with the individual drug products. Of note, a higher incidence of adverse reactions is expected in the DTG+RPV treatment arm, compared to the CAR arm because subjects randomized to the DTG+ RPV treatment group are initiating a new regimen and are expected to experience new adverse reactions and tolerability issues. However, subjects randomized to continue CAR are less likely to experience new AEs because these subjects have been on their current regimen for at least 6 months prior to enrollment. Therefore, an increase in overall reported adverse reactions soon after switching to DTG+RPV regimen does not necessarily confer that DTG+RPV is a less tolerated regimen.

Table 33 summarizes the overall characteristics of the adverse events reported during the Early Switch (ES) Phase. During the ES Phase, more subjects in the DTG+RPV treatment group experienced adverse events (regardless of causality or severity), compared to the CAR treatment group (77% vs. 71%). The most commonly reported AEs (by preferred term) in at least 5% of DTG+RPV treated subjects were nasopharyngitis (10%), headache (8%), diarrhea (6%), and upper respiratory tract infection (5%). In the CAR treatment group, nasopharyngitis (10%), upper respiratory tract infection (7%), headache (5%), back pain (6%) and diarrhea (5%) were the most commonly reported preferred terms.

Most the AEs in both treatment arms were grade 1 or 2. Grade 3 events were also more commonly reported in the DTG+ RPV treatment group, 27(5%) vs. 17 (3%). Grade 4 AEs were reported in 5 (<1%) subjects (7 events) in the DTG + RPV group. The Grade 4 AEs were anxiety and depression (grade 4, n=1); hepatitis A (n=1), acute pancreatitis (n=1), suicidal ideation (n=1), Kaposi sarcoma (n=1). In the CAR treatment group, 3 subjects (3 events) were reported as grade 4 – blood creatine phosphokinase increased (n=1), hepatitis C (n=1), suicide attempt (n-=1).

Table 33 Overall Summary of Reported Adverse Events

	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any AE	**395 (77)**	**364 (71)**
Grade 1	247(48%)	244(48%)
Grade 2	116 (23%)	100 (20%)
Grade 3	27(5%)	17(3%)
Grade 4	5(<1%)	3(<1%)
Fatal SAEs	1 (<1%)	1 (<1%)
Drug-related Fatal SAE	0 (0%)	0 (0%)
Any SAE	27 (5%)	21 (4%)
Drug-related SAEs	4 (<1%)	1 (<1%)
AEs Leading to discontinuation	21 (4%)	3 (<1%)
Drug-related AEs Leading to	14 (3%)	1 (<1%)
Drug-related AEs	97 (19%)	9 (2%)
Grade 2 to 4 AEs	148 (29%)	120 (23%)
Drug-related Grade 2 to 4 AEs	29 (6%)	3 (<1%)

Data Source: FDA Adverse Events Analysis Dataset

Drug related adverse events (ADRs) are adverse events considered by investigator to be at least possibly related to study drug (DTG+ RPV). As expected, ADRs were more commonly reported in the DTG+ RPV treatment group 19% vs. 2%.

Table 34

Table 34 summarizes ADRs reported in at least 2 subjects. Of note, 'depressed mood', 'suicide ideation', 'sleep disorder', 'drug-induced liver injury', 'pruritus', 'abdominal discomfort', 'abdominal pain', 'GERD', 'acute pancreatitis' were also reported in the DTG+RPV treatment group in one subject each. These are AESI and are also reviewed under "Submission-Specific Safety Issues". Overall, the ADRs reported with co-administration of DTG+RPV are generally similar to the ADRs observed with use of the individual drug products, DTG and RPV.

Table 34 Summary of ADRs Reported in at least Two Subjects in the DTG+ RPV Treatment Group

Standardized AE preferred term	DTG + RPV N=516	CAR N=512
Any Subject with ADR	97 (19%)	9 (2%)
Headache	11 (2%)	0 (0%)
Diarrhoea	8 (2%)	1 (0.2%)
Abdominal distension	7 (1%)	0 (0%)
Nausea	7 (1%)	0 (0%)
Abnormal dreams	6 (1%)	0 (0%)
Dizziness	6 (1%)	1 (0.2%)
Insomnia	6 (1%)	1 (0.2%)
Flatulence	6 (1%)	0 (0%)
Abdominal pain upper	5 (1%)	0 (0%)
Anxiety	5 (1%)	1 (0.2%)
Depression	5 (1%)	0 (0%)
Fatigue	5 (1%)	0 (0%)
Asthenia	4 (1%)	0 (0%)
Rash	4 (1%)	0 (0%)
Dyspepsia	3 (1%)	2 (0.4%)
Alopecia	2 (0.4%)	0 (0%)
Constipation	2 (0.4%)	0 (0%)
Somnolence	2 (0.4%)	0 (0%)
Vertigo	2 (0.4%)	0 (0%)
Weight increased	2 (0.4%)	0 (0%)

Data Source: FDA Adverse Events Analysis Dataset

Laboratory Findings

This section presents results of grade 1-4 laboratory analysis for select laboratory parameters observed in the phase 3 trials. In general, the laboratory findings summarized below are similar between treatment groups. Please refer to 'hepatobiliary' and 'renal' sections for laboratory parameters related to serum liver biochemistry and serum creatinine, respectively.

Chemistry

Table 35 Summary of Subjects Meeting Laboratory Abnormality Criteria at Any Post-Baseline Visit

	DTG + RPV N=513	CAR N=511
Creatine Kinase		
Grade 1	19 (4%)	19 (4%)
Grade 2	4 (<1%)	5(<1%)
Grade 3	3 (<1%)	2 (<1%)
Grade 4	3 (<1%)	9 (2%)
Lipase		
Grade 1	15 (3%)	38(7%)
Grade 2	25 (5%)	24 (5%)
Grade 3	9 (2%)	5 (<1%)
Grade 4	2 (<1%)	6 (1%)

Data Source: FDA Electrolytes Analysis Dataset

Hematology

Table 36 Summary of Subjects Meeting Laboratory Abnormality Criteria at Any Post-Baseline Visit

	DTG + RPV N = 513	CAR N = 511
Hemoglobin		
Grade 1	2 (<1%)	7 (1%)
Grade 2	1 (<1%)	1 (<1%)
Grade 3	2 (<1%)	0 (%)
Grade 4	0 (%)	1 (<1%)
Neutrophils		
Grade 1	6 (1%)	12 (2%)
Grade 2	2 (<1%)	2 (<1%)
Grade 3	3 (<1%)	1 (<1%)
Grade 4	1 (<1)	0 ()%)
Platelets		
Grade 1	15 (3%)	3 (<1%)
Grade 2	1 (<1%)	2 (<1%)
Grade 3	1 (<1%)	0 (%)

Data Source: FDA Hematology Analysis Dataset

Vital Signs

As both drugs are previously approved products, vital signs were only recorded at Baseline.

Electrocardiograms (ECGs)

A 12-lead ECG was performed at Screening visit to assure subjects met QTc safety criteria. No additional ECG was performed. During the LS Phase, ECG was also performed for subjects switching to DTG + RPV.

QT

No new QT studies were conducted with the FDC because the individual drug products were already assessed for the potential to prolong QT interval. Please see the original NDA reviews as well as the Prescribing Information for DTG and RPV. RPV prolongs the QT interval at supra-therapeutic levels. DTG was not found to have effect on QT that meets the threshold for clinical concern. The proposed Juluca label appropriately includes a cardiac electrophysiology section (12.2) describing the effect of the individual drugs on QTc interval.

Immunogenicity

Neither DTG nor RPV is a peptide; therefore, immunogenicity effects were not specifically evaluated during the original development programs for the two drug products. Small molecules are highly unlikely to have a potential for immunogenicity.

9.1.5. Analysis of Submission-Specific Safety Issues

The following adverse events of interest were reviewed because these were identified as AESI during the original review for DTG or RPV:

- Hypersensitivity reactions and rash
- Hepatobiliary analysis (hepatobiliary AEs and hepatic laboratory analysis)
- Psychiatric AEs of interest
- Nervous system AEs of interest
- Gastrointestinal AEs of interest
- Musculoskeletal analysis (select musculoskeletal AEs and serum CK analysis)
- Cardiac AEs of interest
- Renal analysis (renal AEs and renal laboratory analysis)

Hypersensitivity Reactions and Rash

Overall, 14% in DTG+RPV treatment group and 9% in CAR treatment group experienced skin or hypersensitivity (HR) - related disorders, regardless of causality or severity (**Table 37**). The most

common events by MedDRA high-level terms include rash, eruption and exanthems (3%, in the DTG+RPV treatment group and <1% in the CAR treatment group); dermatitis/eczema (2% and 3%), and pruritus (2% and <1%). Except for one subject in the CAR treatment arm, none were serious or severe (grade 3 or 4). No event led to treatment discontinuation.

Table 37 Summary of Skin and Hypersensitivity (HR) Disorders

		DTG + RPV N=513	CAR N=511
Any subjects with skin or HR AE		74 (14%)	48 (9.4%)
SAE		0 (0%)	1 (0.2%)
Severity	GRADE 1	65 (13%)	42 (8.2%)
	GRADE 2	12 (2.4%)	6 (1.2%)
	GRADE 3	0 (0%)	1 (0.2%)
Treatment-related		12 (2.3%)	0 (0%)
Leads to discontinuation		0 (0%)	0 (0%)

Data Source: FDA Adverse Events Analysis Dataset

No subjects in the CAR group experienced treatment-related AE (ADR), while 12 subjects in the DTG+RPV treatment group experienced an ADR. By preferred term, selected treatment related AEs included rash (n=4), pruritic rash (n=2), pruritus (n=1) and photosensitivity reaction (n=1). If the rash-related terms are grouped, similar to the analysis methods utilized during DTG or RPV NDA reviews, the overall number of rash-related AEs increased to 7 (1.4%). The clinical review team recommends updating the proposed DTG/RPV label to reflect the incidence for rash based on a grouped term analysis.

In the LS Phase, 29 (3%) subjects experienced skin or hypersensitivity reactions (7 among 'early switchers' and 22 among 'late switchers'). Group terms 'rash', 'rash pruritic', 'hypersensitivity', 'pruritus', and 'blister' were reported. All were grade 1 or 2, non-serious and did not lead to treatment discontinuation. Of these, 2 subjects experienced treatment-related events ('rash', 'rash pruritic').

In summary, the overall incidence of skin and hypersensitivity reactions did not increase with use of DTG+RPV, compared to what is reported in the respective package inserts for DTG or RPV. No serious rash events such as erythema multiforme, Stevens Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN) were reported. Therefore, no new language will be included in Juluca label. The language currently included in DTG and RPV will also be included in the Juluca label.

Hepatobiliary Analysis

As summarized in **Table 38**, hepatobiliary adverse events, regardless of causality or severity were observed in 5(1%) and 2(<1%) of DTG+RPV treated or CAR treated subjects. Two subjects in the DTG+PRV treatment arm experienced an SAE (DILI n=1; chronic cholecystitis n=1). The

DILI event was the only event considered treatment-related. All other events were non-serious and not treatment-related. No Grade 4 events were reported. The remaining events were Grade 3 and included acetaminophen -induced liver injury (DTG+RPV treatment group); Grade 1 jaundice (DTG+RPV treatment group) with normal serum bilirubin level; Grade 1 elevation in transaminase (DTG+RPV treatment group); and Grade 1 cholelithiasis in two subjects, one from each treatment group. No new hepatobiliary adverse events were reported during the Late Switch Phase.

Table 38 Summary of Hepato-biliary Adverse Events

		DTG + RPV N=513	CAR N=511
Any subject with hepato-biliary AE		5 (1%)	2 (0.4%)
SAE		2 (0.4%)	0 (0%)
Severity	GRADE 1	3 (0.6%)	2 (0.4%)
	GRADE 2	1 (0.2%)	0 (0%)
	GRADE 3	2 (0.4%)	0 (0%)
Treatment-related		1 (0.2%)	0 (0%)
Leads to discontinuation		1 (0.2%)	0 (0%)

Data Source: FDA Adverse Events Analysis Dataset

As shown in **Table 39**, graded serum liver biochemistry abnormalities were generally similar for DTG+RPV treatment group, compared to the CAR treatment group.

Table 39 Summary of Worse-Grade Serum Liver Biochemistry Post-Baseline Visit, Early Switch Phase

Parameter Grade	DTG + RPV N=513	CAR N=511
Alanine Aminotransferase		
Grade 1	35 (7%)	22 (4%)
Grade 2	8 (2%)	4 (<1%)
Grade 3	3 (<1%)	2 (<1%)
Grade 4	0 (%)	1 (<1%)
Aspartate Aminotransferase		
Grade 1	25 (5%)	16 (3%)
Grade 2	5 (<1%)	8 (2%)
Grade 3	2 (<1%)	3 (<1%)
Grade 4	1 (<1%)	1 (<1%)
Bilirubin		
Grade 1	17 (3%)	10 (2%)
Grade 2	11 (2%)	18 (4%)
Grade 3	0 (%)	11 (2%)
Grade 4	0 (%)	2 (<1%)

Data Source: FDA Liver Analysis Dataset

In summary, based on the analyses of hepatobiliary adverse events and laboratory toxicities, no

new safety concerns were identified with co-administration of DTG and RPV.

Both the individual drug products have Warnings and Precautions language specific for liver-related events (ADRs). However, the Prescribing Information for DTG describes the observed increase in serum liver biochemistries in patients with co-infection with Hepatitis B or C during the registrational Phase 3 clinical trials. The Division of Antiviral Products (DAVP) consulted the Division of Pharmacovigilance (DVP) in the Office of Safety and Epidemiology (OSE) to review the postmarketing data to determine if there are cases of hepatotoxicity independent of hypersensitivity reaction or hepatitis B or C co-infection. Review of the FDA Adverse Event Reporting System (FAERS) database and the published medical literature identified cases of hepatotoxicity associated with use of DTG-containing regimens. Additionally, DAVP recently identified a literature report describing a case of hepatic failure leading to liver transplant in association with use of a dolutegravir-containing regimen, Triumeq. Therefore, it is recommended that the Juluca Prescribing Information contain Warnings and Precautions language to communicate hepatotoxicity risks associated with use of both DTG and RPV.

Psychiatric Events

Depression, suicidal ideation and behavior, particularly in subjects with a pre-existing history of psychiatric illness are labeled events for both DTG and RPV. Additionally, sleep disorders including insomnia, and anxiety have also been observed with use of DTG and RPV. An analysis of psychiatric AEs was conducted to explore if the frequency of these events would increase with co-administration of DTG plus RPV.

Psychiatric adverse events (regardless of severity or causality) were reported more frequently in the DTG + RPV treatment group compared to the CAR treatment group (12% vs. 6%), as described in **Table 40**. Most events were grade 1 or 2, non-serious and did not lead to treatment discontinuation. In the DTG+RPV treatment group, insomnia (3%), depression (3%), anxiety (2%), and abnormal dreams (1%) were the most common AEs by preferred terms. In the CAR treatment group, anxiety (2%), insomnia (2%) and depression (1%) were the most common AEs. For both treatment groups, no other psychiatric preferred terms were reported in >1% of subjects.

Table 40 Summary of Psychiatric-related Adverse Events

		DTG + RPV N=513	CAR N=511
Any subject with psychiatric AE		62(12%)	32(6%)
SAE		3 (0.6%)	1(0.2%)
Severity	GRADE 1	44 (8.5%)	24 (4.6%)
	GRADE 2	17 (3.3%)	9 (1.8%)
	GRADE 3	4 (0.8%)	1 (0.2%)
	GRADE 4	2 (0.4%)	1 (0.2%)
Treatment-related		26(2%)	2(0.4%)

Leads to discontinuation		9(1%)	1(0.2%)

Data Source: FDA Adverse Events Analysis Dataset

Few subjects experienced SAE; four occurred in the DTG+RPV group and one occurred in the CAR group. The subject in the CAR treatment group attempted suicide and subsequently discontinued treatment. The events reported in the DTG+RPV are further summarized below:

- **Suicide attempt**: This is 39-year-old male, who, after 150 days on DTG+RPV, attempted suicide by ingesting 5 tablets of ebastine and alcohol. He was seen in an emergency department, treated and discharged. The co-suspect product and/or circumstance were identified as 'alcohol intoxication' and 'mother's death'. Subject continued on DTG and RPV and the event was not considered to be related to study medications.

- **Panic attack:** This is a 48-year-old male with concurrent medical condition, including anxiety, requiring medications. Approximately 312 days after initiation of study medications, he experienced grade 3 panic attack, requiring hospitalization. DTG/RPV were discontinued with negative de-challenge. The event was considered to be possibly related to DTG+RPV.

- **Depression:** A 34-year-old male, who developed grade 3 depression, leading to hospitalization and treatment 213 days after initiation of study medication. He had a history of 'nervous breakdown' 10 years prior to enrollment into study but had recovered without requiring intervention of treatment. DTG/RPV were discontinued with negative de-challenge. He recovered after 16 days. The investigator considered DTG/RPV to be possibly related to the event.

A higher proportion of subjects experienced drug-related *psychiatric* AEs in the DTG+RPV group (n= 26, 2%) compared to the CAR treatment group (n=2, <1%). The events reported in the 2 subjects in the CAR treatment group were insomnia, anxiety and suicide attempt. The AEs experienced among DTG+RPV treated subjects includes: abnormal dreams (n=6), insomnia (n=7), anxiety (n=5), and depression (n=5). Additionally, depressed mood, nervousness, nightmare, sleep disorder and suicidal ideation were all reported in one subject each.

When treatment-related preferred terms are grouped to describe depressive disorders (e.g. depression, depressed-mood, suicide attempt or ideation), the proportion of subjects with such treatment-related AEs increases to 1% (n=6) in the DTG+RPV arm, while only one subject reported depressive disorder (i.e. suicide attempt) in the CAR treatment group.

The adverse events reported among the 9 DTG+RPV treated subjects who discontinued study medication (regardless of causality) include anxiety (n=4), depression or depressed mood (n=4), insomnia (n=2), panic attack (n=1) and suicidal ideation (n=1). The one subject who discontinued due to psychiatric AE in the CAR treatment group attempted suicide .

Of the DTG+RPV treated subjects who experienced treatment-related events, 7 discontinued treatment due to the following events: depressed or depressed mood (n=4), anxiety, suicide ideation (n=1). One subject in the CAR group discontinued due to suicide attempt.

Further analysis of psychiatric AEs was conducted based on MedDRA High-Level Terms to identify frequency of events in the categories of mood disorders, sleep-related disorders and anxiety disorders. **Table 41** provides the overall psychiatric AESI. The proportion of subjects who experienced AESI (regardless of severity or causality) was higher in the DTG+RPV group compared to the CAR treatment group. However, the overall treatment-related AESI in the DTG+RPV treatment group remained similar to the events reported during the original review of the NDAs for the individual drug products.

Table 41 Psychiatric Adverse events by MedDRA High-Level Terms

	DTG + RPV N=513	CAR N=511
Any subject with psychiatric AEs	**62 (12.1%)**	**32 (6.3%)**
Mood Disorders	**29 (5.7%)**	**12 (2.3%)**
Depressive disorders	18 (3.5%)	7 (1.4%)
Suicidal and self-injurious behaviour	4 (0.8%)	3 (0.6%)
Mood alterations with depressive symptoms	5 (1.0%)	1 (0.2%)
Fluctuating mood symptoms	0 (0.0%)	1 (0.2%)
Emotional and mood disturbances NEC	2 (0.4%)	0 (0.0%)
Sleep-related disorders	**28 (5.4%)**	**10 (2%)**
Disturbances in initiating and maintaining sleep	17 (3.3%)	10 (2.0%)
Sleep disorders NEC	4 (0.8%)	0 (0.0%)
Parasomnias	7 (1.4%)	0 (0.0%)
Anxiety Disorders	**18 (3.5%)**	**14 (2.7%)**
Anxiety symptoms	14 (2.7%)	10 (2.0%)
Panic attacks and disorders	2 (0.4%)	1 (0.2%)
Fear symptoms and phobic disorders (including social phobia)	1 (0.2%)	0 (0.0%)
Stress disorders	1 (0.2%)	3 (0.6%)

Data Source: FDA Adverse Events Analysis Dataset

During the LS Phase, no new psychiatric AESI was identified as serious, treatment-related, severe or leading to treatment discontinuation. In brief, 8 (2%) of subjects who switched to DTG+RPV early and 14(3%) of subjects who switched to DTG+RPV later experienced psychiatric-related AEs.

In summary, the overall psychiatric AEs and psychiatric AESI identified during SWORD-1 and SWORD-2 trials were generally similar to the events as previously described in the individual drug products. No new terms are proposed for inclusion into the Prescribing Information for Juluca. Because the ADR table proposed for Section 6 of the Juluca table includes ADRs with incidence of ≥2%, depressive disorders events observed during SWORD-1 and SWORD-2 will not

be included. The terms are described under 'Less Common Adverse Reactions'. Of note, 'Depressive Disorders' due to use of rilpivirine was proposed by the Applicant in Section 5 of Juluca Prescribing Information. However, DTG is also associated with depressive disorders (currently in section 6 of the Prescribing Information). Therefore, given the incidence and significance of depressive disorders observed during SWORD-1 and SWORD-2 clinical trials, and, in order for section 5 not to appear that depressive disorders are only related to RPV the label will mention depressive-disorders related to use of DTG in section 5 of the Prescribing Information for Juluca, with cross reference to section 6.1, Less Common Adverse Reactions.

Nervous system Disorders

Dizziness and headache were both previously reported in the DTG and in the RPV development programs. The Prescribing Information for DTG and RPV labels contain these terms in the ADR table.

Overall, 77(15%) and 42(8%) of DTG+RPV- and CAR- treated subjects, respectively experienced nervous system-related AEs. Most were grade 1 or 2 and few led to treatment discontinuation. Only one subject in each treatment group experienced SAE (headache in the DTG+RPV group and toxic encephalopathy in the CAR group). Neither was considered treatment-related or led to treatment discontinuation. There were no grade 4 events and only one subject in the DTG+RPV group experienced a grade 3 events (tremor) while 3 subjects in the CAR group had grade 3 events (toxic encephalopathy, headache, cervico-brachial syndrome). Two subjects from the DTG+RPV treatment group discontinued due to tremor (n=1) and headache (n=1).

Treatment-related AEs were also more commonly reported in the DTG+RPV group [20(4%) vs. 1(0.2%)]. By preferred term, headache (2%) and dizziness (1%) were the most frequency reported treatment-related events in DTG+RPV treatment arm. Somnolence was reported in 2 (<1%) subjects. The only treatment related event in the CAR treatment group was dizziness.

No new nervous system-related safety signals were identified during the LS Phase.

In summary, results from the pooled analysis of the phase 3 trials were consistent with previously described AEs for DTG and RPV; no new safety issues with respect to nervous system disorders was identified.

Gastrointestinal AEs of interest

During the development of DTG, gastrointestinal mucosal inflammation and hemorrhage were observed in nonclinical studies, across different animal species. During the original NDA review for DTG, gastrointestinal adverse events, suggestive of local GI intolerance (e.g. diarrhea, nausea, and vomiting, abdominal pain) or gastric mucosal damage were reviewed. In summary, the vast majority of GI intolerance AEs were mild or moderate in severity. Diarrhea was the most frequent adverse event reported. Nausea and less frequently abdominal pain, discomfort,

flatulence, upper abdominal pain and vomiting were identified as ADRs and are included in DTG label. Gastric or duodenal ulcers were rarely reported and were seen in subjects with pre-existing conditions or risk factors. No subclinical GI bleeding was identified during DTG use in the clinical trials based on assessment of mean hemoglobin change from baseline.

During the review of the original NDA for RPV, abdominal pain, nausea, vomiting, and less frequently diarrhea and abdominal discomfort were identified as ADRs and are included in the RPV label.

Overall, in the pooled data from the SWORD 1 and 2 trials, GI-related events were more common in the DTG+RPV treatment group compared to CAR treatment group (25% vs. 16%). The most frequently (at least 2%) reported preferred terms, regardless of causality or severity, were diarrhea (2%), dyspepsia (3%), abdominal pain upper (3%), constipation (3%), flatulence (3%), abdominal distension (2%), and nausea (2%) in the DTG+RPV treatment group. Diarrhea (5%) and dyspepsia (<1%) were the most frequently reported terms in the CAR treatment group. Most events across the treatment groups were mild or moderate. One SAE was reported in the CAR treatment group, anal fistula, which was not considered treatment-related. There were 4 subjects with SAE in the DTG+RPV treatment group, including acute pancreatitis (n=1), gastroenteritis (1), gastrointestinal hemorrhage (n=1), and GERD (n=1). The acute pancreatitis, as previously discussed (see Serious Adverse Events section) was grade 4, considered treatment-related and led to study drugs discontinuation. GI hemorrhage and GERD were not considered treatment-related. In both cases, there was a pre-existing history of illness consistent with the described adverse events, thus making the events unlikely to be treatment-related. However, the subject who experienced GI hemorrhage discontinued study medications.

Other events leading to treatment discontinuation include abdominal distention (n=2), dyspepsia (n=2), and peptic ulcer (n=1), all in the DTG+RPV treatment group, while no subject discontinued from the CAR treatment group for GI related events.

During the LS Phase, no new GI-related safety signals were identified.

In summary, the AEs reported during the phase 3 trials with DTG+RPV were generally similar to the events reported during the clinical trials with the individual drug products. The GI-related safety profile generally remains unchanged when the two drugs are co-administered.

Musculoskeletal analysis (select musculoskeletal AEs and serum CK analysis)

During the original review for DTG, myalgia, myositis, and CK increased were observed in few DTG-treated subjects and most were not considered drug-related. Grade 3-4 CK elevations (reported as laboratory abnormalities) were observed in 2-5% DTG-treated and majority were asymptomatic without leading to drug discontinuation. Myositis is included Under Section 6 “Less common ADRs”; additionally, CK laboratory findings are also included in the laboratory

abnormality table. Arthralgia and myalgia are also included under section 6.2 Post-marketing Experience.

Overall, the proportion of subjects who experienced musculoskeletal events was comparable between the DTG+RPV treatment group (15%) and the CAR treatment group (16%). Arthralgia (4%), back pain (3%) and pain in extremity (3%) were the preferred terms reported in more than 1% of subjects in the DTG+RPV treatment group. In the CAR treatment group, back pain (6%), arthralgia (2%), and musculoskeletal pain (2%) were the most frequently reported terms. Most were grade 1 or 2 in severity and no subject discontinued treatment due to a musculoskeletal related AEs. Two subjects experienced SAE: hemarthrosis (n=1) in the DTG+RPV group and intervertebral disc protrusion in the CAR group. Neither was considered treatment related. Overall, 3 subjects (all in the DTG+RPV treatment group) experienced treatment-related events: arthralgia, muscle spasm and musculoskeletal pain.

No new terms were identified in the LS Phase. There were no SAE or grade 3 or 4 events. One subject discontinued due to pain in extremity. An additional 4 subjects experienced treatment-related AEs: arthralgia, musculoskeletal disorder, myalgia, and pain in extremity. One was considered treatment-related- pain in extremity.

In summary, no new safety findings were identified with regards to musculoskeletal events during the SWORD-1 and SWORD-2 phase 3 clinical trials. Notwithstanding inclusion of language currently included in DTG and RPV labels, no new additional terms are proposed for the Juluca label.

Cardiac-related Select Events

During the development program for RPV, QT interval prolongation was observed at supra-therapeutic levels. Thus, the Edurant label includes a WARNING AND PRECAUTION statement describing risk of QT prolongation if RPV is co-administered with drugs that could increase RPV exposures. While no cardiac-specific safety issue was characterized for DTG, a literature report was published describing myocarditis associated with DTG. The Office of Safety and Epidemiology (OSE), Division of Pharmacovigilance then evaluated the FDA Adverse Event Reporting System (FAERS) database and published medical literature for case reports of myocarditis associated with dolutegravir (Tivicay and the FDC, Triumeq) Based on the review, there does not appear to be a post-marketing safety signal for myocarditis associated with dolutegravir. OSE recommended routine monitoring for cardiac events.

Overall, few subjects experienced cardiac-related AEs during the SWORD-1 and SWORD-2 clinical trials- 2(<1%) in each arm. In the DTG+RPV group intraventricular conduction defect, palpitations were reported and arrhythmia and cardiovascular disorder were reported in the CAR treatment group. None of the cardiac related events were serious, treatment related or led to discontinuation.

During the LS Phase, three additional subjects experienced AEs including palpitations and pericarditis. The pericarditis was a SAE but not treatment related. No subjects discontinued treatment due to cardiac-related AE.

Renal analysis (renal AEs and renal laboratory analysis)

As described in the Prescribing Information for both DTG and RPV, increases from baseline in mean serum creatinine (SCr.) were observed during treatment with either drug product. In both cases, the increase stabilizes overtime without change in glomeruli filtration rate (GFR). The increase in SCr. is believed to be a result of drug effect on renal tubular secretion of creatinine mediated through OCT2 inhibition. Renal AEs were generally similar to the comparator arms during the DTG or RPV clinical trials.

The primary purpose of the following review was to asses if there is an increase in the frequency of renal-related events, including an increase in the peak in serum creatinine compared to baseline when DTG+ RPV are co-administered. AEs such as kidney or renal failure (acute, chronic), renal impairment, and renal insufficiency were also selected as AEs of interest as these events are associated with decreased renal function. The results from SWORD-1 and SWORD-2 were also compared to the findings from the clinical trials that evaluated the individual drugs. The comparisons should be made with caution as cross-trial comparisons have limitations.

Overall, as summarized in **Table 42**, 15 (3%) of DTG+RPV treated subjects and 9(2%) CAR treated subjects experienced renal-related disorders, regardless of causality or severity. Among the reported AEs were renal failure (n=1 DTG+RPV group), acute renal impairment (n=1 DTG+RPV group), and acute kidney injury (n=1 DTG+RPV group). Most renal-related AEs were grade 1 and none led to treatment discontinuation. Three subjects experienced grade 3 events, including acute kidney injury (also a SAE and further described below), renal impairment (see below), and renal colic (also a SAE).

Table 42 Summary of Renal Disorders

		DTG + RPV N=513	CAR N=511
Any subject with Renal AE		15 (2.9%)	9 (1.8%)
SAE		2 (0.2%)	0 (0%)
Severity	GRADE 1	10 (1.9%)	7 (1.4%)
	GRADE 2	3 (0.6%)	2 (0.4%)
	GRADE 3	3 (0.6%)	0 (0%)
Treatment-related		1 (0.2%)	0 (0%)
Leads to discontinuation		0 (0%)	0 (0%)

Data Source: FDA Adverse Events Analysis Dataset

Brief narratives for the select renal AEs are provided below.

- **Acute kidney injury** (grade 3, serious, not treatment-related; resolved): The subject is a 44-year-old male, who, approximately 2 months after initiating treatment with study drug (DTG+RPV), developed gastroenteritis secondary to rotavirus. The severe fluid loss and dehydration led to hospitalization. The event was followed by a serious Grade 3 event of acute renal insufficiency (pre-renal which resolved post infection). The event was not considered treatment-related.

Note, because neither of the following events were serious or led to treatment-discontinuation, full narratives were not available.

- **Renal failure** (grade 2, treatment-related, non-serious, ongoing): The subject, a 42-year-old male randomized to receive DTG+RPV, had pre-existing history of nephropathy and hypertension. Approximately 171 days after initiation of therapy, he experienced an increase in serum creatinine from 111 mmol/L to 137mmol/L (Grade 1, non-serious, treatment-related). There was no further increase in the subject's serum creatinine and the subject continued therapy with DTG+RPV.

- **Acute renal impairment** (grade 3, not treatment-related, non-serious, ongoing): The subject is a 51-year-old male with Type I DM, nephropathy and hypertension who, approximately 163 days after initiating DTG +RPV, developed Grade 1 increase in serum creatinine (101.7 to 158.2 mmol/L), without any subsequent graded elevations up to his last visit (Week 64). The event was non-serious and not-related to study medication. Subject is continuing study drugs and the event was unresolved based on the last visit.

As summarized in **Table 43** at Week 48, the overall change in mean or median serum creatinine from baseline among subjects treated with DTG+RPV was comparable to the change observed during the clinical trials with the individual drug products, DTG and RPV.

Table 43 Summary of Mean and Median Serum Creatinine Changes from Baseline

Clinical Trials	Baseline Serum Creatinine Mean Median n	Week 48 Serum Creatinine Mean Median n	Change from Baseline Mean Median
SWORD-1 and SWORD-2 DTG+RPV	77.3 77.2 n=393	85.3 84.5 n=368	+8 +7.3
SPRING-2 DTG (plus 2 NRTIs, excluding Truvada)	73.1 73.4 n=159	83.6 83.5 n=144	+10.5 +10.1
SINGLE DTG (plus ABC+ 3TC)	75.2 74.3 n=406	84.9 84 n=360	+9.7 +9.7
C215 RPV (plus 2 NRTIs, excluding Truvada)	73.5 72 n=136	78 80 n=126	+4.5 +8
C209 RPV (plus 2 NRTIs)	75 74 n=344	84 84 n=299	+9 +10

Data Source: Renal Analysis Dataset for NDAs 210192, 202022 and 204790

Additionally, change in serum creatinine was also evaluated by the Applicant using cystatin C. This analysis showed no difference between the DTG + RPV treatment group and the CAR group; minimal or little change was observed in mean serum creatinine at Week 48 compared to Baseline for both treatment groups.

Graded serum creatinine laboratory toxicities were reported in 10 subjects (2%) in the DTG +RPV treatment group and in 4 (<1%) subjects in the CAR treatment group. All events were grade one, with exception of one, grade 2 event in the CAR treatment group.

Analysis of the LS Phase did not identify any new renal-related safety signals. There were no events considered serious, treatment-related, severe or leading to treatment discontinuation.

In summary, select renal adverse events were uncommon during the current clinical trials. Additionally, few grade 1 elevation in serum creatinine were noted. Overall, the change from baseline for both increase in the mean or median serum creatinine was comparable to the change observed during clinical trials with the individual drug products. Therefore, no new language is proposed for the Juluca label. Similar data presentation, as done for the individual drug products is sufficient to allow for the safe use of the product.

Name Safety Issue

No safety issue has been identified after the preliminary review of the proposed name, Juluca. Please refer to review by Nasim Roosta form the Division of Medication Error Prevention and Analysis (DMEPA) for details. The proposed name was found to be conditionally acceptable

9.1.6. Safety Analyses by Demographic Subgroups

As summarized by the Applicant, in the pooled analysis from the SWORD 1 and 2 trials, there was no significant difference noted in the number of AEs (regardless of causality or severity) reported between males (77%) and females (78%) in the DTG + RPV group. Similarly, AEs occurring in subjects <50 vs. ≥ 50 years of age was similar in the DTG+RPV treatment-group - 76% and 80%, respectively.

A difference was observed in the frequency of AEs reported between races; however, most subjects were white and relatively small numbers of subjects were available in the other race groups to allow for robust comparisons. Four hundred and twenty-one subjects were Caucasians, of whom 77% reported an AE. In comparison 37, 38, and 17 subjects were African American, Asians and 'Other', respectively, of whom 84%, 63% and 88% experienced AEs, respectively.

Please refer to the original NDA review for the individual drug products for additional details.

9.1.7. Specific Safety Studies/Clinical Trials

The Applicant conducted an additional (sub-study) to evaluate changes in bone mineral density (BMD) for those subjects who change from TDF-containing ARV regimen to DTG+RPV. Subjects who switched to DTG+RPV regimen at Baseline were compared to subjects who stayed on TDF-containing regimen. The Division of Bone Reproductive and Urologic Products (DBRUP) was consulted to review the changes in total hip BMD over time. Please refer to the review by Dr. Stephen Voss for summary of results and recommendations.

In brief, the bone sub-study findings are sufficiently robust and potentially relevant to clinicians as to warrant inclusion in labeling section 6.1, consistent with the labeling for TDF and TAF products. However, deletion of the term (b) (4) from the proposed language is recommende (b) (4) In addition, (b) (4) (b) (4)

In addition to presenting changes in mean BMD, individual response data is recommended. The percent of patients with treatment-associated BMD declines from baseline >5% (lumbar spine)

or >7% (femoral neck), thresholds is considered *potentially* clinically significant and should be included in product labeling. In the DTG+RPV trials, no patients had a BMD decline >7% at any skeletal site. For consistency with other products' labeling, the following language is recommended in 6.1 BMD:

> *BMD declines of 5% or greater at the lumbar spine were experienced by 2% of Juluca subjects and 5% of subjects who continued their TDF-based regimen.*

For consistency with other products, language such as the following is also recommended:

> *Fractures (excluding fingers and toes) were reported in 3 (0.6%) subjects who switched to dolutegravir plus rilpivirine and 9 (1.8%) subjects who continued their TDF-based regimen through 48 weeks.*

9.1.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No additional carcinogenicity or tumor development studies were conducted for the combination product DTG + RPV. Refer to the original NDA reviews and prescribing product information for additional details.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

9.1.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The FDC or DTG +RPV as a complete regimen is not approved. Therefore, no previous postmarketing information is available for this specific two drug complete regimen. However, postmarketing experience is available for the individual drug products. Please refer to the NDA reviews and Prescribing Information for the individual drug products for details.

Expectations on Safety in the Postmarket Setting

The safety of DTG+RPV is expected to be similar to the individual drug products. Routine pharmacovigilance will be conducted to continue to monitor for unlabeled or unexpected adverse events.

9.2. Integrated Assessment of Safety Summary

RPV and DTG were originally approved on 23 May, 2010 and 17 December, 2012, respectively. Additionally, both RPV and DTG have also been approved as part of a three drug FDC products, Complera, Odefsey and Triumeq. Several Phase 3 trials were conducted to support the approval of the drug products, as single agents or as part of FDC product. Therefore, there is robust clinical trial and post-marketing safety information for both individual drug products.

The safety profile was favorable for DTG+RPV given as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least six months with no history of treatment failure and no known substitutions associated with resistance to DTG or RPV. The Phase 3 trials, SWORD-1 and SWORD-2 were sufficient to characterize the safety profile for this two-drug regimen. Overall no new safety findings were identified and the combination of DTG+RPV did not result in greater frequency of adverse events or laboratory abnormalities as compared to the safety profile of the individual agents in combination with other ARVs.

As expected, during the ES Phase, subjects who switched to DTG+RPV at baseline experienced adverse events more frequency than subjects who had stayed on their CAR (77% vs, 71%). Similarly, treatment-related AEs (ADRs) as defined by investigator to be related to DTG+RPV were more common in the DTG+RVP treatment arm at Week 48 (19% vs. 2%); more subjects in the DTG+RPV treatment group also discontinued to due AEs compared to CAR treatment group (4% vs. <1%). However, the proportion of subjects with SAEs was similar between the two treatment groups. During the LS Phase, subjects who stayed on their CAR and switched to DTG+CAR at Week 52, had an increase in the frequency of AEs compared to subjects who started DTG+RPV at Baseline (34% vs. 31%). Treatment-related AEs were also reported more frequently among subjects who switched to DTG+RPV at Week 52 (8% vs. <1%).

In summary, the result from SWORD-1 and SWORD-2 demonstrated that DTG+RPV is safe and well-tolerated and effective. The FDC of DTG+RPV proves a two-drug maintenance regimen for select individuals who are virologically suppressed. This group of select individuals will clearly benefit from this once-daily NRTI-sparing regimen. As we recognize World AIDS Day 2017, we are also aware that this approval represents a paradigm shift in the treatment of HIV-infected patients.

10 Advisory Committee Meeting and Other External Consultations

Not applicable. This application was not taken to an advisory committee meeting because the both DTG and RPV were previously approved with years of postmarketing use and no concerning efficacy or safety issues were identified during the preNDA meeting.

11 Pediatrics

No pediatric trials have been conducted with DTG + RPV. The Division does not plan to issue a PREA PMR as the dual regimen with DTG + RPV is not considered to add meaningful benefit to the existing products for the treatment of HIV-1 infection in children. In fact, given challenges with adherence particularly with adolescents, there is concern that dual regimen may not be the optimal regimen in pediatric patients.

For data on pediatric trials and assessments with the individual drug products, refer to the respective NDAs and Prescribing Information.

APPEARS THIS WAY ON ORIGINAL

12 Labeling Recommendations

12.1. Prescribing Information

The significant labeling changes are highlighted below.

INDICATIONS AND USAGE

The indication statement was revised to better reflect the patient population studied and was revised for consistency with other complete regimen FDC's. This section was revised to specifically state (1) JULUCA is a complete regimen, and is used (2) to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) and (3) "…on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of JULUCA."

CONTRAINDICATIONS

This section was updated to include a table for the drugs that are contraindicated with Juluca. Also a clinical comment was included in the table for each contraindicated drug.

WARNINGS AND PRECAUTIONS

This section was reorganized in order of clinical significance. Other significant changes included revisions to the hepatotoxicity and drug interaction subsections. Originally the hepatotoxicity section focused on hepatic adverse events with rilpivirine because no significant hepatotoxicity events occurred during clinical trials with Juluca. Also the Tivicay label does not have a specific hepatotoxicity warning. Instead the Tivicay label has a warning regarding the effects on serum liver biochemistries in patients with Hepatitis B or C co-infection. In a recent postmarketing review, cases of acute liver failure and hepatitis were observed with DTG. The postmarketing cases were not limited to patients with Hepatitis B or C co-infection. Therefore, all DTG containing labels will be updated to include DTG cases of hepatic toxicity in patients who had no pre-existing hepatic disease or other identifiable risk factors. Additionally, a case of acute liver failure, including liver transplant was reported with Triumeq. This will be reflected in all DTG containing labels. Finally, monitoring for hepatotoxicity is recommended.

The Drug Interaction warning was renamed Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions per labeling guidance. Reference to known or potentially significant drug interactions along with steps to prevent or manage these possible or known significant drug interactions, including dose recommendations is clearly referenced.

The Tivicay label does not have a warning for depressive disorders; however, depressive

disorders is listed as a less common adverse reaction in section 6 of the Tivicay and Juluca labels. We did not want to give the appearance that depressive disorders were only reported with rilpivirine, therefore reference to section 6.1 was included in this section to acknowledge depressive disorders reported in patients receiving DTG.

ADVERSE REACTIONS

Minor revisions were made based on review of the SWORD 1 and SWORD 2 trials. Further details regarding the bone mineral density effects were added. Specifically, outcomes of BMD declines of 5% or greater at the lumbar spine and overall fracture rates were added.

The pooled phase 3 trial results for the rilpivirine with respect to adrenal function (Edurant label) was included.

DRUG INTERACTIONS

Some details originally proposed in this section (eg detailed information on in vitro study results, mechanism of action for the increased serum creatinine levels, etc) were moved to section 12.3. (b) (4) were deleted because (b) (4) The contraindicated drugs were also added to this section.

USE IN SPECIFIC POPULATIONS

Minor revisions were made for consistency with Edurant and Tivicay labels. Deletion of (b) (4)

CLINCIAL PHARMACOLOGY

Minor revisions were made, specifically moving some text data into tabular format and other reorganization of data. (b) (4) were deleted because (b) (4) (b) (4) was deleted (b) (4) because (b) (4)

In the Microbiology subsection, details were added with respect to the two subjects in the DTG/RPV group with detectable resistance substitutions at rebound.

CLINICAL STUDIES

The treatment difference and adjusted 95% CI were added to the pooled virologic outcome table and reference to (b) (4)

(b) (4) deleted.

12.2. Patient Labeling

Minor updates were made for consistency with other antiretroviral patient labeling standards and updates to the package insert.

13 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

13.1. Safety Issue(s) that Warrant Consideration of a REMS

None.

Not applicable

13.2. Recommendations on REMS

None.

14 Postmarketing Requirements and Commitments

None.

15 Appendices

15.1. References

1. WHO HIV/AIDS Global Statistics, WHO (2017, August 13). Retrieved from http://www.who.int/mediacentre/factsheets/fs360/en/
2. CDC HIV Surveillance Report (2017, October 31). Retrieved from https://www.cdc.gov/hiv/statistics/overview/index.html
3. Antiretroviral Therapy Cohort Collaboration (ART-CC). Durability of first ART regimen and risk factors for modification, interruption or death in HIV-positive patients starting ART in Europe and North America 2002-2009. AIDS 2013; 27:803-813.
4. DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents for discussion on the safety and efficacy evidence considered for selecting preferred regimens in treatment-naïve patients and in patients who are virologically suppressed and are switching regimen.

15.2. Financial Disclosure

As summarized by the Applicant, it is the policy of ViiV Healthcare Company not to allow the participation of investigators in a clinical study if they, their spouse or dependent children have proprietary interest in the tested product. It is also the policy of ViiV not to compensate Investigators in a way that the amount of compensation received could be affected by the outcome of the study.

ViiV follows the GlaxoSmithKline Standard Operating Procedures (SOP) for Investigator Financial Disclosure, and has relied upon investigator financial interest information provided by the investigators through questionnaires.

No investigator had a financial interest in ViiV at the start of his/her participation in the covered study. If ViiV has been unable to collect financial information at the end of the study, then these investigators are included in the Certification of Unavailability of Required Information About Clinical Investigator Financial Interests/Arrangements Report. The appropriate due diligence process as per GlaxoSmithKline (SOP), which is up to 3 documented attempts to collect, was carried out to ensure the best achievable data collection, and documented in the Sponsor Study Record.

No current or former ViiV employee was an investigator in the covered studies.

Significant Payments of Other Sorts was reported for the following Clinical Investigators:

201636

(b) (6)

Again, it is believed that ~ 2% of the overall study totals was unlikely to affect the outcome of the study.

201637

(b) (6)

Covered Clinical Study (Name and/or Number): SWORD-1 and SWORD-2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 128		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

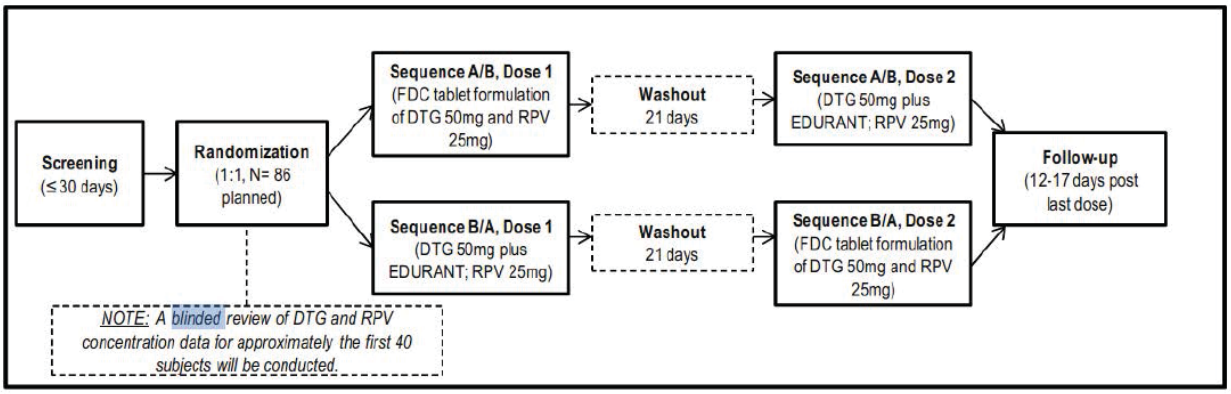
Individual study review

Study title: An Open-label, Randomized, Two-way Crossover, Single dose, Pivotal Bioequivalence Study of a Fixed-dose Combination of Dolutegravir and Rilpivirine in Healthy Volunteers (201676)

Study initiation date: (b) (6)
Study completion date: (b) (6)
Study site: Quintile, Overland Park, KS
Primary objective: To evaluate the bioequivalence between an FDC tablet formulation of DTG/RPV 50 mg/25 mg versus co-administration of the separate tablet formulations of DTG 50 mg and RPV 25 mg in the fed state.

Study design
This study was conducted as an open-label, randomized, 2 way crossover design at a single center. The study design is described in Fig 1. Initially, a total number of 86 subjects was planned. However, after the enrollment of 57 subjects, the sample size was recalculated to meet 90% power based on interim analysis of RPV and DTG PK. Therefore, 118 subjects were enrolled and randomized to receive a single dose of each of the two treatments. Each treatment was administered under fed condition and there was a 21 day washout period between the treatments.

Fig 1. Study design



DTG: TIVICAY clinical image; RPV: EDURANT commercially marketed formulation
DTG/RPV FDC: AW formulation (to-be-marketed)

Reviewer comments
This is a bioequivalence study to bridge the clinical formulations (single entity products used in Phase 3 trials) to the to-be-marketed formulation (JULUCA FDC). The sponsor conducted a fed BE study since Phase 3 trials (SWORD-1/2) were conducted under fed conditions due to rilpivirine (to be administered under fed conditions only).

Inclusion and exclusion criteria
Healthy male or female subjects between 18 and 55 years of age (inclusive) with a body weight > 50 kg (110 lbs) for men and >45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5 to 31 kg/m^2 (inclusive) were eligible to enter the study. Subjects with history or presence of any illness or conditions that might confound the results of the study or poses an additional risk to the subject were excluded.

Prohibited medications
Subjects abstained from taking any other prescription and non-prescription drugs within 7 days (or 14 days if the drug is an inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit (with the exception of <2 grams of acetaminophen any time outside of the first 10 hours post-dose). Use of H2-blockers, proton-pump inhibitors, antacids, vitamins, calcium or iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic assessments
Pharmacokinetic samples were collected pre-dose and up to 264 hours post dose. Standard PK parameters were determined.

Bioanalysis
The plasma concentrations of DTG and RPV were determined by validated analytical methods. The standard curve and QC data indicate that assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data. The Z-isomer can be formed from RPV by ambient light. Therefore, the analyses were conducted under yellow light and the amount of z-isomer was monitored.

Table 1. Summary of Bioanalytical Methods and QC Results

	Dolutegravir	Rilpivirine
Bioanalytical sites	PPD (Middleton, WI)	PRA Health Science (The Netherlands)
Analyte/ Internal standard	Dolutegravir/ Dolutegravir-d_7-^{15}N	Rilpivirine/ Rilpivirine -^{13}C-d^4
Anticoagulant	K_2EDTA	Heparin
Detection method	LC/MS/MS	LC/MS/MS
Calibration range	20 - 20000 ng/mL	1 - 2000 ng/mL
QC concentration	60, 160, 640, 2400, and 15200 ng/mL	3, 50 and 1600 ng/mL
QC results	A: -3.6 to 0.9% P: 3.2 to 7.6%	A: -1.3 to 0 % P: 2.6 to 6.0%

Results

Subject disposition and demographics

A total of 118 subjects were randomized and 113 (96%) subjects completed both periods/treatments of the study. The mean age of the subjects was 30.7 years. Majority of the subjects were men (69%), White/Caucasian/European Heritage (69%).

Pharmacokinetic results

Pharmacokinetic parameters of DTG and RPV following the single dose administration of single entity products and FDC are summarized in Table 2. The single entity products and the final to-be-marketed formulation were bioequivalent under moderate fat conditions. The test to reference ratios of geometric means with corresponding 90% CI for C_{max}, AUC_{0-t} and AUC_{inf} were within the predefined range, 80-125%. Other pharmacokinetic parameters (T_{max}, AUC_{24hr}, C_{24}, T_{lag}, λz, $t_{1/2}$, CL/F, and Vz/F) and time-concentration profiles of DTG and RPV were also comparable between test and reference.

Table 2. Summary of Statistical analysis of DTG and RPV PK parameters of test (FDC) and reference products (single entity products)

	DTG (n=113)			RPV (n=113)		
	Test	**Reference**	**Ratio**	**Test**	**Reference**	**Ratio**
C_{max} (µg/mL)	3.65 (3.53-3.77)	3.47 (3.36-3.60)	**1.05 (1.02-1.08)**	0.093 (0.087-0.101)	0.083 (0.078-0.089)	**1.12 (1.05-1.21)**
AUC_t (µg/mL·hr)	63.6 (60.7-66.6)	61.3 (58.5-64.2)	**1.04 (1.01-1.07)**	3.06 (2.84-3.30)	2.77 (2.56-3.99)	**1.11 (1.04-1.18)**
AUC_{inf} (µg/mL·hr)	65.0 (62.1-68.0)	62.7 (59.8-65.6)	**1.04 (1.01-1.06)**	3.25 (3.02-3.51)	2.93 (2.71-3.17)	**1.11 (1.05-1.17)**
Half life (hrs)	14.5 (14.0-15.1)	14.8 (14.2-15.3)	Not determined	51.7 (48.1-55.7)	52.5 (48.8-56.5)	Not determined

Test: JULUCA FDC; Reference: single entity products (DTG clinical image 50 mg + EDURANT 25 mg)

For Cmax and AUC values, data are expressed as geometric mean (95% CI)
For the ratio of test to reference PK parameters, data are expressed as ratio (90% CI)
Data source: Applicant's CSR. The reviewer's reanalysis confirmed the bioequivalence of the two formulations

Conclusion

The to-be-marketed FDC formulation of JULUCA is bioequivalent to the single entity products of DTG and RPV when administered under a moderate fat condition.

Title: A Phase I, 2-part relative oral bioavailability study of different fixed dose combinations of dolutegravir and rilpivirine in fasted and fed healthy subjects

Study initiation date: (b) (6)
Study completion date: (b) (6)
Study site: Quintile, Overland Park, KS

Primary objectives

1. To evaluate the relative bioavailability in the fed and fasted state of a single dose of DTG 50 mg and RPV 25 mg when administered together in a FDC tablet compared to the co-administration of a single dose of the single-entity DTG and RPV products
2. To evaluate the effect of food on the bioavailability of selected FDC formulation(s) of DTG and RPV

Study design

Part 1 was conducted as a randomized, single dose, open label, three-way, crossover manner in 24 subjects. Each subject received the reference treatment (single entity products of DTG and RPV) and two test formulations. The reference and test formulations were administered to subjects with a high-fat meal (900 total calories with 500 calories from fat).

Part 2 was a randomized, open-label, 3-way crossover design in 3 cohorts each with 12 subjects to evaluate the food effects and relative bioavailability of AK, AM, and AU formulations. Each subject received single doses of a given FDC formulation one administered under fasted conditions (10 hours pre-dose to 4 hours post-dose) and one within 30 minutes of a meal (moderate fat condition; 625 Kcal with 200 Kcal from fat). Each subject also received the reference treatment (single entity products of DTG and RPV) under fasted conditions.

Table 1. Study Design: Part 1 (top) and Part 2 (bottom)

Cohort	Sequence	Period 1[1]	Period 2[1]	Period 3[1]
Cohort 1 (N=24)	1 (n=4)	A	B	C
	2 (n=4)	D	A	B
	3 (n=4)	B	E	A
	4 (n=4)	A	C	D
	5 (n=4)	C	A	E
	6 (n=4)	E	D	A

1There was a wash out of ≥9 days between doses of study medication
Treatment A = DTG 50 mg tablet (clinical image) plus a single EDURANTTM 25 mg tablet
Treatment B = Dolutegravir and Rilpivirine Tablets, 50 mg/25 mg (b) (4)
Treatment C = Dolutegravir and Rilpivirine Tablets, 50 mg/25 mg
Treatment D = Dolutegravir and Rilpivirine Tablets, 50 mg/25 mg
Treatment E = Dolutegravir and Rilpivirine Tablets, 50 mg/25 mg

Cohort	Sequence	Period 1[1]	Period 2[1]	Period 3
Cohort 2 (n=12)	1 (n=4)	F, fasted	F, fed	A, fasted
	2 (n=4)	F, fed	A , fasted	F, fasted
	3 (n=4)	A , fasted	F, fasted	F, fed
Cohort 3 (n=12)	4 (n=4)	G, fasted	G, fed	A , fasted
	5 (n=4)	G fed	A, fasted	G, fasted
	6 (n=4)	A , fasted	G, fasted	G fed
Cohort 4 (n=12)	*7 (n=4)*	*H, fasted*	*H, fed*	*A, fasted*
	8 (n=4)	*H, fed*	*A, fasted*	*H, fasted*
	9 (n=4)	*A, fasted*	*H, fasted*	*H, fed*

1. There was wash out of ≥ 9 days between doses of study medication
Treatment A: DTG 50 mg tablet (clinical image) plus a single EDURANT 25 mg tablet
Treatment F: AK formulation (b) (4)
Treatment G: AM formulation (b) (4)
Treatment H: AU formulation (b) (4)

Reviewer comments
This was a food effect and relative bioavailability trial comparing different FDCs of DTG/RPV (AS, AM, AQ, AU and AK formulations) and single entity products of DTG 50 mg and RPV 25 mg in fasted and fed healthy subjects. Of note, the final to-be-marketed formulation (the AW formulation) was not evaluated in this trial. The sponsor stated that the AM formulation is identical to the AW formulatio (b) (4) *Therefore, this review is focused on the food effect and relative bioavailability of the AM formulation only, as the effect on the AM formulation is likely to be directly translatable to the AW formulation. The effects of food on other FDC formulations are not discussed in this review.*

Study population
Healthy male or female subjects between 18 and 65 years of age (inclusive) with a body weight > 50 kg (110 lbs) for men and >45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5 to 31 kg/m2 (inclusive) were included in the study. Subjects with history or presence of any illness or conditions that might confound the results of the study or poses an additional risk to the subject were excluded.

Concomitant medication
Subjects abstained from taking any other prescription and non-prescription drugs, within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit (with the exception of <2 grams of acetaminophen any time outside of the first 10 hours post-dose). Use of H2-blockers, proton-pump inhibitors, antacids, vitamins, calcium or iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial.

Pharmacokinetic assessments
Plasma samples for DTG and RPV quantitation were collected pre-dose and up to 168 hours post-dose. Calculations were based on the actual sampling times recorded during the study. Standard PK parameters were determined.

Bioanalysis
The plasma concentrations of DTG and RPV were determined by validated analytical methods. The standard curve and QC data indicate that assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of Bioanalytical Methods and QC Results

	DTG	RPV
Bioanalytical sites	PPD (Middleton, WI)	PPD (Middleton, WI)
Analyte/internal standard	Dolutegravir/ Dolutegravir-d_7-^{15}N	Rilpivirine/ Rilpivirine -^{13}C-d^4
anticoagulant	K_2EDTA	Heparin
Detection method	LC/MS/MS	LC/MS/MS
Calibration range	20 to 20000 ng/mL	0.5 to 250 ng/mL
QC concentrations	60, 160, 640, 2400, and 15200 ng/mL	1.2,3, 12, 40 and 200 ng/mL
QC results	CV: 6.2 - 9.3 % bias: 0.1 - 1.3 %	CV: 3.2 - 7.5 % Bias: 0.9 - 1.2 %

Results
Subject disposition and demographics
A total of 63 subjects were randomized in this study; 27 were randomized to Cohort 1 and 36 (12 each) were randomized to Part 2. Four subjects (3 subjects from Part 1 and 1 subject from Part 2) were withdrawn from the study. The median age of the subjects was 40 years. Majority of study population was males (76%), White (62%), not Hispanic or Latino (92%).

Pharmacokinetic results
<Part 1>
Pharmacokinetic parameters of DTG and RPV following the single dose administration of single entity products and FDC under high fat conditions are summarized in Table 3. C_{max} and AUC values of DTG and RPV were comparable between single entity products and the AM formulation under high fat conditions. Other pharmacokinetic parameters of DTG and PRV (T_{max}, C_{24}, $T_{1/2}$, CL/F, AUC_{0-t}) were also comparable between single entity products and the AM formulation under high fat conditions.

Table 3. Summary of DTG and RPV PK Parameters under High Fat Conditions

PK parameters	DTG (n=12)		RPV (n=11)	
	Single entity	AM formulation	Single entity	AM formulation
C_{max} (µg/mL)	3.33 (21%)	3.37 (19%)	0.094 (28%)	0.099 (32%)
AUC_{inf} (µg/mL·hr)	56.1 (24%)	61.8 (28%)	3.43 (49%)	3.74 (39%)
Half-life (hr)	15.3 (18%)	15.6 (21%)	56.7 (42%)	59.8 (27%)

Data are expressed as geometric mean (%CV)
Data source: reviewer's analysis, CSR 201674- Other Data Listings

< Part 2>
Pharmacokinetic parameters of DTG and RPV following the single dose administration of single entity products and FDC under fasting conditions and moderate fat conditions are summarized in Table 4. Under fasting conditions, Cmax and AUC values of DTG and RPV were comparable between single entity products and the AM formulation.

The AUC_{inf} of DTG and RPV were increased by approximately 86% and 57%, respectively, under moderate fat conditions as compared to fasted conditions following the administration of the AM formulation. Based on cross-cohort comparison conducted in different subjects (Part 2 vs Part 1), there was no significant difference in RPV and DTG exposures under high fat conditions as compared to moderate fat conditions.

Reviewer comments
The effects of food on DTG and RPV exposures (AUC ↑86% for DTG and ↑57% for RPV), observed in this trial are largely consistent with findings observed with single entity products (approximately 40 – 70% increase in AUC under various fed conditions compared to fasted conditions).

Table 4. Summary of DTG and RPV PK Parameters Under Fasting and Fed Conditions

Prandial conditions	PK parameters	DTG		RPV	
		Single entity	**AM formulation**	**Single entity**	**AM formulation**
Fasting (n=12)	C_{max} (µg/mL)	2.20 (50%)	1.94 (67%)	0.049 (75%)	0.050 (77%)
	AUC_{inf} (µg/mL·hr)	39.7 (46%)	34.6 (53%)	2.18 (65%)	2.23 (71%)
Moderate fat (n=12)	C_{max} (µg/mL)	Not determined	3.38 (21%)	Not determined	0.095 (33%)
	AUC_{inf} (µg/mL·hr)	Not determined	64.6 (22%)	Not determined	3.51 (43%)

Data are expressed as geometric mean (%CV)
Data source: reviewer's analysis, CSR 201674- Other Data Listings

Conclusion

1. C_{max} and AUC values of DTG and RPV were comparable between single entity products and the AM formulation under high fat conditions and under fasted conditions.
2. The AUC_{inf} of DTG and RPV were increased by 86% and 57%, respectively, under moderate fat conditions as compared to fasted conditions following the administration of the AM formulation.

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/s/

KAREN D WINESTOCK
11/21/2017

DEBRA B BIRNKRANT
11/21/2017

CDTL NDA Review and Evaluation

Application Type	NDA
Application Number(s)	210192
Priority or Standard	Priority
Submit Date(s)	June 1, 2017
Received Date(s)	June 1, 2017
PDUFA Goal Date	December 1, 2017
Division/Office	DAVP/OAP
Review Completion Date	See DARRTS electronic signature page
Established Name	dolutegravir/rilpivirine
(Proposed) Trade Name	JULUCA
Pharmacologic Class	Dolutegravir is an integrase strand-transfer inhibitor (INSTI), and rilpivirine is a non-nucleoside reverse transcriptase inhibitors (NNRTI)
Applicant	ViiV
Formulation(s)	FDC Tablet
Dosing Regimen	
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Recommended Indication(s)/Population(s) (if applicable)	JULUCA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of JULUCA.

The Cross-Discipline Team Leader Review is complete, and has been added to the NDA/BLA Multi-Disciplinary Review and Evaluation. My recommendation for this application is approval

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/s/

KIMBERLY A STRUBLE
11/16/2017

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210192
Priority or Standard	Priority
Submit Date(s)	June 1, 2017
Received Date(s)	June 1, 2017
PDUFA Goal Date	December 1, 2017
Division/Office	DAVP/OAP
Review Completion Date	See DARRTS electronic signature page
Established Name	dolutegravir/rilpivirine
(Proposed) Trade Name	JULUCA
Pharmacologic Class	Dolutegravir is an integrase strand-transfer inhibitor (INSTI), and rilpivirine is a non-nucleoside reverse transcriptase inhibitors (NNRTI)
Applicant	ViiV
Formulation(s)	FDC Tablet
Dosing Regimen	dolutegravir 25 mg/rilpivirine 25 mg
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommended Indication(s)/Population(s) (if applicable)	JULUCA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of JULUCA.

1. Status of Clinical Review

Clinical review for Juluca is complete, and has been added to the NDA Multi-Disciplinary Review and Evaluation document.

2. Clinical Summary of Results and Conclusions

Please refer to the Multi-Disciplinary Review for details. The Applicant provided substantial evidence of effectiveness to support approval of Juluca for the treatment of HIV infection.

The efficacy of DTG + RPV was demonstrated in two identical 48-week, open-label, randomized, active-controlled, non-inferiority trials, SWORD-1 and SWORD-2. Non-inferiority was met between Juluca and the comparator regimens in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of treatment failure and no known substitutions associated with resistance to DTG or RPV. At Week 48, in the pooled analysis, the proportion of subjects with HIV RNA ≥ 50 copies/mL was 0.6% and 1% in the DTG+RPV and CAR treatment groups, respectively [adjusted treatment difference and 95% CI: -0.6 (-1.7%, 0.6%)]. This met the noninferiority margin for 4% for subjects with HIV RNA ≥ 50 copies/mL. In addition, the proportion of subjects with HIV RNA <50 copies at Week 48 were 95% in both the DTG+RPV treatment group and the current antiretroviral regimen (CAR) treatment group [adjusted treatment difference and 95% CI: -0.2% (-3.0%, 2.5%)].

In addition to a relative BA study, a BE study was conducted establishing the bioequivalence of Juluca to the individual drug products, DTG and RPV. Therefore, the two trials conducted using the individual drug products supports the approval of Juluca, an FDC product containing DTG and RPV.

Overall, Juluca was found to be safe and well tolerated with no new safety findings compared to the approved individual drug products, DTG and RPV.

3. Clinical Recommendation for Regulatory Action

From clinical perspective, I recommend approval of Juluca as a complete ARV regimen for the treatment of HIV-1 infected adult patients who are virologically suppressed (i.e. HIV RNA <50 copies/mL) with no previous history of virologic failure or resistance to either DTG or RPV.

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/s/

YODIT BELEW
11/08/2017

KIMBERLY A STRUBLE
11/08/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

BLA:	210192
Drug Name:	JULUCA ((Dolutegravir 50 mg and Rilpivirine 25 mg).
Indication(s):	Treatment of HIV-1 infection in adults who are virologically suppressed (b) (4) (b) (4) (b) (4)
Applicant:	Viiv Healthcare
Date(s):	Letter Date: June 1, 2017 PDUFA Date: December 1, 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Mushfiqur Rashid, Ph.D.
Concurring Reviewers:	Greg Soon, Ph.D.
Medical Division:	Division of Anti-Viral Products (DAVP)
Clinical Team:	Yodit Belew, M.D. / Kimberly Struble, M.D.
Project Manager:	Nina Mani

Summary:
This memo closes the NDA assignment in DARRTS for the statistics team. The statistical review is complete and is included in the Multi-disciplinary Review and Evaluation, which will be signed into DARRTS on November 12, 2017. The statistical analysis of the efficacy findings supports approval. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

MUSHFIQUR M RASHID
11/07/2017

GUOXING SOON
11/07/2017

OFFICE OF CLINICAL PHARMACOLOGY MEMO

NDA Number	210,192
Submission Type	505 (b) (1) Non-NME NDA
Generic/Brand Name	JULUCA (fixed dose combination product containing 50 mg dolutegravir and 25 mg rilpivirine)
Applicant	ViiV Healthcare
Submission Date	6/1/2017
PDUFA Goal Date	12/1/2017
Proposed Indication	Treatment of HIV-1 infection in adults who are virologically suppressed (b) (4)
Dosage form	Tablet for oral administration
OCP Division	DCP4
OND Division	DAVP
Primary reviewer	Su-Young Choi, Pharm.D., Ph.D
Team Leader	Shirley Seo, Ph.D

The clinical pharmacology review is complete and has been added to the NDA 210,192 Multi-disciplinary Review and Evaluation. The Office of Clinical Pharmacology recommendation for this application is approval.

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/s/

SU-YOUNG CHOI
11/03/2017

SHIRLEY K SEO
11/03/2017

Pharmacology/Toxicology Review

Goal Date: November 8, 2017
Completion Date: October 30, 2017
NDA #: 210192
Supporting document#: None
CDER stamp date(s): July 6, 2017
Product name: **JULUCA**
Indication: Treatment of HIV-1 in virologically suppressed adults
Applicant: Viiv
Reviewer: John Dubinion, Ph.D.

Recommendation: It is recommended that **JULUCA** be approved.

Summary: JULUCA™, a once daily fixed-dose combination (FDC) tablet containing dolutegravir (DTG) and rilpivirine (RPV), is intended for the treatment of human immunodeficiency virus-1 (HIV-1) infection in virologically suppressed (HIV-1 <50 copies/mL) (b) (4) DTG and RPV are approved products marketed as TIVICAY (NDA 204790; August 12, 2012) and EDURANT (NDA 202022; May 20, 2011), respectively. DTG is an HIV integrase inhibitor (INI) approved for use in antiretroviral treatment-naïve and treatment-experienced HIV-infected adults and adolescents at a dose of 50 mg once daily, and RPV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for use in antiretroviral treatment-naïve HIV-1-infected adults with a viral load <100,000 HIV-1 RNA copies/mL, at a dose of 25 mg once daily taken with meal. This two-drug, NRTI sparing regimen, differs from the current standard of care, which typically includes 2 NRTIs plus a third agent from the protease inhibitor, NNRTI or INI class, and as a simplified two-drug regimen, offers favorable tolerability and suppression of resistance similar to other DTG based HIV-1 treatment regimens.

DTG and RPV's prior approvals included comprehensive nonclinical packages. In agreement with ICH Guidance M3 (R2), nonclinical combination studies were not conducted with DTG/RPV, except for a combination pharmacokinetic study in dogs, to determine any potential effects of co-administration. Pharmacology/Toxicology Review is complete, and has been added to the NDA Multidisciplinary Review and Evaluation. Pharm/Tox recommendation for this application is approval.

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/s/

JOHN H DUBINION
10/30/2017

HANAN N GHANTOUS
10/30/2017

Pharmacology/Toxicology Review by Dr. John Dubinion is complete, and has been added to the NDA Multidisciplinary Review and Evaluation. Pharm/Tox recommendation for this application is approval.

Clinical Consultation

From: Stephen Voss MD, Medical Officer DBRUP
Through: Theresa Kehoe MD, Clinical Team Leader DBRUP
Christine Nguyen MD, Acting Division Director DBRUP
To: Yodit Belew MD, Medical Officer DAVP
Nina Mani PhD, MPH, SRPM DAVP
Subject: Bone safety of dolutegravir plus rilpivirine, compared to TDF containing regimens for treatment of HIV (NDA 210192)
Date of consult request: June 7, 2017
DBRUP Tracking #: 231

Overview
GSK/ViiV Healthcare has developed Juluca, a fixed dose combination of two HIV antiviral drugs, dolutegravir (DTG) and rilpivirine (RPV), as a complete maintenance regimen for stable, virologically suppressed HIV-infected patients. Two phase 3 trials evaluated switching such patients from their current drug regimen to DTG/RPV, compared to continuing on the same regimen. Among patients whose pre-baseline regimen included tenofovir disoproxil fumarate (TDF), a drug known to depress bone mineral density (BMD), a sub-study evaluated potential improvement in BMD.

NDA 210192 for Juluca was submitted on 6/1/17 and is under priority review by DAVP. The Applicant proposes to include the phase 3 BMD data in labeling section 6. DBRUP previously consulted regarding the bone sub-study protocol (IND 075382, DARRTS 6/16/15), and is now requested to review the submitted BMD data and address the following:

- Do the results of the sub-study support inclusion of the proposed language in the label?
- If so, do you have any additional edits/comments on the proposed label?
- If the trial does support the proposed labeling, please provide your rationale and any recommendations you may have for the sponsor.

Background
HIV-infected adults are at higher than average risk for low BMD, osteoporosis and fracture. In a prospective study of 1006 HIV patients in the US, low baseline BMD was significantly associated with elevated risk of subsequent fracture, adjusted for covariates.[1] The increased risk is believed to be due to multiple factors, including direct effects of the virus; higher prevalence of traditional risk factors e.g. low body weight, smoking, low vitamin D and corticosteroid use; and possibly the effects of cytokines in chronic inflammation. In addition, initiation of nucleotide reverse transcriptase inhibitor (NRTI) based treatment regimens is associated with moderate declines in BMD (~2-6%) during the first 1-2 years of treatment. However, BMD stabilizes with continued treatment, and the clinical significance of the treatment-related BMD changes is unclear.

Among the NRTIs used in treating HIV, TDF is most strongly associated with bone loss. Treatment regimens containing TDF, compared to those containing other NRTIs without TDF, have resulted in significantly greater BMD declines in randomized studies, with TDF minus non-TDF mean differences of -0.8% to -2.0% (spine) and -0.4% to -1.7% (hip).[2-4] The mechanism

appears to be related to increased bone turnover, as evidenced by larger increases in biochemical markers of bone formation and resorption with TDF (in osteoporotic patients, increased bone turnover is associated with increased fracture risk, independent of BMD). Some studies have suggested that BMD declines are larger when TDF is combined with a ritonavir-boosted protease inhibitor (rPI). TDF has also been associated with osteomalacia, usually in conjunction with proximal renal tubule dysfunction and phosphate wasting, in sporadic postmarketing reports and in animal studies. It is not known whether TDF-related BMD declines indicate an increased risk for osteomalacia and/or fractures. TDF clinical trials were not adequately powered for fracture endpoints, and epidemiologic studies have been inconsistent regarding a possible increased fracture risk with TDF. A newer version of this drug, tenofovir alafenamide fumarate (TAF), is metabolized differently from TDF and has a significantly less negative effect on BMD.

Studies have shown that switching patients from TDF to non-TDF regimens may reverse the BMD and bone marker changes:

- Negredo et al randomized 54 HIV patients with low BMD to continue TDF (n=28) or switch to another NRTI, abacavir (ABC) (n=26), with no change in the remainder of the regimen. At week 48, mean hip BMD increased by 2.1% in the ABC group and 0.7% in the TDF group (p=0.23). Various bone turnover markers declined by 41-48% in the ABC group ($p<0.05$ for difference from TDF for each marker).[5,6]
- A phase 3 study randomized 1436 HIV patients to continue their TDF based regimen or switch to Genvoya (TAF-based). Mean BMD in the switch group increased at week 48 by 1.9% (spine) and 2.0% (hip), with minimal change (-0.1% each site) in the continued-TDF group ($p<0.001$ for treatment group differences). Bone turnover marker changes were more negative in switch patients ($p<0.01$). (NDA 207561)
- Bloch et al enrolled 37 HIV patients with low BMD, who were stable on a regimen that included TDF and an rPI, and switched the TDF to an integrase strand transfer inhibitor (INSTI), raltegravir (RAL). Mean BMD increased at week 48 by 3.0% (spine) and 2.5% (total hip), and bone turnover markers declined significantly by week 24.[7]

In addition, a pre-exposure prophylaxis study in HIV-negative, high-risk individuals treated with TDF and emtricitabine (FTC), included evaluations of BMD in 498 participants. Subjects with good adherence had mean BMD changes from baseline of -1.02% (hip) and -1.84% (spine) at the end of treatment (median 64 weeks), with minimal BMD changes in low-adherence and placebo groups. After stopping treatment, BMD returned to near baseline within 1 year.[8]

Regimens that do not include TDF or rPIs may be preferred in HIV patients at risk for bone loss or fracture, per published recommendations.[9] The product currently under review, Juluca, is a once-daily fixed dose combination of dolutegravir (DTG) 50 mg, an INSTI; and rilpivirine (RPV) 25 mg, a non-nucleoside reverse transcriptase inhibitor (NNRTI). In general, unlike NRTIs and PIs, drugs in these two classes have not been associated with BMD declines.

DTG/RPV phase 3 bone-safety: study design

Studies 201636 and 201637 are identical, randomized, active-controlled phase 3 studies which enrolled a total of 1024 adult HIV-1-infected patients, age ≥18 y/o, who were on a stable suppressive antiretroviral regimen containing 2 NRTIs and a third drug (an INSTI, NNRTI or PI). About 70% of participants were receiving TDF as one of the NRTIs prior to enrollment. Patients were randomized 1:1 to switch to DTG/RPV (Juluca) or to continue their current antiviral regimen (CAR). Randomization was stratified by participation in the BMD sub-study, and by baseline third agent class. Treatments were open label, because of the difficulty in blinding with a variety of CAR regimens. The NDA under review includes the week 48 data comparing these two groups. After week 52, all patients receive DTG/RPV in an extension which is ongoing.

BMD sub-study 202094 was designed to evaluate ~150 participants of either of the parent studies (201636 or 201637), whose pre-baseline regimen included TDF (duration of pre-baseline TDF not specified). Patients were enrolled in the sub-study after being deemed eligible for the parent study but before randomization. The primary objective of the sub-study was to evaluate total hip BMD change at 48 weeks between the DTG+RPV and CAR treatment arms. Among the exclusion criteria for the sub-study were thyroid or other endocrine disorders; a history of fragility fractures; BMD T-score (SD compared to young adult mean) ≤ -3.5 on any prior DXA scan; serum 25-OH-vitamin D <15 ng/mL; BMI <18 or >40; prior bisphosphonate treatment; and use of anabolic steroids. Concurrent estrogen or testosterone therapy, or anticonvulsant therapy, was allowed only if stable for >6 months.

DXA of the hip and lumbar spine (L1-L4) was conducted at baseline and week 48. The baseline scans were to be conducted within a week of day 1 (the day of first dose of DTG+RPV in the switch group) per the protocol, but the acceptance window for analysis was extended to day 15 in the statistical plan. A central imaging contractor, Parexel International, coordinated the longitudinal and cross-center calibration of scanners and performed treatment-blinded readings. A correction factor, based on site-specific calibration data, was applied to all submitted BMD data.

BMD data were compared between the DTG/RPV (switch) and CAR (continuing) groups, representing non-TDF and TDF regimens, respectively. The primary endpoint for the sub-study was the percent change from baseline at week 48 in total hip BMD (g/cm^2). Secondary endpoints included percent change in lumbar spine BMD at week 48; BMD changes by third agent in baseline CAR regimen (INSTI, NNRTI or PI); and changes in BMD Z-scores and T-scores. Longer term BMD changes will be assessed at weeks 96 and 148 in future reports.

The sample size calculations were based on data from two published TDF-to-non-TDF switch studies[5,7] with additional SD data from a study of treatment naïve patients[3]. Based on a true population effect of 1.9% treatment difference with SD of 3.5%, the planned sample of 150 subjects with evaluable BMD at week 48 would have 90% power to demonstrate a statistically significant result ($p<0.05$). A protocol amendment provided an additional estimate that with a smaller sample of 100 subjects, the study would have 77% power to demonstrate a significant treatment difference.

Serum biomarkers of bone turnover were assessed at baseline and week 48, including indices of bone formation: bone-specific alkaline phosphatase (BSAP), osteocalcin and procollagen type 1 N-terminal propeptide (P1NP); and an index of bone resorption: C-terminal telopeptide of collagen type 1 (CTX). Changes from baseline for these markers, and relationship to BMD changes, were analyzed as exploratory endpoints.

The WHO Fracture Risk Assessment Tool (FRAX) was also assessed as an exploratory endpoint. FRAX incorporates non-BMD risk factors (age, prior fracture, smoking etc.), with or without femoral neck BMD, and estimates 10-year probabilities for hip fracture and major osteoporotic fracture. FRAX scoring is widely used in management of persons at risk for osteoporosis, and has been recommended for all HIV patients ≥40 y/o.[9] HIV status is not a FRAX input variable, although some experts recommend that HIV-positivity be counted as a "secondary cause" of osteoporosis for the risk estimates (this was not done in this sub-study).[9]

Incident fracture was not an endpoint in either the BMD sub-study or the parent studies, which would likely have insufficient power for such an evaluation. Fracture events were recorded as AEs, with no special procedures (e.g. review of x-ray reports) for adjudication.

Sub-study results

There were 32 study sites that participated in the BMD sub-study. Out of 151 patients screened, 49 failed screening, and the remaining 102 patients were enrolled in the sub-study (ITT-ED population) at sites in Spain (n=46), Argentina (21), Canada (12), US (9), Belgium (9), and UK (5). Of these 102 patients, there were 12 whose baseline DXA was outside the designated window (i.e. after day 15), and another 9 who discontinued (from both parent study and bone sub-study) for various reasons and so had no post-baseline DXA. Data from the remaining 81 patients, with evaluable DXA at both baseline and week 48, were used for the Applicant's analyses of BMD.

Bone sub-study 202094: Disposition and analysis populations

	DTG+RPV	CAR	Total
Enrolled/randomized (ITT-ED*)	53	49	102
Completed week 52	49	44	93
Withdrew before week 52	4	5	9
Evaluable hip DXA at baseline**	50	40	90
Evaluable hip DXA at baseline** and week 48	46	35	81

*ITT-ED = ITT Exposed DXA = patients enrolled in sub-study who received at least one dose (same as Safety DXA population)
**12 patients had baseline hip DXA outside window (after day 15)

Calcium and/or vitamin D supplements were taken concomitantly by 23% of DTG+RPV and 16% of CAR recipients within the sub-study. There were 2 patients, both DTG+RPV recipients, who took prohibited co-medications for a substantial time: one who was on Fosamax, beginning ~10 years pre-enrollment and during the study to week 48 (this patient was enrolled in error); and one who began the anticonvulsants lacosamide and topiramate ~12 weeks prior to the week 48 visit. These patients were not excluded from BMD analyses.

Demographics
The median age of bone sub-study participants was 45 years. The treatment arms were similar in baseline characteristics (table on next page), and also similar to the parent studies (201636, 201637) with the exception of gender: women made up only 22% of the parent studies but 52% of the sub-study. It appears that this was by design, although not stated in the protocol; the study report says that "enrollment of female subjects was a key goal of this sub-study". About 1/3 of the women were post-menopausal.

Although most (99/102) participants had been receiving a TDF based regimen for at least 48 weeks prior to baseline, they generally had normal BMD, with mean Z-scores of 0.0 (hip) and -0.2 (spine), and mean T-scores of -0.3 (hip) and -0.7 (spine). Similarly, the baseline FRAX scores (incorporating femoral neck BMD, and non-BMD risk factors) indicated low fracture risk, with 10-year mean probabilities of 0.3% for hip fracture, and 2.2% for major osteoporotic fracture.

Reviewer comment*: For comparison, FRAX 10-year probability scores of >3% for hip fracture or >20% for major osteoporotic fracture, in combination with low BMD, are considered to represent high risk for the purpose of osteoporosis treatment guidelines in the US. Only one sub-study patient (*(b) (6)*), a 76 y/o white woman with femoral neck T-score of -2.4, met one of these thresholds with a hip fracture 10-year probability of 3.4%.*

Sub-study 202094: Demographic and baseline characteristics (ITT-ED)

	DTG + RPV N=53	**CAR** N=49	**Total** N=102
Age (years)			
Median (range)	43 (21-62)	46 (22-76)	45 (21-76)
Age group (years), n (%)			
<35	14 (26)	10 (20)	24 (24)
35-49	24 (45)	23 (47)	47 (46)
≥50	15 (28)	16 (33)	31 (30)
Sex, n (%)			
Female	27 (51)	26 (53)	53 (52)
Male	26 (49)	23 (47)	49 (48)
Menopausal status (women), n (%)			
Pre-menopause	17 (63)	17 (65)	34 (64)
Post-menopause	10 (37)	9 (35)	19 (36)
Ethnicity, n (%)			
Hispanic/Latino	17 (32)	18 (37)	35 (34)
Not Hispanic/Latino	36 (68)	31 (63)	67 (66)
Race, n (%)			
White	44 (83)	40 (82)	84 (82)
African American/ African Heritage	3 (6)	7 (14)	10 (10)
American Indian/ Alaska Native	4 (8)	1 (2)	5 (5)
Asian	2 (4)	1 (2)	3 (3)
BMI (kg/m^2)			
Mean	25.2	25.8	25.5
Duration of pre-enrollment TDF exposure, n			
≥ 48 weeks	52	47	99
< 48 weeks	1	2	3
T-/Z-scores* (mean)			
Hip T-score	-0.3	-0.3	-0.3
Hip Z-score	-0.1	-0.0	-0.0
Spine T-score	-0.7	-0.6	-0.7
Spine Z-score	-0.2	-0.2	-0.2
Serum 25-OH-vitamin D (ng/mL)	34.8	30.8	32.9

*T-scores = SD from mean BMD of healthy young adults; Z-scores = SD from mean BMD of healthy adults normalized for age and gender
Source: CSR Tables 1.160, 2.410, 2.520 and 3.530 and Listing 108

BMD results

Among the 81 patients with evaluable DXA at baseline and week 48, the DTG+RPV group demonstrated increases in total hip and lumbar spine BMD that were significantly different from the minimal changes occurring in the CAR group, using an ANCOVA model adjusted for baseline BMD, age and BMI.

Sub-study 202094: Total hip BMD (ITT-ED*)

	DTG + RPV N=53	**CAR** N=49	Difference (95% CI)**	p-value**
Baseline, n	50	40		
Mean BMD, g/cm^2	0.964	0.974		
Week 48, n	46	35		
Mean adjusted % change from BL (95% CI)*	1.34 (0.68, 2.01)	0.05 (-0.71, 0.82)	1.29 (0.27, 2.31)	0.014

*Data on patients with evaluable BMD at baseline (day <15) and week 48
**estimates and associated p-value from an ANCOVA model adjusted for baseline BMD, age, baseline BMI
Source: CSR Tables 2.200 and 2.240

Sub-study 202094: Lumbar spine BMD (ITT-ED*)

	DTG + RPV N=53	**CAR** N=49	Difference (95% CI)**	p-value**
Baseline, n	52	42		
Mean BMD, g/cm^2	1.063	1.086		
Week 48, n	46	35		
Mean adjusted % change from BL (95% CI)*	1.46 (0.65, 2.28)	0.15 (-0.79, 1.09)	1.32 (0.07, 2.57)	0.039

* Data on patients with evaluable BMD at baseline (day <15) and week 48
**Estimates and associated p-value from an ANCOVA model adjusted for baseline BMD, age, baseline BMI
Source: CSR Tables 2.260 and 2.280

Results were similar for femoral neck BMD, with mean changes from baseline to week 48 of 1.18% (DTG+RPV group) and -0.04% (CAR group). This was not a prespecified endpoint so the ANCOVA analysis was not conducted.

As noted above, there were 12 patients excluded from the Applicant's BMD analyses because their baseline hip DXA occurred after day 15:

Sub-study 202094: Patients with baseline DXA outside of 15-day window (ITT-ED)

Subject #	Treatment group	Age/sex	Hip DXA		Spine DXA	
			Day of baseline DXA	% change BMD, BL to week 48	Day of baseline DXA	% change BMD, BL to week 48
(b) (6)	DTG+RPV	33/M	57	1.54	1	1.18
	DTG+RPV	33/M	27	-1.17	27	-0.55
	DTG+RPV	33/M	19	3.84	1	0.73
	CAR	52/F	26	0.84	26	0.83
	CAR	51/F	31	-3.30	31	3.53
	CAR	46/M	25	-1.40	25	-1.38
	CAR	59/F	20	-2.98	20	-1.08
	CAR	22/F	52	-3.58	1	-5.58
	CAR	33/M	22	-1.54	5	-4.12
	CAR	67/M	22	5.53	6	-1.27
	CAR	34/M	19	0.26	19	-1.73
	CAR	35/M	22	-2.08	1	2.22

Day of baseline hip and day of baseline spine DXA do not match for some patients because of re-scanning
Source: ADXA dataset

Reviewer comment: *It would be unusual for BMD to change markedly within 1-2 months of any intervention, so baseline data from some of these 12 patients may be valid, especially the 9 CAR patients whose treatment regimen did not change.*

In addition, the Applicant's analyses excluded a patient (b) (6) assigned to CAR who switched to DTG+RPV on the same day as the week 48 DXA scan, thereby assigning this scan to the single-arm extension phase. If BMD data from this patient and the 12 patients listed in the above table are added to the 81 patients' data considered in the Applicant's analyses (i.e. to include all patients with baseline and week 48 data), results are similar to those of the Applicant:

Sub-study 202094: Mean BMD changes at week 48, including patients with DXA outside of visit windows (ITT-ED)

	DTG + RPV	CAR	Difference
Total hip BMD, n	49	45	94
mean % change from BL	1.38	-0.20	1.58
Lumbar spine BMD, n	47	43	90
mean % change from BL	1.51	-0.13	1.64
Source: ADXA dataset			

Reviewer comments:
The number of patients with evaluable week 48 DXA was much smaller than anticipated. The protocol had stated that ~198 patients would be screened to achieve ~150 evaluable patients. Instead, 151 were screened and, because of screen fails and out-of-window DXA, only 81 were considered evaluable. The study had adequate (77%) power to detect a significant difference in total hip BMD with a sample size of 100. In this reviewer's opinion, per the above table, the study had valid data on 94 patients, and data on the 13 patients excluded from the Applicant's

analyses were consistent with data from the other 81 patients. Despite the smaller than expected sample, the sub-study demonstrated a statistically significant treatment effect for both total hip and lumbar spine BMD, and there is no good reason to doubt the conclusions regarding BMD.

The treatment group differences of about 1.3-1.6% for hip and spine BMD are, respectively, similar to and greater than non-TDF-minus-TDF differences in a published controlled switch study[5]; but smaller than those in an uncontrolled switch study[7] and the Genvoya switch study (#109). Because these studies differed in sample size and presumably many other aspects, conclusions about the relative effects on BMD of the various non-TDF drugs used are not justified.

There were 14 patients who exhibited >5% increases from baseline at ≥1 site at week 48, listed in the table below. Most of these (11) were DTF+RPV recipients, of whom 3 had low baseline BMD (T-score < -2.0).

Sub-study 202094: Patients with >5% BMD increase during study

Treatment arm	Subject # (b) (6)	Age/ Race/ Sex	Baseline hip/spine T-scores	BMD % change at week 48		
				Total hip	Femoral neck	Lumbar spine
DTG+RPV		53/Asian/F	-2.3/ -3.6	1.6	**6.9**	**5.1**
		23/W/M	0.4/ -1.1	1.7	2.6	**5.2**
		24/W/F	-0.9/ -0.8	**6.3**	4.0	1.7
		49/W/F	-1.9/ -2.1	**8.0**	**9.1**	-1.9
		58/Afr. Am./F	-0.2/ 0.7	1.0	**6.1**	-0.3
		29/W/F	-0.9/ -2.1	**5.7**	2.2	**8.2**
		40/W/F	-0.1/ -0.4	2.5	2.4	**5.9**
		46/W/M	-1.5/ 0.5	**8.1**	**5.3**	**4.7**
		21/Amer. Ind./M	0.3/ 0.2	3.3	**7.6**	**6.7**
		52/W/F	-1.3/ -2.3	**5.3**	0.6	0.4
		37/W/M	-1.5/ -3.7	-3.3	-1.2	**5.0**
CAR		55/W/M	-0.1/ -0.9	0.1	-0.1	**7.3**
		30/W/M	-1.3/ -1.3	1.3	4.6	**5.9**
		53/W/F	0.2/ 0.2	2.9	**5.4**	**-**
Source: ADXA						

There were 5 patients who exhibited >5% declines from baseline BMD at ≥1 site during the study, including a 61 y/o woman with low baseline BMD, assigned to CAR, who sustained a fibula fracture on day 164:

Sub-study 202094: Patients with >5% BMD decline during study

Treatment arm	Subject # (b) (6)	Age/ Race/ Sex	Baseline hip/spine T-scores	BMD % change at week 48			
				Total hip	Femoral neck	Lumbar spine	
DTG+RPV		31/W/M	0.0 / 0.2	-0.8	-0.2	**-5.8***	Smoker BMI 21.8→20.5
CAR		61/W/F	-2.0 / -0.9	**-5.4**	**-5.1**	-0.7	"Non-traumatic" fibula fracture on day 164
		43/W/F	-0.7/ 0.3	-0.4	**-5.5**	2.4	
		22/W/F	0.3 / 1.4	-3.6	-1.7	**-5.6**	
		47/W/M	1.0 / 0.3	-1.8	-1.4	**-5.8**	Smoker

*For subject (b) (6) "Week 48" DXA of spine was actually conducted at week 59
Source: ADXA

Consistent with the BMD changes, T-scores and Z-scores (secondary endpoints) increased moderately in the DTG+RPV group, with minimal change in the CAR control group:

Sub-study 202094: BMD T-/Z-scores: mean change from baseline at week 48 (ITT-ED*)

	DTG + RPV N=53	**CAR** N=49	Difference (95% CI)**	p-value**
Total hip T-score	0.09	0.01	0.09 (0.02, 0.16)	0.016
Total hip Z-score	0.11	0.02	0.08 (0.01, 0.15)	0.026
Lumbar spine T-score	0.13	0.01	0.12 (0.00, 0.23)	0.049
Lumbar spine Z-score	0.17	0.02	0.15 (0.03, 0.27)	0.013

* Data on patients with evaluable BMD at baseline (day <15) and week 48
**Estimates and associated p-values from an ANCOVA model adjusted for baseline T-/Z-score, age, baseline BMI
Source: Study 202094 Table 2.530

Reviewer comment: *In adults, changes in BMD Z-scores and T-scores generally add no meaningful information beyond the absolute BMD changes, and may be affected by the use of different reference databases. Therefore DBRUP would consider these data to be of limited value as supportive data. Regarding the p-values listed in the table, it should be noted that secondary endpoints were not adjusted for multiplicity.*

BMD by subgroups

Analyses of BMD, T- and Z-score changes by baseline third antiviral agent (INSTI, NNRTI or PI), were prespecified as secondary endpoints. Changes in BMD (table below) and changes in T- and Z-scores (not shown) were generally consistent across these subgroups.

Sub-study 202094: BMD percent changes from baseline at week 48, by baseline third agent (ITT-ED*)

Baseline third agent	DTG + RPV		CAR	
Total hip BMD	n	Mean % change	n	Mean % change
INSTI	7	2.03	4	1.38
NNRTI	28	1.33	24	-0.27
PI	11	1.11	7	0.12
Lumbar spine BMD	n	Mean % change	n	Mean % change
INSTI	7	1.43	3	-2.42
NNRTI	28	1.38	26	0.12
PI	11	1.78	6	1.40

* Data on patients with evaluable BMD at baseline (day <15) and week 48
Estimates are from an ANCOVA model adjusted for baseline BMD
Source: CSR Table 2.330

Reviewer comment: *Most of these DTG+RPV vs. CAR differences for third-agent subgroups did not reach nominal statistical significance, so there is no conclusive evidence that switching to DTF+RPV leads to BMD increases for patients with each of these baseline regimen types. Subgroup evaluations in this study were adversely affected by the smaller than expected number of evaluable patients (discussed above).*

BMD changes within other subgroups (age, gender, race, BMI, CD4+ lymphocyte count, smoking and alcohol use, calcium and vitamin D supplement use) were analyzed as exploratory endpoints. Treatment arm differences were generally consistent across all these subgroups (CSR Tables 13-18), though with small numbers of patients in many of the categories. Age, race and gender subgroups are shown in the tables below.

Sub-study 202094: BMD percent changes from baseline at week 48, by age groups (ITT-ED*)

	DTG + RPV		CAR	
	n	Mean % change	n	Mean % change
Total hip BMD				
<35 years	11	1.43	6	0.63
35 – 49	22	1.42	18	0.08
≥ 50	13	1.24	11	-0.42
Lumbar spine BMD				
<35 years	11	2.80	8	-0.09
35 – 49	22	1.00	16	-0.08
≥ 50	13	1.32	11	0.41

* Data on patients with evaluable BMD at baseline (day <15) and week 48
Estimates are from an ANCOVA model adjusted for baseline BMD
Source: CSR Tables 2.250 and 2.470

Sub-study 202094: BMD percent changes from baseline at week 48, by racial groups (ITT-ED*)

	DTG + RPV		CAR	
	n	Mean % change	n	Mean % change
Total hip BMD				
White	37	1.43	29	0.00
African American/ African Heritage	3	1.49	5	0.67
Lumbar spine BMD				
White	37	1.45	30	0.02
African American/ African Heritage	3	0.75	4	-0.27

* Data on patients with evaluable BMD at baseline (day <15) and week 48
Not included in table: data on American Indian/Alaska Native patients (n=5) and Asian patients (n=3)
Estimates are from an ANCOVA model adjusted for baseline BMD
Source: CSR Tables 2.250 and 2.470

Sub-study 202094: BMD percent changes from baseline at week 48, by gender (ITT-ED*)

	DTG + RPV		CAR	
	n	Mean % change	n	Mean % change
Total hip BMD				
Female	25	1.66	18	0.03
Male	21	1.04	17	-0.01
Lumbar spine BMD				
Female	25	1.34	16	0.53
Male	21	1.54	19	-0.11

* Data on patients with evaluable BMD at baseline (day <15) and week 48
Estimates are from an ANCOVA model adjusted for baseline BMD
Source: CSR Tables 2.250 and 2.470

Results for female patients by menopausal status (not analyzed by the Applicant) are presented in the table below. Within the DTG+RPV group, pre-menopausal women showed trends of greater increases in hip and spine BMD, but the number of patients per group was small.

Sub-study 202094: BMD percent changes from baseline at week 48 in female patients, by menopausal status (ITT-ED*)

	DTG + RPV		CAR	
Total hip BMD	n	Mean % change	n	Mean % change
Pre-menopausal	17	2.02	12	0.46
Post-menopausal	8	1.00	6	-0.97
Lumbar spine BMD	n	Mean % change	n	Mean % change
Pre-menopausal	17	1.85	10	-0.22
Post-menopausal	8	0.98	6	0.23

* Data on patients with evaluable BMD at baseline (day <15) and week 48
Source: ADXA and RP datasets

BMD changes by treatment group were similar for patients above and below a serum 25-OH-vitamin D level of 30 ng/mL (the generally accepted threshold of vitamin D "sufficiency"):

Sub-study 202094: BMD percent changes from baseline at week 48, by baseline serum 25-OH-vitamin D status (ITT-ED*)

	DTG + RPV		CAR	
Total hip BMD	n	Mean % change	n	Mean % change
25-OH-D ≥ 30 ng/mL	22	1.31	20	-0.24
25-OH-D < 30 ng/mL	25	1.71	16	0.25
Lumbar spine BMD	n	Mean % change	n	Mean % change
25-OH-D ≥ 30 ng/mL	24	1.29	21	-0.42
25-OH-D < 30 ng/mL	26	1.15	16	0.43
* Data on patients with evaluable BMD at baseline (day <15) and week 48 Source: ADXA and LB datasets				

Among patients treated with DTG+RPV, BMD percent increases were somewhat greater in those with baseline hip T-scores of < -1.0:

Sub-study 202094: BMD percent changes from baseline at week 48, by baseline hip T-score categories (ITT-ED*)

	DTG + RPV		CAR	
Total hip BMD	n	Mean % change	n	Mean % change
Hip T-score ≥ -1	32	0.82	28	0.17
Hip T-score < -1	14	2.66	7	-0.69
Lumbar spine BMD	n	Mean % change	n	Mean % change
Hip T-score ≥ -1	31	1.11	24	0.17
Hip T-score < -1	14	2.60	7	0.81
* Data on patients with evaluable BMD at baseline (day <15) and week 48 Source: ADXA				

Reviewer comments:
There are no longitudinal data to indicate whether BMD increases with DTG+RPV were in proportion to the patients' presumed previous BMD declines with TDF.

In osteoporosis studies, patients with the lowest baseline BMD generally have the greatest percent BMD increases on treatment. Because baseline BMD is the denominator for this calculation, this is expected to some extent. However, patients with more severe osteoporosis also appear to benefit the most from treatment: several studies of bisphosphonates have demonstrated significantly larger non-vertebral and hip fracture reductions in patients with lower baseline BMD.

Although extremely limited and inconclusive, data in the above table are consistent with current recommendations[9], whereby HIV patients with lower BMD may benefit from discontinuation or avoidance of TDF when possible.

The Applicant had planned an exploratory analysis of BMD changes according to the patient's duration of TDF therapy prior to the switch to DTG+RPV (<48 weeks vs. ≥48 weeks). The analysis was not done because, among the 81 patients in their BMD analyses, there was only one with <48 weeks of prior TDF.

Bone turnover markers
Consistent with previous studies in which patients were switched from a TDF to non-TDF regimen, serum markers of bone formation (BSAP and P1NP) declined in the DTG+RPV group from baseline to week 48, a significant difference from the CAR control group (table below). Data for serum osteocalcin (not shown) were similar. These data were generally consistent across baseline third antiviral agent groups (INSTI, NNRTI or PI).

Sub-study 202094: Markers of bone formation, percent changes from baseline at week 48 (ITT-ED)

	DTG + RPV		CAR	
	n	Mean % change	n	Mean % change
Serum BSAP	48	-25	45	15
Serum P1NP	49	-34	44	-11
Adapted from CSR Table 3.550 which presented (as ratio of week 48 over baseline) analyses of log transformed data, with estimates from an ANCOVA model adjusting for original ART third agent class, age, sex, BMI category, smoking status and baseline level; in these analyses, p-values for DTG+RPV vs. CAR were <.001 for both markers				

Within the DTG+RPV treatment arm, there were significant negative correlations between change in BSAP and change in either hip or spine BMD; and between change in P1NP and change in hip BMD, in post hoc analyses by the Applicant.

Data for a bone resorption marker, serum CTX, were not yet available for the study report.
Reviewer comment*: In adults, bone formation and resorption are generally tightly coupled processes. Without resorption marker data, the changes in markers of bone formation are difficult to interpret.*

Serum 25-OH-vitamin D declined ~20% from baseline to week 48 in both treatment groups.

FRAX
Fracture risk factors were assessed at baseline and week 48 for this exploratory endpoint. Because few subjects had substantial interval changes in weight, smoking status etc., and the changes in femoral neck BMD in the DTG+RPV group were modest, there were minimal changes in 10-year fracture probability scores in either treatment group (CSR Table 12).

Reviewer comment: *It is not appropriate to use FRAX to measure changes in fracture risk in response to interventions such as drug treatment; FRAX was not designed for this purpose. Moreover, the analyses used data from all patients with evaluable BMD, many of whom were less than 40 y/o - a population for which FRAX is not applicable.*

Clinical fractures

Fractures were not analyzed in the study reports. As noted above, one patient in the sub-study ([redacted] sustained a fracture, and also had low BMD. In the overall parent studies combined (201636 and 201637, total N=1024), there were14 patients with fracture AEs reported up to week 48, listed in the following table. None of these patients received prednisone for a total of >7 days, or other concomitant meds that would significantly affect bone metabolism.

Studies 201636/201637: Clinical fracture AEs

Treatment arm	Subject #	Age/Race/Sex	Study day	Fracture site description
DTG/RPV	[redacted]	51/W/M	294	Wrist Motorcycle accident
DTG/RPV		31/W/M	318	Tibia, medial condyle
DTG/RPV		51/W/M	156	Finger
DTG/RPV		27/Asian/M	122	Nasal bone
			327	Foot, cuneiform bone
CAR		44/W/M	45	Humerus
CAR		68/W/F	7	Fibula
CAR		40/Amer. Ind./F	133	Clavicle
CAR		46/W/F	169	Wrist (Colles)
CAR		47/W/M	271	Tibial spine
CAR		52/W/M	336	Rib
CAR		59/W/M	246	Fibula
CAR		61/W/F	164	Fibula "non-traumatic" Enrolled in sub-study: T-scores -2.0/ -0.9 BMD decline during study: -5.4% total hip, -5.1% femoral neck
CAR		64/W/F	49	Rib
CAR		40/W/M	263	Digit

Source: ADAE dataset, events listed under AEHLGT Bone and joint injuries, and occurring during Early Switch Phase (prior to treatment switch of CAR patients to DTG+RPV)

Reviewer comment: *In osteoporosis clinical trials, fractures of fingers, toes, face and skull are typically excluded from clinical fracture endpoints, because BMD and bone fragility appear to play no role in their occurrence. Therefore in these phase 3 studies, there were 3 DTG+RPV and 9 CAR patients who sustained fractures for which TDF bone toxicity cannot be ruled out as a possible contributing factor. However, trauma was probably the most important factor in nearly every case (patient [redacted] may be an exception); therefore the apparent 3 vs. 9 patient imbalance between treatment arms was most likely the result of chance.*

Discussion

Sub-study 202094 demonstrated that HIV patients switched from a TDF-based 3-drug regimen to DTG+RPV, a non-TDF, "NRTI-sparing" regimen, experienced statistically significant increases of ~1.3% in both hip and spine BMD over 48 weeks, relative to a control group that continued their baseline TDF regimen. Although the study was fairly small, the data were generally consistent across different types of pre-baseline regimens and other patient subgroups, and also

qualitatively consistent with prior studies suggesting that discontinuation of TDF reverses the bone loss associated with initiating TDF. A decline in markers of bone turnover in patients undergoing the switch is also consistent with prior studies.

The clinical significance of the findings, as in studies of this type generally, is unclear. Despite long term treatment with a TDF regimen, most patients had normal BMD at baseline and low risk for fracture, and BMD increases during the study were modest. As noted in previous DBRUP consults regarding TDF or TAF, bone mass is only one of many factors influencing fracture risk. BMD generally correlates with fracture risk, including within an HIV population[1], however changes in BMD (e.g. in response to osteoporosis drug treatment) do not always adequately predict changes in fracture risk. Thus for drugs indicated to treat osteoporosis, DBRUP requires direct evidence of fracture reduction for efficacy or comparative efficacy claims, with BMD data as supportive evidence. We believe that this should apply to any drug that affects BMD, either positively or negatively. In the case of TDF and other HIV drugs, it would be difficult to show definitive effects on fracture: clinical fracture endpoints typically require a minimum of several thousand subjects in clinical trials of women with postmenopausal osteoporosis, who are at much higher risk for fracture than the HIV population.

BMD related labeling proposed by Applicant
Based on the phase 3 data, the Applicant proposes to include the following in labeling:

> ***6.1 Clinical Trials Experience***
> *Bone Mineral Density Effects*
> *Mean bone mineral density* [(b) (4)] *increased from baseline to Week 48 in subjects who switched from an antiretroviral treatment (ART) regimen containing tenofovir disoproxil fumarate (TDF) to dolutegravir plus rilpivirine (1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a TDF-containing antiretroviral regimen (0.05% total hip and 0.15% lumbar spine) in a dual-energy X-ray absorptiometry* [(b) (4)] *substudy.*

DBRUP recommendations
We agree with the Applicant that the bone sub-study findings are sufficiently robust and potentially relevant to clinicians as to warrant inclusion in labeling section 6.1, consistent with the labeling for TDF and TAF products.

Regarding the Applicant's proposed labeling, we recommend avoiding an implication of clinical significance of the BMD data. Deletion of the term [(b) (4)] [(b) (4)]

Regarding treatment-naïve HIV patients experiencing initial BMD declines associated with treatment, labeling for TDF and TAF products includes statements such as "the long-term clinical significance of these BMD changes is not known" (Genvoya), and "the effects….on long-term bone health and future fracture risk are unknown" (Viread). A similar statement might be considered for inclusion in the Juluca labeling.

In addition to presenting changes in mean BMD, individual response data may be relevant. Thus, labeling for TDF or TAF products has generally presented the percent of patients with treatment-associated BMD declines from baseline >5% (lumbar spine) or >7% (femoral neck), which are thresholds that DBRUP considers to represent *potential* clinical significance. In the DTG+RPV studies, no patients had a BMD decline >7% at any skeletal site. For consistency with other products' labeling, we would consider adding to the section 6.1 BMD language such as the following:

> *BMD declines of 5% or greater at the lumbar spine were experienced by 2% of Juluca subjects and 5% of subjects who continued their TDF-based regimen.*

Although no TDF or TAF studies have been powered to evaluate fractures, data on clinical fractures has generally been included in labeling and may be relevant. For consistency with other products, we would consider adding to section 6.1 language such as the following, which is similar to Genvoya labeling:

> *Fractures (excluding fingers and toes) were reported in 3 (0.6%) subjects who switched to dolutegravir plus rilpivirine and 9 (1.8%) subjects who continued their* (b) (4) *regimen through 48 weeks.*

It should also be noted that, as recommended by the International Society for Clinical Densitometry and other groups, the preferred nomenclature is "DXA", not "DEXA".[10]

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