22 March 2018
EMA/243517/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Juluca

International non-proprietary name: dolutegravir / rilpivirine

Procedure No. EMEA/H/C/004427/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

3TC	Lamivudine, EPIVIR
AAG	α1-acid glycoprotein
ABC	Abacavir
AE	Adverse event
ALAG	Absorption lag time
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
ASMF	Active substance master file
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC	Area under the concentration-time curve
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AZT	Zidovudine
BA	Bioavailability
BCS	Biopharmaceutics classification system
BE	Bioequivalence
c/mL	copies/milliliter
C_{0avg}	Average pre-dose concentration
C_{0h}	Observed plasma concentration prior to the beginning of a dosing
C_{24h}	Plasma concentration after 24 hours
CAR	Current antiretroviral regimen
cART	Combination antiretroviral therapy
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CL	Systemic clearance of parent drug
CL/F	Apparent clearance following oral dosing
CL/F/kg	Apparent oral clearance adjusted for body weight
C_{max}	Maximum concentration
CMH	Cochran-Mantel Haenszel
C_{min}	Minimum observed concentration
CPP	Certificate of Pharmaceutical Product
CPP	Critical process parameter
CQA	Critical Quality Attribute
Cr_{CL}	Creatinine clearance
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
$C_{ss,avg}$	Average steady-state plasma concentration, calculated by AUC24h/τ at
Ct	Last observed quantifiable concentration
CV	Coefficient of variance
CVW	Confirmed Virologic Withdrawal
CYP	Cytochrome P450
C_{τ}	Pre-dose (trough) concentration at the end of the dosing interval
DCV	Daclatasvir
ddI	Didanosine

DDI	Drug-drug interaction
DoE	Design of experiments
DRV	Darunavir
DSC	Differential scanning calorimetry
DTG	Dolutegravir, TIVICAY
DTG + RPV	Dolutegravir + Rilpivirine
DTG/RPV	DTG/RPV 50 mg/25 mg FDC
DVS	Dynamic vapour sorption
EC	European Commission
EC_{90}	Concentration at which 90% of the maximal effect is achieved
ECG	Electrocardiogram
EE	Ethinyl estradiol
EFV	Efavirenz
ERPF	Effective renal plasma flow
ESRD	End-stage renal dysfunction
ETR	Etravirine
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FI	Fluctuation index
FMEA	Failure mode effects analysis
FPV	Fosamprenavir
FTC	Emtricitabine
GC	Gas chromatography
GFR	Glomerular filtration rate
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
h or hr	Hour(s)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HSA	Human serum albumin
IB	Investigator's Brochure
IC_{50}	Concentration at which 50% inhibition was observed
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INI /INSTI	Integrase strand transfer inhibitor
IP	Investigational Product
IPC	In-process control
IPC-AES	Inductively coupled plasma atomic emission spectroscopy
IR	Immediate release
IR	Infrared
Ito	cardiac transient outward potassium channel
ITT	Intent-to-treat
ITT-E	Intent-to-treat exposed

Ka	First-order rate of absorption
KF	Karl Fischer titration
KTZ	Ketoconazole
LC-MS-MS	Liquid chromatography tandem mass spectroscopy
LDL	Low-density lipoprotein
LDPE	Low density polyethylene
LOCF	Last observation carried forward
LOD	Loss on drying
LPV/RTV	Lopinavir/ritonavir
LS	Least square
MAH	Marketing authorisation holder
MATE	Multidrug and toxin extrusion transporter
N(t)RTI	Nucleotide HIV-1 reverse transcriptase inhibitor
NA	Not applicable
NDA	New Drug Application
NF	National formulary
NGMN	Norelgestromin/norgestimate
NMR	Nuclear magnetic resonance
NNRTI	Non-nucleoside HIV-1 reverse transcriptase inhibitor
NQ	Non-quantifiable (<4 ng/mL)
NRTI	Nucleoside HIV-1 reverse transcriptase inhibitor
NVP	Nevirapine
OBT	Optimized background therapy
OC	Oral contraceptive
OCT2	Organic cation transporter 2
PA IC90	Protein-adjusted concentration required for 90% viral inhibition
PAH	Para-aminohippurate
PD	Pharmacodynamic
PDVF	Protocol-defined virologic failures
P-gp	P-glycoprotein
PGx	Pharmacogenetics
Ph. Eur.	European Pharmacopoeia
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per protocol
PP	Polypropylene
PP	Process parameter
QbD	Quality by design
QC	Quality control
QTc	Corrected QT interval
QTc (B or F)	QT interval corrected for heart rate by Bazett's or Fridericia's formula
QTPP	Quality target product profile
RAL	Raltegravir
RAM	Resistance-associated mutation
RAP	Reporting and Analysis Plan
RBT	Rifabutin
RH	Relative humidity
RIF	Rifampin
rpm	Revolutions per minute

RPV	Rilpivirine, EDURANT
RT-PCR	Reverse transcriptase polymerase chain reaction
RTV	Ritonavir
SD	Standard deviation
SE	Single entity
SmPC	Summary of product characteristics
SPV	Simeprevir
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
t	Time of last observed quantifiable concentration
$t_{½}$	Terminal phase half-life
TAMC	Total aerobic microbial count
TDF	Tenofovir disoproxil fumarate
TGA	Thermogravimetric analysis
t_{lag}	Lag time before observation of drug concentrations in sampled matrix
t_{last}	Time of last quantifiable concentration
TLOVR	Time to loss of virologic response
t_{max}	Time of occurrence of Cmax
TMC278	Tibotec Medicinal Compound 278 (rilpivirine)
TPV	Tipranavir
TTC	Threshold of toxicological concern
TVR	Telaprevir
TYMC	Total combined yeasts/moulds count
UDP	Uridine diphosphate
UGT1A1	Uridine diphosphate glucuronosyltransferase isozyme 1A1
USP	United States Pharmacopoeia
UV	Ultraviolet
V/F or Vd/F	Apparent volume of distribution after extravascular (e.g., oral)
WT	Wild type
VF	Virologic failure
XRD	X-ray diffraction
XRPD	X-ray powder diffraction
τ	Dosing interval
λz	Terminal phase rate constant

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ViiV Healthcare UK Limited submitted on 23 May 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Juluca, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 April 2016.

The applicant applied for the following indication "Juluca is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) without known or suspected resistance to either antiretroviral component".

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0028/2017 on the agreement of a paediatric investigation plan (PIP) and the granting of a product-specific waiver.

At the time of submission of the application, the PIP P/0028/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25 September 2014. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: Johann Lodewijk Hillege

The application was received by the EMA on	23 May 2017
The procedure started on	15 June 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	1 September 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	1 September 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	21 September 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 October 2017
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product: • A GCP inspection at two clinical investigator's sites in UK and Taiwan and the Sponsor site Viiv Healthcare (UK) between October and November 2017. The outcome of the inspection carried out was issued on 08 January 2018.	11 January 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 November 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	2 January 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 January 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 January 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	8 March 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Juluca on	22 March 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant seeks the following therapeutic indication for Juluca:

”Treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-RNA < 50 copies/ml) without known or suspected resistance to either antiretroviral component”

2.1.2. Aetiology and pathogenesis

Since the beginning of the epidemic, more than 70 million people have been infected with HIV, of which about 35 million people have died. Globally, 36.7 million [30.8–42.9 million] people were living with HIV at the end of 2016. An estimated 0.8% [0.7-0.9%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 25 adults (4.2%) living with HIV and accounting for nearly two-thirds of the people living with HIV worldwide (WHO Global Health Observatory (GHO) data).

2.1.3. Biologic features

HIV-1 infection results in chronic activation of the immune system and a subsequent gradual loss of CD4+ T cells eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the level of HIV-1 RNA in the blood (i.e. viral load). The aim of treatment of HIV-1 infection is therefore to suppress, and subsequently maintain, the HIV-1 viral load to levels that are at least below the limit of detection of most commonly used assays (50 copies/ml of blood).

2.1.4. Clinical presentation, diagnosis

Acute HIV-1 infection is often missed, as it usually presents with nonspecific signs and symptoms (including fever, rash, or diarrhoea), or goes without clinical symptoms. If symptoms are present, these generally emerge approximately 2 weeks following HIV infection. Among those presenting with symptoms, the number of symptoms correlates with higher pre-seroconversion peak plasma viral load.

Diagnosis therefore most often occurs during chronic infection. Recent estimates suggest that even in high income settings; about 25-35% of people living with HIV starting ART have a CD4 cell count of less than 200 cells/mm3. In some settings, up to half of people present to care with advanced HIV disease – defined by WHO as having a CD4 cell count <200 cells/mm3 or a WHO clinical stage 3 or 4 disease. Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia.

Diagnostic tests for HIV-1 infection include assays for HIV-1 RNA, p24 antigen, and HIV-1 and HIV-2 antibodies.

2.1.5. Management

According to EU HIV treatment guidelines, antiretroviral therapy (ART) is recommended in all patients with HIV infection, irrespective of CD4 cell counts. For ART-naïve HIV-infected patients, treatment guidelines recommend that initial therapy consists of 2 N[t]RTIs and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted PI, or an integrase strand-transfer inhibitor (INSTI).

The main goal of ART is to suppress viral replication to below detectable limits (<50 c/ml), increase CD4+ cell counts, and prevent transmission. It is a life-long treatment, as the viral load will rebound as soon as an individual stops taking effective antiretroviral therapy.

Current treatment options are generally considered to be potent, with an overall acceptable toxicity profile. Mutations in the viral genome can, however, occur when the virus replicates, which can make the virus resistant to antiretroviral drugs or classes of drugs. Therefore, there is a continued need for development of new antiretroviral treatment options.

About the product

DTG/RPV FDC is a 2-drug, NRTI-sparing regimen, differing from the current standard of care, which typically includes 2 NRTIs plus a third agent from the PI, NNRTI, or INSTI class. The proposed new 2-drug regimen of RPV and DTG targets HIV replication at the early and late stage of the virus life cycle, respectively.

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Dolutegravir, in combination with abacavir (ABC) and lamivudine (3TC) or in combination with emtricitabine (FTC) and tenfovir (either as TDF or TAF), is currently listed as one of the recommended initial “2 NRTIs+INSTI” regimens for ART-naïve adults (EACS guideline 2017).

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT).

Rilpivirine, in combination with FTC+TDF/TAF is one of the recommended initial “2 NRTIs+NNRTI” regimens for ART-naïve adults (EACS guideline 2017).

Juluca (DTG+RPV) is the first dual antiretroviral therapy, indicated specifically as maintenance therapy for HIV-1 infected patients who are already virologically suppressed. The proposed benefits of dual vs standard triple therapy would be to reduce (long-term) side-effects, spare drug options for the future, reduce costs and improve adherence. However, one of the concerns with dual therapy is the risk of virologic failure and subsequent selection of resistance mutations compared with standard triple therapy.

Of note, several independent studies investigating Dolutegravir as monotherapy have been performed or were ongoing until recently. Although these studies initially seemed to be successful, the development has now been halted due to the development of integrase resistance mutations in the patients that failed DTG monotherapy (see for more information the review by Jones et al., CROI 2017: Advances in Antiretroviral Therapy, Top Antivir Med. 2017 May/Jun;25(2):51-67). It was concluded that the genetic barrier of dolutegravir monotherapy is insufficient to allow for maintenance monotherapy, and all patients receiving DTG monotherapy were advised to at least add lamivudine to their current ART or to return to triple ART.

2.2. Quality aspects

2.2.1. Introduction

The finished product is a fixed-dose combination product presented as film-coated tablets containing 52.6 mg dolutegravir sodium (equivalent to 50 mg dolutegravir free acid) and 27.5 mg rilpivirine hydrochloride (equivalent to 25 mg rilpivirine free base) as active substances. The two active substances are well-known anti-retroviral agents used for the treatment of HIV and are marketed in the EU in the single component products Tivicay and Edurant respectively.

Other ingredients are:

Tablet core: mannitol (E421), magnesium stearate, microcrystalline cellulose, povidone K29/32, sodium starch glycollate, sodium stearyl fumarate, lactose monohydrate, croscarmellose sodium, povidone K30, polysorbate 20 and silicified microcrystalline cellulose.

Tablet coating: partially hydrolysed polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172) and iron oxide red (E172).

The product is available in white HDPE bottles containing desiccant, closed with polypropylene child-resistant closures, with polyethylene faced induction heat seal liners as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

Rilpivirine hydrochloride

The information on rilpivirine hydrochloride is provided in an ASMF, which is also used in the Edurant dossier.

General information

The chemical name of rilpivirine hydrochloride is 4-[[4-[[4-[(*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride corresponding to the molecular formula $C_{22}H_{18}N_6$.HCl. It has a relative molecular mass of 402.88 g/mol and the following structure (Figure 1):

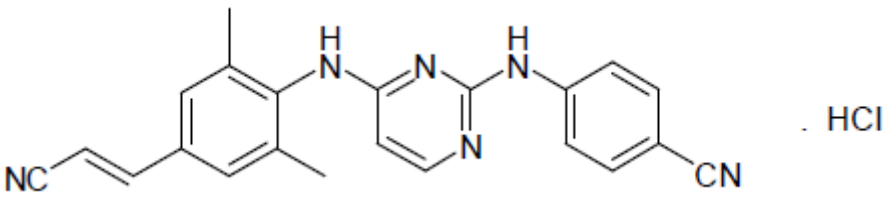


Figure 1 rilpivirine hydrochloride structure

Rilpivirine hydrochloride is a white to almost white powder, practically insoluble in aqueous media across the physiological pH range. It is milled in order to reduce particle size, increase overall surface

area and thus increase dissolution rate *in vivo*. The active substance is achiral and is not considered hygroscopic.

The chemical structure of rilpivirine hydrochloride was elucidated by a combination of elemental analysis, UV absorption spectroscopy, IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Three polymorphic forms (A, B and C) and a hydrated form (D) have been identified and characterised by a combination of IR spectroscopy, XRD, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and dynamic vapour sorption (DVS). Form A was found, during slurry experiments, to be the most thermodynamically stable form, is the chosen commercial polymorphic form, and is routinely produced by the manufacturing process.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. There are two manufacturers of the active substance listed in the ASMF and both use the same convergent synthetic process which starts with 2 well-defined starting materials with acceptable specifications and consists of 3 synthetic steps. A subsequent salt formation step ensures that the correct polymorphic form of the hydrochloride salt is formed, and the subsequent milling step reduces the particle size to the required levels.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double, antistatic, low-density polyethylene (LDPE) bags. Both the inner and the outer bag are appropriately closed and placed in a fibreboard container. The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The rilpivirine hydrochloride specification ncludes tests for appearance, identity (IR, chloride), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), particle size distribution (laser diffraction), heavy metals (USP), and residue on ignition (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Genotoxic impurities are controlled to a level well below the TTC.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 10 production scale batches of the active substance, as well as multiple development batches, are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 11 production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 60 months under long term conditions (25 ºC /

60% RH), for up to 36 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, water content, polymorphism, assay, impurities, particle size distribution and microbiological quality. The analytical methods used were the same as for release, (other than polymorphism which is not a release test, but which is checked by XRD), and were stability indicating. No significant trends to any of the measured parameters were observed under any of the storage conditions, other than a slight increase in particle size at 40 °C.

Photostability testing following the ICH guideline Q1B was performed on 3 batches. A slight increase in impurity content and particle size was observed, which means that the active substance should be protected from light during storage.

Forced degradation studies were carried out in aqueous acid, base and peroxide. Degradation was observed under the oxidative and basic conditions. The studies demonstrated that the HPLC impurity method is stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 48 months when in the proposed container in order to protect from light.

Dolutegravir sodium

The information on dolutegravir sodium is provided in a module 3.S and is identical to the data included in the Tivicay dossier.

General information

The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9{[(2,4difluorophenyl)methyl] carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate corresponding to the molecular formula $C_{20}H_{18}F_2N_3NaO_5$. It has a relative molecular mass of 441.36 g/mol and the following structure:

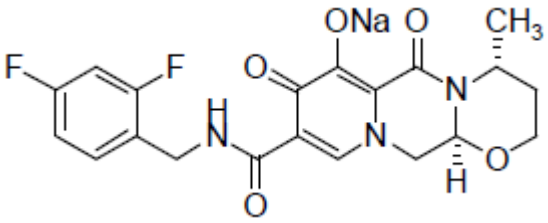


Figure 2. Dolutegravir sodium structure

Dolutegravir sodium is a white to light yellow non-hygroscopic crystalline powder. It is slightly soluble in water, but becomes less soluble as pH decreases to 1, at which point, it is practically insoluble. It is micronised in order to reduce particle size, increase overall surface area and thus increase dissolution rate *in vivo*. Dolutegravir has 2 chiral centres, one of which originates in a starting material and the other of which is formed selectively during the process. Stereoisomers are limited in the active substance specification.

The chemical structure of dolutegravir sodium was elucidated by a combination of elemental analysis, IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. A single thermodynamically

stable polymorphic form was identified and characterised by a variety of techniques including x-ray powder diffraction (XRPD) and DSC.

Manufacture, characterisation and process controls

Two separate synthetic routes are used to manufacture dolutegravir sodium. Route B is a convergent process from three well defined starting materials with acceptable specifications. Seven manufacturers are responsible for various stages of the synthetic process including the micronisations step. The correct polymorphic form of the sodium salt is ensured by the crystallisation conditions, and the subsequent milling step reduces the particle size to the required levels.

Route C is also a convergent process from three well defined starting materials with acceptable specifications, 2 of which are the same as used in route B. Two manufacturers are used, one for the synthetic chemistry and one for the micronisations step. Both are also responsible for equivalent parts of the route B process.

Adequate in-process controls are applied during both synthetic processes. The specifications and control methods for intermediate products, starting materials and reagents have been presented and have been justified based on impurity spike and purge data. The specifications for the only common intermediate, dolutegravir free acid, are different depending on the route as the impurities generated and solvents and reagents used are different. However, both routes have been shown to produce dolutegravir sodium of acceptable and comparable quality.

The correct polymorphic form of the sodium salt is ensured by the crystallisation conditions, and the subsequent milling step reduces the particle size to the required levels. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Both manufacturing processes were developed using QbD principles, including risk assessment, prior knowledge, and multivariate experiments (e.g. DoE studies), to define which process parameters (PPs) impact the critical quality attributes (CQAs) of dolutegravir sodium. Critical process parameters (CPPs) were defined, as appropriate, for different steps of the manufacturing processes. Design spaces are claimed for several steps of the manufacturing process. For each design space, CPPs are listed, along with ranges based on the results of DoEs. The applicant demonstrated that each CPP included in a design space is scale-independent during scale up from lab to pilot scale, and by studying reaction kinetics. Thus, no commercial scale design space verification is considered necessary.

The active substance is packaged in LDPE bags sealed with ties and stored in metal, fibre or plastic containers. The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The dolutegravir sodium specification includes tests for appearance, identity (IR), sodium content (ICP-AES), assay (HPLC), impurities (HPLC), enantiomer (chiral HPLC), residual solvents (GC), water content (KF), polymorphic form (XRPD), and particle size distribution (laser diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies. The impurities present differ depending on which route of synthesis is used. However, the limits set for each individual impurity are considered acceptable and dolutegravir sodium made by either route is considered equivalent and of adequate quality. A risk assessment for potentially genotoxic impurities was carried out for both manufacturing routes in line with ICH M7. The fate of these impurities is well understood based on spiking studies. They are controlled by limits in the

specifications of raw materials, intermediates or by control of the manufacturing process, and are therefore not included in the proposed active substance specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 3 production scale batches of dolutegravir sodium manufactured *via* route B from each of the listed manufacturing sites, as well as 6 production scale batches manufactured *via* route C, are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 production scale batches of dolutegravir sodium manufactured *via* route B from each of the proposed manufacturers stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH), for up to 60 months under intermediate conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. In addition, data was provided on 4 production scale batches of dolutegravir sodium manufactured *via* route C stored under intermediate conditions for up to 12 months and 3 batches stored under accelerated conditions for up to 6 months. The following parameters were tested: appearance, identity, assay, water content, solid state form, impurities (including stereoisomer content) and particle size distribution. The analytical methods used were the same as for release and were stability indicating as indicated by forced degradation studies. No significant trends to any of the measured parameters were observed under any of the storage conditions and all were within specification.

For the stressed stability studies, data was presented following short-term storage under stressed conditions for one batch manufactured via route B. Samples were stored exposed to high temperature, high humidity, or light according to ICH guideline Q1B. Assay decreased slightly in samples exposed to light, whereas impurity content increased slightly in samples stored at high temperature.

Forced degradation studies were also performed to identify potential degradation products that might be formed in active substance and finished product, to elucidate the mechanisms of formation and to demonstrate the stability indicating nature of the analytical methods. Degradation products were formed under basic, acidic, and photo-oxidative conditions. However, none of the impurities identified have been observed at significant levels under long-term or accelerated storage conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. Although limited data is available for some manufacturing sites, the combined evidence and the similarity of results at equivalent time-points indicates that there are unlikely to be significant differences in the stability profile of dolutegravir sodium manufactured at different sites or by different routes. The stability results justify the proposed retest period of 60 months protected from light.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Juluca is a fixed dose combination, immediate release film-coated tablet containing dolutegravir sodium and rilpivirine hydrochloride as active substances. The finished product is a bilayer tablet which allows each active substance to be formulated separately and maintain its requisite physicochemical

properties during manufacture and storage. The tablets are pink, bioconvex, and debossed with SV J3T on one face.

Pharmaceutical development of the finished product contains QbD elements and applies the quality risk management approach as discussed in ICH Q8-10. The development also draws on prior knowledge of two marketed single entity products, Tivicay (which contains dolutegravir sodium) and Edurant (which contains rilpivirine hydrochloride). The same container closure system, an HDPE bottle with PP child-resistant closure, as used for the single entity products is used with addition of a silica gel desiccant.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The quality target product profile (QTPP) was defined as a film-coated immediate release tablet containing the correct amount of each active substance, of a suitable size such that patients can swallow it, for daily dosing. The product should be of suitable quality and meet compendial requirements. Each active substance should be bioequivalent to the corresponding single entity tablet. The stability of the product should be suitable for worldwide marketing and the container closure system should provide adequate protection and be child-resistant. The critical quality attributes identified were description, identity, assay, content uniformity, impurities and dissolution.

Dolutegravir sodium is practically insoluble in aqueous media across the physiological pH range. It is slightly soluble in water and above pH 8. The polymorphic form and particle size distribution are controlled in its specification following micronisations. Rilpivirine hydrochloride is also practically insoluble from pH 1 to 13. The polymorphic form and particle size distribution are controlled in its specification following milling. Both active substances are non-hygroscopic BCS class II molecules. Since one active substance has an acidic counter ion whereas the other bears a basic counter ion, there is potential for disproportionation to the respective free bases during manufacture and storage which could adversely impact dissolution characteristics and thus, bioavailability. Therefore, a bilayer formulation was pursued, in order to segregate the active substances and prevent disproportionation. Compatibility with the excipients was previously demonstrated in the single entity products.

During development, five prototype bilayer formulations were evaluated against Edurant and Tivicay in relative bioavailability studies. All formulations were found to be bioequivalent. One was selected for commercialisation and for clinical studies, and a pivotal bioequivalence study was conducted to conclusively demonstrate bioequivalence with the co-administered single entity products.

Development of the dissolution method took into account prior knowledge from the single entity product methods. A method able to monitor dissolution of both active substances was identified is considered to be sufficiently discriminatory.

The risk management process was initiated following selection of the finished product manufacturing process. This began with a detailed overview of the manufacturing process and identification of risks (failure modes) and process variables that could impact quality by using risk identification tools and prior knowledge. An overall risk priority number was then assigned using failure mode effects analysis (FMEA) and used to guide univariate and multi-factorial DoE studies. Risk assessments were updated throughout the development.

Process stretching studies were carried out on commercial scale in multi-variate fashion in order to assess potential CPPs and identify design spaces. Although not all combinations of input variables were studied, the most extreme conditions, based on risk assessment and prior knowledge, were identified and investigated.

A series of DoE studies were undertaken in order to optimise different steps of the process. This allowed confirmation of CPPs for individual unit operations and definition of design spaces. The design spaces were developed through experimentation at production scale and hence no additional verification was required.

The finished product CQAs are controlled through the quality and quantity of input materials, the manufacturing process and its process parameters and/or the finished product specification. The control strategy and design spaces, along with the applied ranges for CPPs are considered acceptable.

The primary packaging was selected in accordance with the QTPP and is an HDPE bottle, with PP child resistant closure. Each bottle contains a silica gel desiccant canister to prevent formation of rilpivirine free base. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 3 main parts and is carried out by a single manufacturer: production of dolutegravir compression blend; production of rilpivirine compression blend; combination of the two into the final film-coated tablet. The overall process is considered to be a standard manufacturing process.

The production of dolutegravir compression blend consists of 6 main steps: blending of intra-granular excipients; high shear wet granulation; wet milling; drying; dry milling; blending with extra-granular excipients. The compression blend is used within 30 days so intermediate holding times are defined.

The production of rilpivirine compression blend consists of 6 main steps: blending of intra-granular excipients; fluid bed granulation; drying; dry milling; blending with extra-granular excipients; lubrication. Stability data have been provided to justify a holding time for the intermediate of up to 6 months at 15-25 ^{o}C at < 60% RH, stored in double PE bags with a desiccant between the layers, all within a suitable secondary container.

Production of the final tablets consists of 4 main steps: compression of the dolutegravir layer; compression of the rilpivirine layer; film-coating; packing. Stability data has been provided to justify a bulk holding time for the film-coated tablets of up to 6 months at ≤25 ^{o}C when sealed within double LDPE bags with desiccant between the layers, all stored within a rigid plastic container. The primary bulk packaging material complies with regulation 10/2011 and Ph. Eur. 3.1.3.

A process validation scheme for a minimum of 3 production scale batches was provided. This is acceptable since the manufacturing process is considered standard. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Design spaces have been proposed for the following steps of the manufacturing process of the medicinal product: dolutegravir granulation and drying; dolutegravir granule blending; rilpivirine granulation; compression; film-coating. The design spaces were all developed at commercial scale so no further verification is needed. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprise tests for description, identity (UV, HPLC), dolutegravir and rilpivirine assay (HPLC), uniformity of dosage units (both active substances, HPLC), dissolution (both active substances, UV or HPLC), and microbiological quality (Ph. Eur.).

The absence of a test for degradation products has been justified by provision of batch analysis from 10 production scale batches of finished product, as well as 3 batches manufactured with a slightly shallower cup depth during compression. A test for degradation products is included in the shelf-life specification. A risk assessment for elemental impurities was carried out in line with ICH Q3D, which concluded that no tests for elemental impurities were required. Based on the information and data supplied, this is considered justified. Water content is controlled as an IPC and so is not needed in the release specification. A desiccant is included in the container closure system and test for water content by KF is included in the shelf-life specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing (at shelf-life) has been presented.

Batch analysis results were provided for 3 pilot scale and 6 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 approximately production scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are representative of those proposed for marketing, differing only slightly in shape, and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, degradation products, dissolution, microbiological quality, water activity, water content and rilpivirine free base content. The analytical procedures used are the same as used for release and were demonstrated to be stability indicating during forced degradation studies. Additional analytical methods not included in the release specifications were suitably validated.

No significant changes to any of the measured parameters were observed, other than for a slight increase in rilpivirine free base content, more so under accelerated conditions, but still below the limit of detection.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed. The same batch was exposed to other stressed conditions including freeze/thaw and 50 °C at ambient humidity. Again, no changes were observed other than a slight increase in rilpivirine free base at the higher temperature.

An in-use stability study was carried out by simulating the daily dosing regimen over 30 days. Bottles were opened daily, leaving the desiccant in place, and a tablet was removed and tested for appearance, assay, related substances, dissolution, water content and rilpivirine free base content. No significant changes were observed for any of the tested parameters other than a slight increase in rilpivirine free base. The applicant has committed to perform another study on a second batch towards the end of its shelf-life.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose monohydrate is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The development program was largely based on prior knowledge of the two standalone single component products. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. Design spaces have been proposed for five steps in the manufacturing process of the finished product and have been adequately verified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should perform another in-use stability study on a second batch of finished product towards the end of its shelf-life.

2.3. Non-clinical aspects

2.3.1. Introduction

Dolutegravir (DTG) is a potent, selective and novel integrase inhibitor (INI) and rilpivirine (RPV) is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) against human immunodeficiency virus type 1 (HIV-1).

The structure of DTG and RPV is shown in Figure 3 and Figure 4.

Figure 3. Structure of DTG

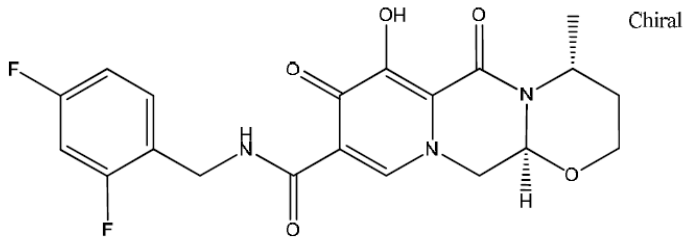
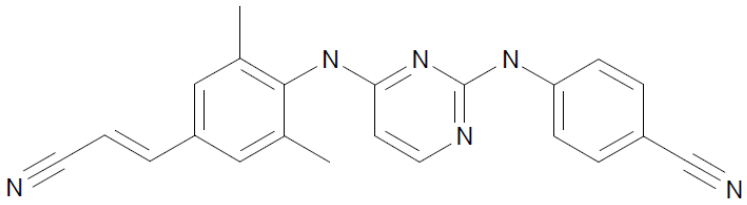


Figure 4. Structure of RPV



2.3.2. Pharmacology

Primary pharmacodynamics

Dolutegravir is a second generation integrase inhibitor. The IC50 of dolutegravir against the purified enzyme HIV-1 integrase ranged from 2.7 nM to 12.6 nM. EC50 in cell-based assays ranged from 0.51 to 2.1 nM.

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor. In cell-based assays, EC50 against HIV-1 was 0.07 – 1.01 nM against group M and 2.88 – 8.45 nM against group O.

Secondary pharmacodynamics

For dolutegravir, inhibition was observed only at the melanocortin receptor at concentrations > 100-fold above the unbound clinical C_{max}.

Rilpivirine has no antiviral activity against various human viruses other than HIV and no potential off-target activity, but showed low cytotoxic potential in various human cell lines.

Safety pharmacology

No significant effects of dolutegravir were observed in safety pharmacology studies with single oral doses of dolutegravir up to 500 (rat) and 1000 (monkey) mg/kg on major organ function in brain, respiratory and cardiovascular system.

Results of the in vitro hERG test revealed that rilpivirine has the potential to prolong the QT-interval. This QT prolonging potential and its delayed onset was confirmed by the results of additional in vitro cardiovascular safety studies. The respiratory and central nervous system were not affected by rilpivirine at therapeutic concentrations.

Pharmacodynamic drug interactions

Dolutegravir and rilpivirine were additive or synergistic in in vitro combination studies with common anti-HIV agents. The combination of dolutegravir and rilpivirine was shown to be additive in an in vitro study in CEM-SS cells with the HIV-1 strain IIIB.

2.3.3. Pharmacokinetics

Absorption

Bioavailability of dolutegravir in rat and monkey ranged from 25 to 34% and increased to levels of 76 to 87% after fasting. In non-fasted beagle dogs, bioavailability was 39%.

After oral administration of rilpivirine base, the absolute oral bioavailability of rilpivirine was 32%, 54%, 31% and 24% to rats, rabbits, dogs and monkeys, respectively.

Distribution

Protein binding of dolutegravir was > 99% in rat, monkey and human and 95% in dog. The highest levels of drug-related material were found at 6 h after dosing in liver, adrenal medulla, myocardium, pigmented skin, renal cortex and renal medulla, lung and lymph nodes. Dolutegravir crossed the placenta of pregnant rats and was excreted into rat milk.

Protein binding of rilpivirine was > 99% in human, monkey, dog, rat, rabbit and mouse. The highest levels of drug-related material were found at 4 h after dosing in the uveal tract, liver and adrenal gland. Rilpivirine-related material crosses the blood-brain barrier and was found to be binding to melanin. Rilpivirine-related material crossed the placenta barrier in rats. Concentrations of rilpivirine were quantifiable in blood samples from rat pups, demonstrating that pups were exposed to rilpivirine via the milk.

Metabolism

In human hepatocytes, the notable route of metabolism for [14C]-dolutegravir was glucuronidation. Metabolite profiles of rat, monkey and human were qualitatively similar. Dolutegravir was the major radiolabelled component in plasma of mice, rats and monkeys.

Rilpivirine is metabolised via Phase I and Phase II reactions and a large number of metabolites were detected in all species. The most important pathway is oxidation and hydroxylation and to a minor extent conjugation with glutathione and glucuronide. Overall, identified metabolites that were detected in human matrices were also detected in at least one animal species except for one, glucuronidated metabolite which is expected to be inactive and non-toxic.

Excretion

Regarding dolutegravir, drug related material was excreted for the major part via the faeces (91 – 94% in rats and mice and 67 – 78% in monkeys). Urinary excretion was less than 2% of administered dose in mouse, less than 4% in rat and 4 - 6% in monkey. In bile duct cannulated animals, biliary excretion accounted for approximately 2.5% of dose in mouse, 7% of the dose in rat and 12% of dose in monkey.

The predominant route of elimination of rilpivirine drug-related material in all species following oral administration was via faeces (>85%), with a small contribution eliminated in urine (<6.2%). The majority of the eliminated radioactivity is unchanged rilpivirine (25-47% of the dose). In rats, biliary excretion is limited (18-25%).

Pharmacokinetic drug interactions

Three combination studies were submitted in which dogs were treated orally with either individual tablets containing dolutegravir or rilpivirine co-dosed or combination tablets containing dolutegravir and rilpivirine. The dog studies show no significant differences in exposure between treatments with dolutegravir and rilpivirine as separate tablets and as combination tablets. A clear increase in exposure was observed for the fed state compared to the fasted state for both dolutegravir and rilpivirine. Gastric emptying seemed somewhat prolonged for the combination tablets compared to the co-dosed tablets in one study, but not in the other study where there was less variability in stomach emptying and gastrointestinal transit.

2.3.4. Toxicology

Single dose toxicity

No single dose studies were performed with dolutegravir. Investigations for acute effects were incorporated in oral repeat dose toxicity studies. Dolutegravir was not tolerated in monkeys at doses ≥ 300 mg/kg (severe gastrointestinal intolerance) and in dogs at doses ≥ 150 mg/kg (vomiting).

In single dose oral studies with rilpivirine, no relevant effects were observed in mice up to 1600 mg/kg and rats up to 800 mg/kg. In dogs, 80 mg/kg was the maximum feasible dose (vomiting and soft stool).

Repeat-dose toxicity

Dolutegravir induced slight increases in bilirubin and liver transaminases and mucous neck cells in stomach in mice. In rats, gastric mucosal changes and lesions were observed which were attributed to local irritating properties. In monkeys, liver toxicity, atrophy and haemorrhage of mucosal epithelium in the stomach, atrophy of cecum, colon and rectum as well as decreases in red blood cells and reticulocytes and lymphocytes were observed.

Rilpivirine induced liver enzyme induction in rodents and evidence of cholestasis in dogs. Effects on the kidney were noted in mice (pale and enlarged/swollen kidneys, (necrotic) nephropathy), dogs (acute interstitial nephritis, corticomedullar mineralization) and possibly also rats (reduced weight, changes in urine parameters). Inhibition of adrenal steroid synthesis was observed in all species and ascribed to inhibition of cytochrome CYP21 and CYP17. This may be the cause of effects on the reproductive organs such as early sexual maturation, activation of ovaries, atrophic tubuli and hypertrophy of Leydig cells in testes in dogs, and reduced weight/size of ovaries/uterus, absence of ovulation, uterus atrophy and hyperkeratosis/mucification of vaginal epithelium in mice. In addition, in mice, rats and dogs, small reduction in red blood cell parameters were noted and in rats increases in coagulation parameters.

Toxicity studies with the combination of dolutegravir and rilpivirine have not been performed. This is in accordance with a scientific advice (EMA/CHMP/SAWP/544739/2014, 25 September 2014) in which it

was concluded that non-clinical studies with the combination are not necessary and that monitoring for adverse liver effects should be implemented in clinical studies.

Genotoxicity and carcinogenicity

Dolutegravir and rilpivirine tested negative in standard packages of genotoxicity studies.

No clinically relevant carcinogenicity was observed in long-term carcinogenicity studies with dolutegravir in mice and rats. In 2-year carcinogenicity studies with rilpivirine in mice and rats, increased tumours were found in liver and/or thyroid, which were considered associated with liver enzyme induction and not relevant for humans.

Reproductive and developmental toxicity

No effects on fertility and early embryonic development were observed for dolutegravir and rilpivirine in rats.

In embryofoetal development studies with dolutegravir and rilpivirine in rats and rabbits, no relevant embryotoxicity and teratogenicity were observed.

Dolutegravir caused no effect on pre- and postnatal development in rats except for a decrease in maternal and pup body weight at the highest dose. No marked effects were noted in the peri/post-natal development study with rilpivirine in the rat.

Juvenile rats treated with dolutegravir were more sensitive to adverse effects compared to adults, with deaths occurring at 75 mg/kg/day while in adult rats no deaths were seen up to 1000 mg/kg/day. No effects were observed in juvenile rats treated with rilpivirine. In studies in immature dogs and monkeys, rilpivirine had a similar toxicological profile as in adult animals.

Local tolerance and antigenicity

Dolutegravir had mild irritant effects on abraded skin and slight ocular irritating effects. Rilpivirine was not irritating to skin and a moderate eye irritant in the in vitro bovine corneal opacity-permeability eye irritation assay.

Dolutegravir and rilpivirine showed no potential for sensitization in the local lymph node assay in mice.

Immunotoxicity

Dolutegravir had no effect on T-cell dependent antibody formation in rats and on several immunological endpoints in juvenile rats.

No immunotoxic potential was found in rilpivirine-treated rats challenged with sheep red blood cells.

Impurities

No changes are reported for the fixed dose combination compared to the impurity profiles in Tivicay (dolutegravir) and Edurant (rilpivirine).

Phototoxicity

Dolutegravir was phototoxic when tested in the Neutral Red Uptake assay using Balb/c 3T3 fibroblasts but not phototoxic in an in vivo study in pigmented rats.

Rilpivirine was not phototoxic in the in vitro Balb/c mouse fibroblast assay.

2.3.5. Ecotoxicity / environmental risk assessment

Dolutegravir

Summary of main study results

Substance (INN / Invented Name): dolutegravir sodium					
CAS-number (if available): 1051375-16-6 (free acid)					
PBT screening		Result		Conclusion	
Bioaccumulation potential- log D_{ow}	OECD107	-2.28 at pH 5 -2.45 at pH 7 -3.21 at pH 9		Potential PBT: NO	
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**		**Conclusion**	
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.25 (default) 0.0117 (refined)	µg/l		> 0.01 threshold YES Refined PEC accepted for Phase II	
Other concerns (e.g. chemical class)				No	
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**		**Remarks**	
Adsorption-Desorption	OPPTS 835.1110	Kf: 5 773 l/kg Kf,oc: 14047 l/kg		Sludge only	
Ready Biodegradability Test	OECD 302C	0% CO2 at day 28; not inherently biodegradable			
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 1.5 – 2.5 d (20 °C) $DT_{50,\ sediment}$ ND $DT_{50,\ total\ system}$ >1000 d (20 °C) Mineralisation: 2.3 and 1.8% d 100 Non-extractable residues: 9.3% and 8.7% d 100 Shift into sediment: 88% and 82% (day 14)		Dolutegravir is very persistent in sediments.	
Phase II A effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/	OECD 201	NOEC	95.4	µg/l	*Pseudokirchnella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	239.0	µg/l	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	220.0	µg/l	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	24000.0	µg/l	
Phase II B studies					
Bioaccumulation	OECD 305	BCF	Not required	l/kg	%lipids:

Aerobic transformation in soil	OECD 307	DT50 $\%CO_2$ %NER	>1000 (20 °C) 2.2 5.8/8.3/22.9/ 4.2%	days	4 soils; application of spiked sludge. Dolutegravir is very persistent in soils
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	NOEC EC50 NOEC	>984.0 196.0 <95.0	mg/kg	Inhibition Promotion
Terrestrial Plants, Growth Test	OECD 208	NOEC	12.0	mg/kg dw	*Pisum sativum*
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	≥1000	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	29.0	mg/kg dw	
Sediment dwelling organism	OECD 219	NOEC	≥ 858	mg/kg dw	*Chironomus sp.*

Conclusions on studies for dolutegravir

Dolutegravir is not a PBT substance and is not expected to pose a risk to the environment.

Rilpivirine

Summary of main study results

Substance (INN / Invented Name): rilpivirine hydrochloride			
CAS-number (if available): 500287-72-9 (free base)			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD123	4.66	Potential PBT: YES
PBT assessment	Result relevant for conclusion		Conclusion
Bioaccumulation	BCF	170 – 184 (normalised to 5% lipid)	Not B
Persistence	DT50	$DT_{50\ sediment\ 20°C}$ 527-321 d $DT_{50\ sediment\ 12°C}$ 1125-1505 d	vP
Toxicity	NOEC or CMR	NOEC ≥ 0.20 µg/l	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.125 (default) 0.014 (refined)	µg/l	> 0.01 threshold YES Refined PEC accepted for Phase II
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 OECD 121	K_{oc} = 19372 – 23077 l/kg K_{oc} = 13800 l/kg (pH 9)	
Ready Biodegradability Test	OECD 301	Not determined	
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 1.3 – 1.2 d (20 °C) $DT_{50,\ sediment}$ = 527 - 705 d (20	$DT_{50sediment}$ calculated by rapporteur

		°C) $DT_{50,\ total\ system}$ = 307 - 321 d (20 °C) Mineralisation: 0.8 and 1.2% on d 100 Non-extractable residues: 12.7 and 14.4 % on d 100 49.3 % on d 148 Shift into sediment: 87% and 84% (day 14)	Rilpivirine is very persistent in sediments
Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 4.7 – 15.7 d Mineralisation: <0.1% NER: 96.7 on d 100 95.5% d 100 shift into sediment	

Phase II A effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/	OECD 201	NOEC	≥22.0	µg/l	*Scenedesmus subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥32.0	µg/l	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	≥20.0	µg/l	*Brachydanio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000000	µg/l	
Phase II B studies					
Bioaccumulation	OECD 305	BCF	184/170	l/kg	Normalised to 5% lipid
Aerobic transformation in soil	OECD 307	DT50 $\%CO_2$ %NER	100/71/79 15.1/31.5/20.4 15.1/13.1/14.7/12.5	days	3 soils; rilpivirine is very persistent in soils
Anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$ %NER	289 (20°C) 2.7-5 8.6	days	1 soil
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	EC50	>100	mg/kg	
Terrestrial Plants, Growth Test	OECD 208	NOEC	≥1000	mg/kg dw	*Pisum sativum*
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	≥1000	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	≥1000	mg/kg dw	
Sediment dwelling organism	OECD 219	NOEC	≥ 100	mg/kg dw	*Chironomus sp.*

Conclusions on studies for rilpivirine

Rilpivirine is not a PBT substance and is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Based on the nonclinical data provided on the individual agents, there appears to be no significant potential for adverse interactions between the two components. An extensive number of nonclinical toxicity studies have been conducted for each of the agents individually in support of the single components marketing authorisation applications. No significant toxicological finding was identified for either compound that would indicate a concern for dolutegravir and rilpivirine co-administration.

No new non-clinical studies were submitted except for an in vitro pharmacodynamics interaction study and three pharmacokinetic interaction studies in dogs.

Non-clinically, both dolutegravir and rilpivirine have some potential for liver toxicity. Toxicity studies with the combination of dolutegravir and rilpivirine have not been performed. This is in accordance with a scientific advice (EMA/CHMP/SAWP/544739/2014, 25 September 2014) in which it was concluded that non-clinical studies with the combination are not necessary and that monitoring for adverse liver effects should be implemented in clinical studies.

The ERA for RPV and DTG are considered complete and acceptable. For DTG, the study on adsorption/desorption has been performed on sludge only which is acceptable for use in Phase II Tier A. For the risk assessment of the sediment and soil compartment in Phase II Tier B, an adsorption/desorption study on 3 soils in accordance with OECD TG 106 with DTG should have been provided. However, under consideration of the very low risk quotient for sediment organisms and a resulting margin of safety of over 10 000, it is considered very unlikely that a Koc derived on soils will be increased by four orders of magnitude compared to the Koc for sludge. Hence, a study on adsorption/desorption on soils can be waived in this case.

DTG and RPV are not PBT substances. Both are not readily biodegradable in sewage treatment plants and have to be considered very persistent in water/sediment systems and soils.

Results from Phase II Tier A and Tier B studies do neither indicate any risk from RPV and DTG to the surface water, groundwater and sediment compartment nor to sewage treatment plants. RPV does not pose a risk to the soil compartment; data on terrestrial fate and effects for DTG are considered not necessary as the cut-off criteria are not fulfilled.

The evaluation of the bioaccumulation potential is considered not necessary for DTG due to its logDow of -2.28 to -3.21 at pH 5-9, however, has been performed for RPV due to its logKow of 4.66. It was shown that RPV is not bioaccumulative.

2.3.7. Conclusion on the non-clinical aspects

Non clinical safety data from the individual components in addition to the clinical data supports the safe use of the applied fixed dose combination of dolutegravir and rilpivirine.

Considering the above data, RPV and DTG are not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study	Study design	Population	Treatment details	Key conclusions
201636 (SWORD 1)	Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1 infected ART experienced subjects	DTG 50 mg + RPV 25 mg once daily with a meal CAR: 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	The primary analysis demonstrated that DTG + RPV is noninferior to CAR, with 95% of subjects in the DTG + RPV group and 96% of subjects in the CAR group achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm [adjusted treatment difference and 95% CI; -0.6%, -4.3% to 3.0%] for the ITT E Population.
201637 (SWORD 2)	Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1 infected ART experienced subjects	DTG 50 mg + RPV 25 mg once daily with a meal CAR: 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	The primary analysis demonstrated that DTG + RPV is noninferior to CAR, with 94% of subjects in both treatment groups achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA at Week 48 based on the (Snapshot) algorithm [adjusted treatment difference and 95% CI; 0.2%, -3.9% to 4.2%] for the ITT-E Population.
202094 (DEXA Sub-study)	Open-label, parallel-group study	HIV-1 infected ART experienced subjects	DTG 50 mg + RPV 25 mg once daily with a meal TFV-containing ART regimen CAR: 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	Switching to a once daily 2-drug regimen of DTG + RPV demonstrated numerical improvement in BMD for virologically suppressed HIV-1-infected adults when compared with continuing treatment with a TDF containing ART regimen.
201676 Pivotal bioequivalence study	Randomized, open-label, 2-period, single dose, crossover study	Healthy adult subjects	Reference Treatment = DTG 50 mg + RPV 25 mg once daily with a moderate fat meal Test Treatment = DTG/RPV FDC 50 mg/25 mg (Product Code AW) with a moderate fat meal	DTG/RPV FDC is bioequivalent to combined administration of the SEs. The 90% CI of the GLS mean PK parameter ratios was within 80 to 125% for all primary PK parameter endpoints (AUC(0-t), AUC(0-∞), and Cmax) for both DTG and RPV.
201674 relative bioavailability and food effect	2-part, single dose, open-label, randomized, crossover, relative oral bioavailability study in the fed and fasted states	Healthy adult subjects	Reference Treatment = DTG 50 mg + RPV 25 mg single dose 5 Test Formulations = DTG/RPV FDC 50 mg/25 mg (Product Codes AS, AM, AQ, AK, and AU) single dose	Part 1: The AUC(0-∞) and Cmax of DTG following administration of various FDC tablets in presence of high fat diet were comparable to those following the reference DTG single agent co-administered with RPV. The AUC(0-∞) and Cmax of RPV following administration of various FDC tablets in presence of high fat diet were comparable to or ranged from 8% lower to 10% higher (depending on the FDC tablet) than those of the reference RPV single agent co administered with DTG. Part 2: Systemic exposure of DTG following all DTG/RPV FDC formulations was lower than exposure following co-administration of the SE tablets under fasted conditions. Systemic exposure of RPV

Study	Study design	Population	Treatment details	Key conclusions
				following all DTG/RPV FDC formulations was comparable to or higher than exposure following co-administration of the SE tablets under fasted conditions. Food Effect: All test DTG/RPV FDC formulations showed increases in DTG and RPV systemic exposures with a moderate fat meal (Part 2). This finding is consistent with previous food effect studies of the SEs. Cross-cohort comparisons between fed (High Fat Part 1) and fasted (Part 2) showed that a high-fat meal increased DTG and RPV systemic exposure following administration of 3 FDC formulations (AK, AM and AS/AU) and as co-administration as the SE tablets.
LAI116181 (DTG + RPV DDI study)	Cohort 1: Open label, Repeat dose, Single sequence, 3- period study	Healthy adult subjects	Treatment A = DTG 50 mg with a moderate fat meal every 24 hours for 5 days Treatment B = RPV 25 mg with a moderate fat meal every 24 hours for 11 days Treatment C = DTG 50 mg + RPV 25 mg with a moderate fat meal every 24 hours for 5 days	Co-administration of DTG with RPV resulted in no change in DTG AUC(0-τ) and Cmax, and a 22% increase in C_T. Co-administration of DTG with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and a 21% increase in C_T. There was no significant drug interaction between DTG and RPV. DTV and RPV can be co-administered without dose adjustment.

2.4.2. Pharmacokinetics

Absorption

Dolutegravir

Following oral administration of tablet formulations, DTG absorption is rapid with no absorption lag time and a median t_{max} of 2 to 3 hours post dose. DTG concentration declines mono-exponentially with an average t½ of approximately 14 hours.

DTG absorption is increased with co-administration of food and decreased when co-administered with polyvalent metal cation-containing products. Following oral administration of tablet formulations, in general, DTG exhibits nonlinear PK with less than dose-proportional increases in plasma exposure from 2 to 100 mg (Study ING111521 and Study ING114005), however, increase in DTG exposure appears dose proportional from 25 mg to 50 mg, i.e. the therapeutic doses currently used (as observed in Study ING112276).

The absolute BA of DTG has not been directly measured due to low solubility and its non-specific binding, which present significant challenges to an IV formulation for DTG even at very low doses. However, based on accumulated data from in vitro permeability, metabolism, and biliary excretion in animals, and a human mass-balance study (ING111853), the absolute BA of DTG is estimated to be approximately 67% to 80% from the suspension formulation and 49% to 56% from the tablet formulation.

Following single oral administration as a tablet formulation, food was noted to modestly increase systemic exposure to DTG (66%) resulting in an estimated fraction absorbed of 81% to 93%.

Rilpivirine

The absolute BA of RPV has not been directly measured due to low solubility and its non-specific binding, which present significant challenges to an IV formulation for RPV even at very low doses.

The effect of concomitant food intake on the oral BA of RPV administered as a tablet (study TMC278-TiDP6-C137) showed that the mean exposure to RPV administered as the 75 mg Phase III tablet was higher after a standardized (normal fat or high fat) breakfast than under fasted conditions. Administration of RPV after a high-fat breakfast or after a standard breakfast resulted in similar exposures. It is recommended that RPV is always taken with a meal. Administration of RPV under fasted conditions decreased RPV AUC0-∞ by 41% and Cmax by 46%. Administration of RPV (Phase III tablet) with only a protein-rich nutritional drink decreased RPV AUC0-∞ by 49% and Cmax by 50% compared with a standard meal (study TMC278-TiDP6-C137).

The highest solubility of RPV is obtained at pH 2.0 (0.003 g/100 mL). At pH values above 2.0, the solubility decreases (< 0.001 g/100 mL). Drugs that alter intragastric pH affect the solubility of RPV and thus indirectly affect the absorption of RPV. Co- administration of the proton-pump inhibitor omeprazole (20 mg once daily) resulted in a 56% decrease in the AUC24h of a single dose of RPV (150 mg) and a 40% decrease after multiple doses of RPV (150 mg once daily) at steady state compared with administration of RPV alone.

PH-dependent absorption was confirmed in a DDI Study (TMC278-C140) with RPV and famotidine, a histamine H2-receptor antagonist that inhibits gastric acid production. When a single dose of RPV was administered 2 hours after a single dose of famotidine, RPV AUC0-∞ was decreased by 76% compared with administration of RPV alone. There was an inverse relationship between intragastric pH and RPV exposure after famotidine administration.

Overall, RPV permeation is thought to occur predominantly via a passive transcellular diffusion mechanism.

Although an in vitro P-gp inhibitory effect was seen, an in vivo effect of RPV at the intestinal absorption level is unlikely, given that the in vivo RPV total plasma concentrations at the therapeutic dose of 25 mg are more than 10-fold lower than the IC50 value of 3371 ng/mL.

Bioequivalence

Three pharmacokinetic studies pivotal for the development of the fixed dose combination of DTG + RPV have been conducted; one dug-drug interaction study, one also investigating the food effect on the formulation (Study 201674) and a bioequivalence study (Study 201676).

Study 201674

Study 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

This study evaluated the relative bioavailability of four prototype FDC DTG 50 mg/RPV 25 mg tablet formulations and the food effect of single doses of three prototype FDC DTG 50 mg/RPV 25 mg tablet formulations (relative to co-administration of the individual components in healthy adult subjects).

This study served as a guide for pharmaceutical development and provided information on the study design and sample size required for the pivotal BE study 201676. Moreover, the food effect on the fixed dose formulation was investigated.

Part I:

First, the relative bioavailability of a single dose of DTG 50 mg and RPV 25 mg when administered together (FDC vs. single tablets) was evaluated under fed conditions. For this, a randomised, open-label, three-way, crossover, single-center, incomplete-block and Youden square design study was conducted. Each subject received the reference treatment A (co-administration of the single tablets DTG 50 mg and RPV 25 mg) and two of the four FDC tablet formulations (AS, AM, AQ, AK) with a wash-out period of at least 9 days between dosing periods. Reference and test formulations were administered with a high-fat meal (about 900 total calories: 150 calories from protein, 250 calories from carbohydrate, and 500 calories from fat). 27 healthy subjects were enrolled in this study and 24 subjects completed the study.

Part II:

To evaluate the effect of food on the bioavailability, the FDC tablet formulations “AK” and “AM” were selected (based on bioavailability results from part I and manufacturing/stability conditions) as well as the previously untested FDC formulation “AU”. A randomised, open-label, 3-way crossover study with 36 subjects was performed. Each subject received a single dose of one FDC formulation (AK, AM, or AU) under fasted and fed conditions (moderate fat meal: approximately 625 total calories: 125 calories

from protein, 300 calories from carbohydrate, and 200 calories from fat) and the reference treatment (DTG 50 mg and RPV 25 mg as single tablets) under fasted conditions.

Result:

1) Relative Bioavailability

Under fed conditions (high-fat meal), DTG systemic exposure in terms of C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ of all FDC formulations was comparable to co-administration of the single agent. 90% CIs for all comparisons were within the acceptance bioequivalence interval of 80-125%. Under fasted conditions systemic exposure of DTG was lower after administration of all FDC formulations tested compared to the co-administration of the SE tablets.

For RPV, AUC_{0-t} and $AUC_{0-\infty}$ for all FDC formulations were comparable to those for the SE tablets with 90% CIs within conventional acceptance criteria for bioequivalence. For the formulations “AM” and “AQ”, the upper limit of 90% CI (C_{max}) was outside of 1.25, and for the formulation “AS”, the lower limit of 90% CI (C_{max}) was outside of 0.8. However, this study was not designated to assess formal bioequivalence between the FDC formulations and co-administration of the single tablets. Under fasted conditions systemic exposure of RPV was lower than under fed conditions with comparable or higher exposures after administration of all FDC tested compared to the co-administration of the SE tablets.

The pharmacokinetic data for formulation “AM”, differing only slightly from the formulation “AW” used in the pivotal BE study 201676, and the reference treatment are shown in 1.

Table 1. Summary results of DTG (a) and RPV (b) PK parameter treatment comparison for relative bioavailability under high fat conditions (part I). Formulation A: DTG 50 mg plus RPV 25 mg; Formulation AM: FDC DTG 50 mg/RPV 25 mg; high-fat meal: 900 total calories: 150 calories from protein, 250 calories form carbohydrate, and 500 calories from fat

Dolutegravir		Geometric LS Mean		
Parameter (units)	Comparison Test vs. Reference	Test (n = 12)	Reference (n = 25)	GLS Means Ratio (90% CI)
AUC_{0-t} [1] (h*µg/ml)	AM (Fed) vs A (Fed)	64.032	60.439	1.059 (0.993, 1.130)
$AUC_{0-\infty}$ (h*µg/ml)	AM (Fed) vs A (Fed)	65.427	61.895	1.057 (0.992, 1.126)
C_{max} (µg/ml)	AM (Fed) vs A (Fed)	3.382	3.439	0.983 (0.917, 1.055)

[1] t=tlast; Median tlast ~72 h for A (Fed), ~73 AM (Fed)

Rilpivirine		Geometric LS Mean		
Parameter (units)	Comparison Test vs. Reference	Test (n = 12)	Reference (n = 25)	GLS Means Ratio (90% CI)
AUC_{0-72} (h*ng/ml)	AM (Fed) vs A (Fed)	2105	2320	1.102 (0.999, 1.215)
AUC_{0-t} [1] (h*ng/ml)	AM (Fed) vs A (Fed)	3493	3093	1.129 (1.021, 1.249)
$AUC_{0-\infty}$ [2,3] (h*ng/ml)	AM (Fed) vs A (Fed)	3834	3635	1.055 (0.960, 1.160)
C_{max} (ng/ml)	AM (Fed) vs A (Fed)	112.1	101.6	1.104 (0.944, 1.295)
C_{max} [4] (ng/ml)	AM (Fed) vs A (Fed)	102.3	101.6	1.007 (0.887, 1.143)

[1] $t=t_{last}$; Median t_{last} ~168h for all treatments
[2] One subject AM (Fed) was excluded from the statistical analysis of $AUC_{0-\infty}$ because > 40% of $AUC_{0-\infty}$ extrapolated and λ_z time duration <2x calculated $t_{1/2}$
[3] Interpret with caution as ~20% of profiles across study have $AUC_{0-\infty}$ with % extrapolated >20% or poorly estimated $t_{1/2}$
[4] n=11, excluding one subject which had an outlier C_{max} value following Formulation AM dosing

2) Food Effect

Administration of the FDC tablets after a moderate and high fat meal significantly increased the systemic exposure of DTG, consistent with what was observed with the reference treatment and previous food effect studies of the single agents.

After a moderate-fat meal DTG $AUC_{0-t}/AUC_{0-\infty}$ was increased by 73% to 88% and C_{max} by 75% to 88%.

A cross-cohort comparison between part I (high fat) and part II (fasted) showed that co-administration of the various FDC tablets with a high-fat meal increased DTG $AUC_{0-t}/AUC_{0-\infty}$ by 71% to 89% and C_{max} by 71% to 85%.

In case of RPV $AUC_{0-t}/AUC_{0-\infty}$ was increased by 38% to 58% and C_{max} by 74% to 94% after administration of the different FDC formulations under moderate fat conditions.

In the cross-cohort comparison between part I (high fat) and part II (fasted) RPV $AUC_{0-t}/AUC_{0-\infty}$ was increased by 55% to 85% and C_{max} by 73% to 117%. The pharmacokinetic data for formulation “AM”, claimed to be similar to formulation “AW” used in the pivotal BE study 201676, are shown in Table 2.

Table 2. Summary of DTG (a) and RPV (b) pharmacokinetic parameters under fasted and fed conditions (part I and part II). Formulation A: DTG 50 mg plus RPV 25 mg; Formulation AM: FDC DTG 50 mg/RPV 25 mg; high-fat meal: 900 total calories: 150 calories from protein, 250 calories form

carbohydrate, and 500 calories from fat; moderate-fat meal: 625 total calories: 125 calories from protein, 300 calories from carbohydrate and 200 calories from fat.

a) DTG

Parameter	Geometric LS Mean		GLS Means Ratio (90% CI)
	Test	Reference	
Formulation A: High Fat	**A (Fed) Part 1 (N=25)**	**A (Fasted) Part 2 (N=36)**	
AUC(0-t) (µg.h/mL)[c]	60.22	38.78	1.553 (1.340, 1.800)
AUC(0-∞) (µg.h/mL)	61.67	39.91	1.545 (1.337, 1.786)
Cmax (µg/mL)	3.429	2.267	1.513 (1.313, 1.743)
Formulation AM: High Fat	**AM (Fed) Part 1 (N=12)**	**AM (Fasted) Part 2 (N=12)**	
AUC(0-t) (µg.h/mL)[c]	63.68	33.61	1.895 (1.545, 2.324)
AUC(0-∞) (µg.h/mL)	65.03	34.72	1.873 (1.533, 2.289)
Cmax (µg/mL)	3.397	1.977	1.718 (1.411, 2.092)
Formulation AM: Moderate Fat	**AM (Fed) Part 2 (N=12)**	**AM (Fasted) Part 2 (N=12)**	
AUC(0-t) (µg.h/mL)[c]	62.94	33.56	1.875 (1.547, 2.274)
AUC(0-∞) (µg.h/mL)	64.62	34.64	1.865 (1.542, 2.257)
Cmax (µg/mL)	3.395	1.941	1.749 (1.403, 2.181)

c. t = tlast. Median tlast ~72h for all treatments

b) RPV

Parameter	Geometric LS Mean		GLS Means Ratio (90% CI)
	Test	Reference	
Formulation A: High Fat	**A (Fed) Part 1 (N=25)**	**A (Fasted) Part 2 (N=36)**	
AUC(0-t) (ng.h/mL)[c]	3090	1902	1.625 (1.364, 1.934)
AUC(0-∞) (ng.h/mL)[d, e]	3643	2168	1.680 (1.400, 2.016)
Cmax (ng/mL)	101.3	53.12	1.907 (1.541, 2.360)
Formulation AM: High Fat	**AM (Fed) Part 1 (N=12)**	**AM (Fasted) Part 2 (N=12)**	
AUC (0-72) (ng*h/mL)	2362	1318	1.792 (1.427, 2.249)
AUC(0-t) (ng.h/mL)[c]	3542	1911	1.853 (1.480, 2.321)
AUC(0-∞) (ng.h/mL)[d, e]	3886	2265	1.716 (1.360, 2.164)
Cmax (ng/mL)	114.2	52.66	2.168 (1.619, 2.902)
Cmax (ng/mL)[f]	101.7	52.96	1.919 (1.450, 2.541)
Formulation AM: Moderate Fat	**AM (Fed) Part 2 (N=12)**	**AM (Fasted) Part 2 (N=12)**	
AUC (0-72) (ng*h/mL)	1931	1192	1.621 (1.260, 2.085)
AUC(0-t) (ng.h/mL)[c]	2907	1843	1.577 (1.241, 2.004)
AUC(0-∞) (ng.h/mL)[e]	3508	2236	1.569 (1.244, 1.980)
Cmax (ng/mL)	95.08	50.29	1.891 (1.339, 2.669)

c) t = tlast. Median tlast ~168h for all treatments
d) 4 subjects (2 fed, 2 fasted) were excluded from the statistical analysis of AUC(0-∞) because >40% of AUC(0-∞) extrapolated and λz time duration <2x calculated t½
e) Interpret with caution as large number of profiles (~20% across study) have AUC(0-∞) with % extrapolated >20% or poorly estimated t½
f) n=11, excluding Subject 118 which had an outlier Cmax value after Formulation AM dosing

Study 201676

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

The development of a FDC tablet of DTG 50 mg and RPV 25 mg occurred in parallel with the ongoing phase 3 studies (SWORD-1 and SWORD-2), which are being conducted with the separate DTG 50 mg

and RPV 25 mg tablets. This pivotal BE study compared the bioavailability of DTG and RPV when administered as FDC tablet with co-administration of the individual single entity products to serve as a bridge to the clinical efficacy and safety data.

For this study the formulation “AW” was selected based on *in vitro* testing, stability, and manufacturability considerations, and supported by the results of the relative BA study 201674. The formulation “AM” used in the relative BA study 201674 is slightly different from the formulation “AW”.The dissolution profiles of these two FDC formulations are comparable under the conditions tested.

Study design

This was an open-label, randomized, two-period, cross-over, single dose, oral bioequivalence study under fed conditions with a wash-out period of 21 days between dosing periods.

Starting and end date of the study

Clinical phase: 11th May to 24th October 2016 (first blood sampling on 7th June 2016)

Bioanalytical phase: 12th July to 20th October 2016 (DTG)

19th July to 7th November 2016 (RPV)

Applied dose

FDC tablet formulation “AW” or single tablets of DRV and RPV were administered with 240 ml water 30 minutes after a moderate fat breakfast (approximately 625 total calories: 125 calories from protein, 300 calories from carbohydrate, and 200 calories from fat).

Sample collection

Blood samples were collected prior to study drug administration and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 12.0, 16.0, 24.0, 48.0, 72.0 and 120 hours post-dose into tubes containing K_2EDTA (DTG) and sodium heparin (RPV) as anticoagulant. Additional blood samples were collected for RPV at 168, 216, and 264 hours post-dose.

Within 45 minutes after collection, the samples were centrifuged and the separated plasma samples were stored at -20°C. Samples were shipped frozen on dry ice at the end of each period to the bioanalytical sites.

Table 3. Test and reference product

	Reference Treatments		Test Formulation
Product name	Dolutegravir (TIVICAY clinical image)	Rilpivirine (EDURANT; commercially marketed formulation)	Dolutegravir and Rilpivirine FDC tablets (Product Code AW)
Strength	50 mg	25 mg	Dolutegravir 50 mg, Rilpivirine 25 mg
Batch number	132373670 (R634503)	162396354 (GAL7E00)	162395454 (R759861)
Measured content (% of label claim)	100.1%	97.2%	Dolutegravir: 100.5% Rilpivirine: 97.9%
Batch size	233,333 (approx.)	120,000	67,000*
Expiry date	7-2017	12-2018	12-2016

* Although the final film-coated tablet batch of the test formulation comprised only 67,000 tablets, the compression batch size comprised 117 kg of tablet cores (corresponding to about 234,000 units which corresponds to about 54% of full production scale).

Population studied

118 healthy male and female subjects aged between 18 and 55 years with a BMI of 18.5-31 kg/m^2 were enrolled and randomized. 113 subjects completed both treatment periods. A total of 115 subjects received treatment A (FDC) and 116 received treatment B (single tablets).

Five subjects were excluded from the statistical analysis for plausible, not PK-related reasons.

Initially, 86 subjects were planned for this study based on historical PK data for DTG and RPV (in the BA study 201674 and DDI study LAI116181 the highest within-subject coefficient of variation (CVw) for RPV C_{max} was 26.8% and 28%, respectively). A blinded sample size re-estimation was performed after 56 subjects had been dosed to evaluate the appropriateness of the assumed PK parameter variability and associated sample size. Based on the higher RPV CVw observed (32.9% for C_{max}), 32 additional subjects were recruited.

Results

The pharmacokinetic variables of DTG and RPV for both treatments (A: FDC tablet formulation DTG/RPV 50 mg/25 mg; B: DTG 50 mg plus RPV 25 mg) are shown in Table 8 and Table 9 respectively. DTG and RPV systemic exposure in terms of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ following administration of the FDC tablet formulation were comparable to those of the co-administered single agents. The 90% CIs of all PK parameters were within the 80-125% acceptance range.

Thus, the FDC tablet formulation of DTG/RPV 50 mg/25 mg is considered bioequivalent to co-administration of the single tablets with the same contents of actives with respect to both rate and extent of absorption under moderate-fat conditions.

Table 4. Summary of DTG pharmacokinetic parameters; A= FDC tablet formulation DTG/RPV 50 mg/25 mg; B = DTG 50 mg plus RPV 25 mg n = number of subjects per treatment with non-missing value

PK Parameter	Test vs. Reference[1]	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
C_{max} (µg/mL)	A vs B	113	3.646	113	3.474	1.050	(1.022, 1.078)
$AUC_{(0-t)}$ (h*µg/mL)	A vs B	113	63.583	113	61.265	1.038	(1.011, 1.066)
$AUC_{(0-\infty)}$ (h*µg/mL)	A vs B	113	64.968	113	62.655	1.037	(1.010, 1.064)
C_{24} (µg/mL)[1]	A vs B	112	1.001	112	0.958	1.044	(1.012, 1.077)
	A vs B[1]	113	1.003	112	0.960	1.045	(1.012, 1.078)

[1] For C_{24}, one subject was excluded due to no result for Period 2; in a separate supportive analysis this subject's Period 1 C_{24} was included

Table 5. Summary of RPV pharmacokinetic parameters; A= FDC tablet formulation DTG/RPV 50 mg/25 mg; B = DTG 50 mg plus RPV 25 mg n = number of subjects per treatment with non-missing value

PK Parameter	Test vs. Reference[1]	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
C_{max} (µg/mL)	A vs B	113	0.093	113	0.083	1.124	(1.047, 1.207)
$AUC_{(0-t)}$ (h*µg/mL)	A vs B	113	3.062	113	2.767	1.107	(1.042, 1.176)
$AUC_{(0-\infty)}$ (h*µg/mL)[1]	A vs B	112	3.248	112	2.933	1.108	(1.045, 1.174)
	A vs B[1]	113	3.254	112	2.936	1.108	(1.046, 1.175)
C_{24} (µg/mL)	A vs B	113	0.031	113	0.028	1.101	(1.034, 1.173)

[1] For $AUC_{0-\infty}$, one subject was excluded due to a result "not determined" in Period 1 because $AUC_{0-\infty}$ >20%, R^2<0.85 in estimation of terminal phase rate constant, and range of time over which $t_{1/2}$ calculated was <2 x $t_{1/2}$; in a separate supportive analysis this subject's Period 1 $AUC_{0-\infty}$ was included.

Commercial formulation

A slight change to the tablet shape was made between the FDC formulation "AW" used in the BE study and the proposed commercial formulation. This change is not expected to have any impact on the bioavailability. The dissolution profiles show the two tablet shapes are comparable.

The bioanalytical methods for studies 201674 and 201676 have been validated and were considered satisfactory.

Distribution

Dolutegravir

Apparent volume of distribution was estimated at 17.4 L following oral tablet dosing based on a population PK analysis in treatment-naïve subjects. The estimated Vd/F is greater than the total plasma volume (~3 L for a 70-kg person), but similar to the volume of total water in the extracellular space (~15 L for a 70-kg person). Total blood and plasma drug-related radioactivity concentration ratios, as measured in the human mass balance Study ING111853 were averaged at 0.441 to 0.535, indicating minimal association of DTG with blood cellular components.

In vitro, the protein binding of DTG in human serum and plasma is high (approximately 99.3%). DTG appears to primarily bind to albumin based on the hepatic impairment Study ING113097 where the DTG unbound fraction showed better correlation with albumin than AAG.

DTG is present in CSF at levels similar to the unbound concentration in plasma. Median DTG concentrations in CSF were 18 ng/mL at Week 2 and 13 ng/mL at Week 16 in 13 HIV-1 infected male subjects receiving DTG (50 mg) + abacavir/lamivudine (600/300 mg) once daily. Ratios of DTG CSF to total plasma concentration were similar to the unbound fraction of DTG in plasma. Median changes from baseline in CSF (n = 11) and plasma (n = 12) HIV-1 RNA were -3.42 and -3.04 $\log_{10}$ c/mL, respectively. Nine of 11 subjects (82%) had plasma and CSF HIV-1 RNA levels < 50 c/mL and 10 of 11 (91%) had CSF HIV-1 RNA levels < 2 c/mL at Week 16 [*Letendre, 2014*].

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

Rilpivirine

After a single oral dose of 150 mg 14C-RPV in healthy adults (TMC278-C119), the blood-to-plasma ratios of total 14C-radioactivity were time-independent, with values ranging between 0.65 and 0.75, indicating that RPV and its metabolites were not distributed to blood cells to any significant extent. The *in vitro* plasma protein binding of RPV, determined by equilibrium dialysis, was on average 99.7%, irrespective of the RPV concentration (10-3000 ng/mL). RPV was extensively bound to human albumin and to a lesser extent to AAG. The blood-to-plasma concentration ratio was approximately 0.67, irrespective of the RPV concentration. A very limited fraction of RPV was distributed to the plasma water compartment (0.003). The fraction of RPV distributed to plasma proteins was 0.773 and the fraction distributed to blood cells was 0.224.

The distribution of RPV into compartments other than plasma (e.g. CSF or genital tract secretions) has not been evaluated in humans by the applicant. In the literature, individual RPV CSF concentrations were above the EC_{50} in 13 HIV-1 infected male subjects who switched from TDF + FTC + NVP (245 + 200 + 400 mg) once daily to TDF + FTC + RPV (245 + 200 + 25 mg) once daily and above the EC_{90} in 85% (11/13) of the subjects. HIV-1 RNA in CSF remained undetectable (<5 copies/mL) in all patients through 60 days. The mean plasma RPV trough concentration was 29.7 ng/mL and the mean RPV concentration in CSF was 0.8 ng/mL, representing a CSF/plasma ratio of 1.4% [*Mora-Peris, 2014*].

Elimination

Excretion

Dolutegravir

Renal elimination of unchanged drug is low (<1% of the dose). Following oral administration of a 14C-DTG in a suspension formulation, 31% of the total oral dose is excreted in the urine, represented by three main (M1, M3, M7) and other minor metabolites. Sixty-four percent of the total oral dose is recovered in the faeces, represented mainly by DTG (53% of total dose). It is unknown if all or part of the parent compound in faeces is due to unabsorbed drug or biliary excretion of the glucuronide conjugate, which can be converted back to the parent compound in the gut lumen. In bile duct-cannulated animals, 7% of the administered dose was recovered as DTG in rat bile, and 12% in monkey bile; the percentage of administered drug recovered as DTG in faeces was similar for humans

(64%) and monkeys (59%), and higher in rats (88%). Other notable components in faeces include metabolites M13 and M1 (<2% of total dose) (Study ING111853).

DTG has a terminal half-life of ~14 hours and a low CL/F of 0.56 L/hr (Study ING111853), which represents <2% of liver plasma flow; therefore, the hepatic extraction ratio is low (lower than 2%). As CYP3A4 is a secondary route of elimination of DTG, the first-pass metabolism of DTG following oral dosing is expected to be very low.

Rilpivirine

A mass-balance trial (TMC278-C119) showed that most of the 14C-RPV-related radioactivity from a single 150-mg dose administered as an oral solution was excreted in faeces. At 168 hours after dosing, a mean of 85.1% of the administered radioactivity was recovered in faeces, and a mean of 6.1% of the administered radioactivity was recovered in urine. Unchanged RPV accounted for a mean of 25.5% of the dose in faeces. Only trace amounts (<1%) of unchanged RPV were detected in urine.

After oral administration of the tablet formulation, the C_{max} of RPV is generally achieved within 4 to 5 hours. The mean terminal elimination $t_{1/2}$ of RPV is approximately 45 hours. The mean apparent oral clearance (CL/F) ranged from 6.89 to 8.66 L/h.

Metabolism

Dolutegravir

Following oral administration of 20 mg 14C-DTG in humans, unchanged DTG is primarily eliminated through metabolism, and renal elimination of unchanged DTG represents less than 1% of the total dose administered. The quantified metabolites in humans include an ether glucuronide of DTG (M3), an N-dealkylation metabolite (M1), a product from oxidation at the benzylic carbon (M7), and a product of oxidative defluorination with cysteine addition (M13). M3 is the major metabolite observed in urine, and represents 18.9% of the total dose administered. The total radioactivity of the metabolites formed through oxidation (M1, M7, and M13) that are recovered in urine and faeces accounts for approximately 9.7% (mean) of the total dose administered. The enzymes responsible for the formation of M3 are UDP glucuronosyl transferase UGT1A1 (major), and UGT1A3 and UGT1A9 (minor). The enzyme responsible for forming M7 is CYP3A4, while the enzyme responsible for forming M13 is unknown. M1 is formed by hydrolysis of M7. Therefore, UGT1A1 is the primary route of metabolism, with CYP3A4 as a secondary metabolic pathway in humans. DTG is the predominant circulating compound in plasma, representing 97% of plasma total radiocarbon, while M3 represents <2.4% (Study ING111853). These human metabolites were observed in animals.
The primary metabolite, ether glucuronide of DTG (M3), in plasma shows formation rate-limited elimination following oral administration of DTG (Study ING113125). Apparent half-life of the ether glucuronide in plasma is similar to the parent compound, DTG, and renal excretion is a primary route of elimination of this metabolite (Study ING113125).

DTG and 11 metabolites were identified in pooled human urine.

As CYP3A4 is a secondary route of elimination of DTG, the first-pass metabolism of DTG following oral dosing is expected to be very low.

The primary metabolite, M3, is ether glucuronide of DTG, and is not expected to have antiviral activity. As M3 is presented at very low concentrations in plasma, it is not expected to exhibit pharmacological activity leading to toxicity.

Rilpivirine

A major metabolic pathway of RPV, representing the main *in vitro* biotransformation, was aromatic hydroxylation at the pyrimidinyl moiety (to metabolite 42), followed by glucuronidation (to metabolite 25). Another major metabolic pathway was aliphatic hydroxylation at one of the methyl groups of the cyanoethenyl-2,6-dimethylphenyl moiety (to metabolite 33), followed by dehydration to form a tricyclic metabolite (metabolite 27).

The metabolites of 14C-RPV were determined in faeces, urine, and plasma collected from healthy adults after a single oral dose of 150 mg 14C-RPV (TMC278-C119). The most abundant metabolite originated from oxidation at the 5-position of the pyrimidinyl moiety (metabolite 42), and accounted for 16.1% of the RPV-related radioactivity in faeces. Three other metabolites each accounted for 2.2 to 3.0% of RPV.

In urine, apart from the carboxylic acid metabolite (metabolite 30, 0.03%), the other metabolites were phase-2 metabolites (glucuronides or glutathione derived conjugates) including 2 glycine conjugates (metabolites 13 and 14) and a mercapturic acid conjugate (metabolite 18).

Unchanged drug accounted for the major part of the total radioactivity in plasma (76% based on C_{max}, 51% based on AUC_{last}). Several minor plasma metabolites were detected, including the glucuronide of RPV (metabolite 15, ~10.2% of the sample radioactivity), the tricyclic metabolite (metabolite 27, ~9.7% of the sample radioactivity), and hydroxymethyl RPV (metabolite 33, ~5.1% of the sample radioactivity).

The primary RPV metabolism was mainly catalyzed by CYP3A enzymes, which play the major role in the biotransformation of RPV *in vitro*.

Dose proportionality and time dependencies

Dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg. For rilpivirine less than dose proportional increase in exposure at higher doses was observed, which is likely due to the limited solubility of the substance. Since the applicant applied for only one dose strength of the FDC (50/25 mg) with no dose adjustment, the assessment of dose proportionality in patients was not considered essential.

For dolutegravir no time dependent pharmacokinetics has been observed. For rilpivirine, no time dependency was obvious. Based on interaction data for rilpivirine, limited induction is expected at a dose of 25 mg.

Intra- and inter-individual variability

After administration of the Dolutegravir/Rilpivirine HCl 50/25 mg FDC tablet, an inter-subject variability is observed for dolutegravir of 24% for AUC(0-inf), 18% for Cmax and 23% for Cl/F and for rilpivirine of 40% for AUC(0-inf), 34% for Cmax and 49% for Cl/F (study 201676).

The intra-subject variability is not evaluated.

Special populations

Impaired renal function

Dolutegravir:

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <30 ml/min) and matched healthy controls. The exposure to dolutegravir was decreased by approximately 40% in subjects with severe renal impairment. The mechanism for the decrease is unknown. No dosage adjustment is considered necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, but as dolutegravir is highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis

Rilpivirine:

The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. No dose adjustment is needed for patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution, as plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction. In patients with severe renal impairment or end-stage renal disease, the combination of rilpivirine with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Impaired hepatic function

Dolutegravir:

Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5- to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of Tivicay has not been studied.

Rilpivirine:

Rilpivirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate hepatic impairment.

No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, rilpivirine is not recommended in patients with severe hepatic impairment.

Gender

No clinically relevant differences in the pharmacokinetics of dolutegravir and rilpivirine have been observed between men and women.

Race

Population pharmacokinetic analysis of dolutegravir and rilpivirine in HIV infected patients indicated that race had no clinically relevant effect on the exposure to dolutegravir and rilpivirine.

Elderly

Population pharmacokinetic analysis of dolutegravir and rilpivirine using data in HIV-1 infected adults indicated that there was no clinically relevant effect of age on dolutegravir or rilpivirine exposure. Of note, pharmacokinetic data in subjects >65 years of age were limited.

Pharmacokinetic interaction studies

Dolutegravir

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicinal products that induce those enzymes may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other medicinal products that inhibit these enzymes may increase dolutegravir plasma concentration

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters.

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

Rilpivirine

Rilpivirine is primarily metabolised by cytochrome P450 (CYP)3A. Medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of rilpivirine and medicinal products that induce CYP3A has been observed to decrease the plasma concentrations of rilpivirine, which could reduce the therapeutic effect of rilpivirine.

Co-administration of rilpivirine and medicinal products that inhibit CYP3A has been observed to increase the plasma concentrations of rilpivirine.

Co-administration of rilpivirine with medicinal products that increase gastric pH may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine.

Dolutegravir and rilpivirine

The interaction between dolutegravir and rilpivirine was evaluated in study LAI116181.

Study LAI116181

Study Title: A Phase 1, Open-Label, Crossover Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 and Rilpivirine and Dolutegravir and Rilpivirine in Healthy Adult Subjects

This was a single-center, two-cohort, open-label, three-period, fixed-sequence cross over study in healthy adult subjects. In Cohort 1, 16 healthy volunteers, 2 females and 14 males, aged 18 - 50 years, received dolutegravir 50 mg every 24 hours (q24h) for 5 days (Treatment A) followed by a 7 day washout period. Subjects were then administered rilpivirine 25 mg q24h for 11 days (Treatment B), followed by dolutegravir 50 mg q24h in combination with rilpivirine 25 mg q24h for 5 days (Treatment C). All doses were administered within 30 minutes after the start of a moderate fat meal. Blood samples were taken over 24 h at the end of each treatment. All subjects completed the study. The pharmacokinetic results are shown in Table 6 and 7.

Table 6. Summary of dolutegravir pharmacokinetic parameters and statistical treatment comparisons following repeat dose administration of dolutegravir with and without rilpivirine

Plasma DTG PK Parameter	DTG[1] (n=16)	DTG + RPV[1] (n=16)	DTG + RPV vs DTG[2]
AUC(0-τ) (µg.h/mL)	48.8 [40.8, 58.4] (35)	54.7 [46.1, 64.9] (33)	1.12 [1.05, 1.19]
Cmax (µg/mL)	3.46 [2.96, 4.04] (30)	3.90 [3.43, 4.44] (25)	1.13 [1.06, 1.21]
Cτ (µg/mL)	1.07 [0.850, 1.34] (45)	1.31 [1.04, 1.65] (46)	1.22 [1.15, 1.30]
Tmax[3] (h)	3.50 (1.0-4.0)	3.50 (1.0-4.0)	-------

1. Geometric mean [95% CI] (Between subject variability CVb%)
2. GLS Mean Ratio [90% CI]
3. Median (range)

Treatments:

DTG = DTG 50 mg QD x 5 days

DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days

Table 7. Summary of rilpivirine pharmacokinetic parameters and statistical treatment comparisons following repeat dose administration of rilpivirine with and without dolutegravir

Plasma RPV PK Parameter	Cohort 1: RPV with or without DTG		
	RPV[1] (n=16)	DTG + RPV[1] (n=16)	DTG + RPV vs RPV[2]
AUC(0-τ) (ng.h/mL)	2227 [1872, 2649] (33)	2368 [1985, 2825] (34)	1.06 [0.976, 1.16]
Cmax (ng/mL)	148 [128, 173] (29)	164 [136, 197] (36)	1.10 [0.992, 1.22]
Cτ (ng/mL)	74.5 [60.3, 92.2] (41)	90.5 [70.9, 115] (48)	1.21 [1.07, 1.38]
Tmax[3] (h)	4.00 (4.0-6.0)	4.00 (2.0-5.0)	------

1. Geometric mean [95% CI] (CVb%)
2. GLS Mean Ratio [90% CI]
3. Median (range)

The results of this study support the concomitant use of DTG and RPV from a pharmacokinetic perspective.

2.4.3. Pharmacodynamics

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT).

Primary pharmacology

Dolutegravir

DTG is a second generation integrase inhibitor demonstrating antiviral activity at nanomolar levels to HIV 1 of various strains and subtypes (IC50 0.22 to 1.07 nM) and HIV-2 (0.29 nM). The activity of DTG is reduced 75-fold in the presence of 100% serum (extrapolated; IC50 38 nM). The selectivity index for DTG is >9400. When tested against other viruses, DTG did not exhibit significant antiviral activity. Drug combination analysis of DTG with other ARV drugs resulted in additive or synergistic effects.

Only few substitutions conferring minor FCs on DTG susceptibility in vitro were selected in WT HIV-1 (112 days, increasing concentration of DTG): S153Y and S153 F (4.1 FC), E92Q (3.1 FC), and G193E (3.2 FC), underscoring the relatively high resistance barrier of DTG. However, when starting with Q148 mutants this barrier was broken down due to selection of further mutations conferring a substantial increase in FC (47 to190). Presence of the double mutations G140/Q148 lead to the selection of further mutations conferring decrease in antiviral activity: N155H (FC 85-120), E92Q (FC >110), L74M (FC 15 to 95). The clinical isolates analysis of subtype B mutation R263K and G118R found that FCs for G118R varied from 2.5 to 11.2 while R263K had no effect on DTG activity, although selected in 2 ART

experienced, INI naive patients. *In vitro* DTG retained activity (<10 FC) against 94% of 704 RAL resistant clinical isolates and was also active against 91% of Q148+1 and 73% of Q148+≥2 INSTI-resistance mutations.

In the clinical studies of treatment-naïve patients, no cases of treatment emergent resistance to the IN- or NRTI-class were seen in DTG-treated subjects failing therapy. In treatment-experienced, INI naïve subjects, the IN resistance mutations T97, E138, and polymorphic V151, and R263 emerged without conferring phenotypic resistance (FC <2.5). This finding supports the in vitro data demonstrating that considerable phenotypic resistance for DTG is only seen when Q148 +≥2 INSTI-RAMs are present while single mutations in IN seem not to confer resistance to DTG.

Rilpivirine

RPV is a non-nucleoside reverse transcriptase inhibitor and exhibits low nanomolar activity for various strains and subtypes (EC50 0.07 to 1.01 nM); the median EC50 in PBMCs against all HIV-1 primary clinical isolates tested was 0.26 nM. The selectivity index for RPV in MT4-cells is >8000. The antiviral activity against HIV-2 is less pronounced (5.22 µM). In human serum the antiviral activity of RPV is considerably reduced (19-fold) due to high protein binding (99%). RPV has no antiviral activity against various human viruses other than HIV.

A large-scale evaluation of the antiviral activity of RPV was done in vitro on a panel of 4,786 HIV-1 clinical isolates resistant to a first-generation NNRTI (FC > 2.5 to EFV or NVP). The results show that 62% of these HIV-1 clinical isolates retained sensitivity to RPV or ETR (as compared to 11.3% to EFV and 4.6% to NVP).

When testing the antiviral activity of RPV against 216 HIV-1 SDMs containing single, double, triple and quadruple RT mutations, RPV retained activity against 63% of all mutants and 96% of single RAMs; only RAMs K101P, Y181I/V conferred resistance to RPV (FCs of 51.7, 15.3 and 12.2, respectively) but are uncommon in NNRTI-experienced patients (2.04%, 1.05%, 0.63% of>100,000 clinical isolates analysed). Cross-resistance was observed between RPV, EFV and NVP.

Although it was demonstrated in vitro that single mutations could lead to notable changes of FC, in vivo this effect was not found. Here, treatment-emergent mutations associated with considerable RPV FCs consisted of NNRTI + NRTI RAMs, often E138K + M184I or K101E + M184I/V, conferring a FC of 8. Baseline viral load >100.000 c/mL seems to influence RPV viral failure and incidence of treatment-emergent RAMs while it does not affect the resistance profile itself. This finding is reflected in the indication of Juluca as only virologically suppressed patients are included. Considering the in vitro and in vivo data, the following RAMs, when present at baseline, may affect the activity of RPV: K101E/P, E138A/G/ K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L.

Cross-resistance is seen in vivo and vitro for RPV and other NNRTIs and could be of relevance for patients pre-treated with etravirine, efavirenz and to a lesser extend withnevirapine. The indication includes only patients without known or suspected resistance to the NNRTI class.

RPV + DTG

The pivotal studies 201636 and 201637 demonstrated that treatment of HIV 1 infected patients with HIV-1 <50 c/ml on cART when switching to DTG+RPV did not lead to increased virologic failure compared to continued treatment with CAR. In both studies very low level of virologic failures was observed (2 patients in each group for 201636, 1 patient on DTG+RPV and 3 patients on CAR in 201637). Overall, resistance mutations were seen only in 2 patients treated with DTG+RPV: K101K/E

in RT which was treatment-emergent (due to non-adherence) and G193E in IN which was already present at baseline. Both mutations did not confer reduced susceptibility to RPV or DTG.

Secondary pharmacology

DTG 50 mg component

A phase I, randomized, partial-blind, single-dose, three-period, crossover thorough QT study (ING111856) has been performed to investigate the effect of GSK1349572 (DTG) on cardiac repolarization as compared to placebo and moxifloxacin in healthy adult males and females. The main conclusion from this study was that DTG had no effect on cardiac repolarization at a supra-therapeutic dose of 250 mg suspension. The study was sensitive enough to detect the effect of moxifloxacin, the positive control, on QTcF, which confirmed that this study was valid for assessing the effects of DTG on cardiac repolarization.

RPV 25 mg component

There is limited information available on the potential for a pharmacodynamic interaction between RPV and drugs that prolong the QTc interval in the electrocardiogram. In a study of healthy subjects (C131), supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram; this was not observed with the RPV 25 mg dose (C152). RPV should be used with caution when co-administered with a drug with a known risk of torsades de pointes.

2.4.4. Discussion on clinical pharmacology

Apart from studies 201674 and 201676, all pharmacokinetic studies were performed with DTG and RPV as single entities only.

ADME as well as the interaction profiles of DTG and RPV, the individual components of the FDC, have been well characterized.

Based on the interactions study LAI116181 no clinically relevant drug-drug interactions between DTG and RPV were reported.

The relative BA study 201674 showed a difference in the relevant PK parameters of RPV of different FDC formulations when administered after a moderate or high fat meal, particularly for the FDC “AM” which is claimed to be similar to the formulation “AW” used in the pivotal BE-study 201676. AUC and Cmax were higher under high-fat meal conditions as compared to moderate-fat meal conditions. The pivotal BE study 201676, which served as the bridge to the clinical efficacy and safety data, was conducted under moderate fat conditions as the applicant claims that these are more representative of a typical diet in the HIV-infected population. The CHMP concluded that the use of a moderate fat meal in the pivotal bioequivalence study as sufficiently sensitive and discriminatory to detect a difference between formulations.

Virological failure and subsequent development of drug resistance mutations seems to be infrequent in the DTG+RPV arms of the SWORD studies, which is reassuring. However, a re-analysis using deep-sequencing techniques should be performed for all subjects with confirmed or suspected virological failure in order to confirm the absence of additional resistance associated mutations in subjects failing on DTG+RPV.

Persistence of HIV replication in sanctuary sites can occur despite undetectable viraemia in plasma, and this could be more pronounced with dual than with triple therapy. Viral replication in sanctuary sites has been associated with persistent systemic inflammation, immune activation and with accelerating neurocognitive dysfunction. As a consequence, neurocognitive dysfunction will be monitored post-authorisation.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of DTG and RPV as fixed dose combination tablet has been sufficiently characterized.

2.5. Clinical efficacy

The efficacy, safety and tolerability of the treatment regimen of DTG 50 mg / RPV 25 mg is being evaluated in 2 pivotal, identical, ongoing, randomized, parallel group, 148-week, Phase III studies (201636 [SWORD-1] and 201637 [SWORD-2]). In addition, a safety study for the assessment of bone mineral density (BMD) in a subset of subjects in the 201636 and 201637 studies is being conducted. Supportive data on DTG and RPV was provided from the single entity development programs.

Overview of key clinical studies

Study	Study Design	Numbers by Treatment Regimen	Primary endpoint
Pivotal Efficacy and Safety Studies			
201636 (SWORD-1) HIV-1 infected ART-experienced subjects	148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	ITT-E Population: DTG + RPV: 252 CAR: 256	Proportion of subjects with plasma HIV-1 RNA <50 c/ml at Week 48 (Snapshot algorithm) in ITT-E Population
201637 (SWORD-2) HIV-1 infected ART-experienced subjects	148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	ITT-E Population: DTG + RPV: 261 CAR: 255	Proportion of subjects with plasma HIV-1 RNA <50 c/ml at Week 48 (Snapshot algorithm) in ITT-E Population
Additional Safety Study			
202094 (DEXA) HIV-1 infected ART-experienced subjects	Open-label, parallel group substudy of SWORD-1 and SWORD-2	DTG + RPV: 53 CAR: 49	Percentage change from baseline at Week 48 in total hip BMD as assessed by areal density in g/cm2

2.5.1. Dose response studies

Dolutegravir (study ING112276): No major difference in efficacy was seen for the different doses of dolutegravir. A numerically higher relapse rate was seen with the lowest dose of dolutegravir than with the 50 mg dose. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1.20 µg/mL; around 20 times higher than the estimated protein adjusted IC90 for WT virus. As no major differences were observed with respect to adverse events between the investigated doses, 50 mg DTG/d was selected as the dose to be further investigated in INSTI-naïve patients.

Rilpivirine (study TMC278-C204): A dose-response relationship could not be demonstrated. However, initially the 75 mg q.d. dose was selected for the Phase III trials and further development of rilpivirine because, though not statistically significant, the proportion of virologic failures in the RPV 25 mg q.d. group was 8.6% compared to 5.3% and 6.6% in the 75 mg q.d. and 150 mg q.d. dose groups,

respectively. Furthermore, there was a trend towards lower efficacy of the 25 mg q.d group among those with a high baseline viral load. Later, data became available demonstrating a possible dose-response relationship with respect to QT-prolongation.

A statistically significant positive correlation was observed between change from baseline in QTcF interval and exposure (AUC24h) to rilpivirine ($p < 0.001$). Thus rilpivirine 25 mg q.d. formulation was finally chosen for further evaluation in phase III studies as well as the prolonged arm of this phase IIb study.

2.5.2. Main studies

The DTG+RPV development programme consisted of a 2-drug, "NRTI-sparing" regimen for the treatment of HIV-1 infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) without known or suspected resistance to either antiretroviral component. The main studies for this application are Study 201636 (SWORD-1) and Study 201637 (SWORD-2). Both are identical 148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority studies. These are ongoing studies, conducted in 508 (study 201636) and 516 (study 201637) adult HIV-1 infected patients who are on stable suppressive cART containing 2 NRTIs (Nucleoside and nucleotide reverse transcriptase inhibitors) plus either an INSTI (integrase strand transfer inhibitor), an NNRTI (non-nucleoside reverse transcriptase inhibitor), or a PI (protease inhibitor).

Title of studies:

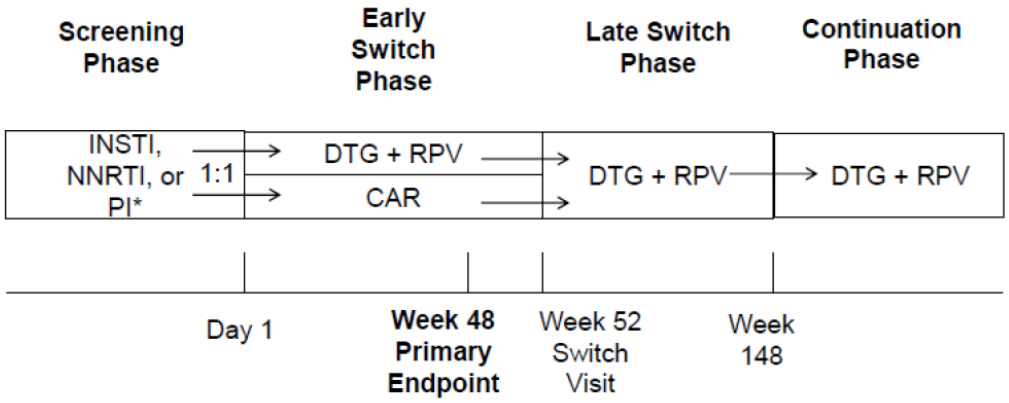
Study 201636 (SWORD-1) – *A Phase III, Randomized, Multicenter, Parallel-Group, Non- Inferiority Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Dolutegravir plus Rilpivirine from Current INI-, NNRTI-, or PI-Based Antiretroviral Regimen in HIV-1-Infected Adults who are Virologically Suppressed*

Study 201637 (SWORD-2). - *A Phase III, Randomized, Multicenter, Parallel-Group, Non- Inferiority Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Dolutegravir plus Rilpivirine from Current INI-, NNRTI-, or PI-Based Antiretroviral Regimen in HIV-1-Infected Adults who are Virologically Suppressed*

Methods

Eligible subjects were randomized 1:1 to continue their current antiretroviral regimen (CAR) or be switched to a 2-drug regimen of DTG + RPV administered once daily. At Week 48, individuals who were originally assigned to continue their CAR and remained virologically suppressed switched to DTG + RPV at Week 52 and are followed to Week 148 (Figure 5).

Figure 5. Study Schematic for 201636 (SWORD-1) and 201637 (SWORD-2)



*Plus 2 NRTIs

CAR = current antiretroviral regimen

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

Must be on uninterrupted current regimen (either the initial or second CAR) for at least 6 months prior to Screening.

Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening:

1 within the 6 to 12 month window, and 1 within 6 months prior to Screening.

No history of virologic failure.

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

No current or prior history of etravirine use.

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

Study Participants

Study participants had to be on an uninterrupted stable suppressive cART (either the initial or second regimen) containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI for at least 6 months prior to screening and any prior switch due to virological failure (with or without resistance) was not allowed. 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. Also, any current or prior use of etravirine was not allowed. Subjects included in the pivotal studies were on cART since a median time of approximately 4.5 years (range 8 - 270 months).

Treatments

Following randomization patients were assigned to DTG + RPV or to remain on their CAR for the first 52 weeks of the study.

Objectives

Primary Objective

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 experienced subjects.

Secondary Objectives

- To evaluate the immunological and antiviral activity of DTG + RPV once daily compared to continuation of CAR;
- To evaluate the safety and tolerability of DTG + RPV compared to continuation of CAR over time;
- To evaluate renal (in urine and blood), bone (in blood), cardiovascular biomarkers (in blood) and fasting lipids over time in subjects treated with DTG + RPV compared to continuation of CAR;
- To assess viral resistance in subjects that met Virologic Withdrawal Criteria;
- To evaluate DTG and RPV trough concentrations and over time during the initial post-switch period in the first 20 subjects who switched from EFV or NVP to DTG + RPV;
- To assess the impact of Baseline third agent treatment class (INSTI, NNRTI, or PI) on efficacy, safety and tolerability of DTG + RPV compared to continuation of CAR;
- To assess and compare treatment satisfaction and change in treatment symptom index for the two treatment groups

Exploratory Objectives

- To assess change in health-related quality-of-life, willingness to switch, and change in adherence
- To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4+) on antiviral and immunological responses to DTG + RPV compared to continuation of CAR
- To evaluate the effects of TDF on the change in eGFR using cystatin C and other renal biomarkers in subjects treated with DTG + RPV compared with continuation of TDF-containing CAR in the Early Switch Phase
- To evaluate the longer term antiviral/immunological effects, safety and tolerability of DTG + RPV in both, patients switching early or late.

Outcomes/endpoints

The primary endpoint was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E Population. Hypothesis testing was performed to confirm that maintenance of the suppression of HIV-1 replication by DTG + RPV would be non-inferior to that observed in the CAR arm of the study through Week 48.

A sub-study, 202094 (DEXA), is also being conducted to evaluate any change from Baseline in bone mineral density in subjects enrolled in either of the 201636 or 201637 studies following the switch from a triple ART regimen containing TDF to DTG + RPV.

The secondary efficacy endpoints for this study included change from Baseline in CD4+ lymphocyte counts and the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24. These efficacy endpoints were also assessed by Baseline third agent class.

Safety endpoints included incidence and severity of adverse events (AEs) and laboratory abnormalities, the proportion of subjects who discontinued treatment due to AEs, changes from Baseline in renal, bone, cardiovascular biomarkers, and change from Baseline in fasting lipids. These safety endpoints were also assessed by Baseline third agent class.

The virology endpoint was the incidence of observed genotypic and phenotypic resistance to CAR and to DTG or RPV for subjects meeting Virologic Withdrawal Criteria. This endpoint was also assessed by Baseline third agent class.

PK endpoints included pre-dose concentrations of DTG and RPV at Weeks 4, 24, 48, 56, 76, 100, or Withdrawal in subjects switching to DTG + RPV. In addition, pre-dose samples of DTG and RPV concentrations were collected at Weeks 2, 4, and 8 in the first 20 subjects who switched from EFV or NVP to DTG + RPV.

Health outcomes endpoints included change from Baseline in pre-specified treatment symptoms (using the Symptom Distress Module [SDM]) at Weeks 4, 24, 48, 56, 76, 100, and 148 (or Withdrawal), and treatment satisfaction as assessed by the HIV treatment satisfaction questionnaire (HIVTSQ) at Weeks 4, 24, 48, 56, 76, 100, and 148 (or withdrawal from the study).

Sample size

Non-inferiority of DTG+RPV versus CAR could be concluded if the lower bound of a 2-sided 95% confidence interval for the difference in response rates between the 2 treatment arms was greater than -10%. If rg is the response rate on DTG + RPV and rr is the response rate on comparator arm then the hypothesis can be as follows:

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

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

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

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

The final sample size was increased in order to recruit at least 100 subjects who would consent to participate in the follow-up 202094 sub-study to achieve 77% power in that study.

Randomisation

Randomization and study treatment assignment was facilitated by the interactive response technology (IRT) through the central Randomization and Medication Ordering System Next Generation (RAMOS NG). After a screening period of up to 28 days eligible subjects were registered using RAMOS NG and randomised in a 1:1 ratio to DTG + RPV or to remain on their CAR through Week 52, in accordance with the computer generated randomization schedule. Subject randomization was stratified by Baseline

third agent class (INSTI, NNRTI, or PI), age group (< or ≥ 50 years old), and planned participation in the DEXA substudy.

At Week 52, subjects who were originally randomly assigned to continue their CAR and who maintained viral suppression (HIV-1 RNA <50 c/mL), were switched to DTG + RPV once daily and were followed until Week 148. Subjects initially randomly assigned to receive DTG + RPV during the Early Switch Phase continued on that treatment arm through Week 148.

Blinding (masking)

Administration of DTG + RPV and CAR was in an open-label fashion throughout the study. A double-dummy design was not 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 enrolment.

Statistical methods

Analysis populations

The ITT population consisted of all randomised subjects. Subjects were assessed according to their randomised treatment even if no study treatment was taken or the wrong treatment was received.

Efficacy analyses were conducted based on the ITT-E population, which consisted of all randomly assigned subjects who received at least one dose of study drug. Subjects were assessed according to their randomised treatment, regardless of the treatment they received.

The PP population was defined as subjects in the ITT-E population with the exception of 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%.

Primary analysis

Primary endpoint was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E Population.

The Snapshot algorithm as recommended by US FDA is a detailed algorithm to determine a subject's response in in a time interval of interest (i.e., 'Virologic Success', 'Virologic Failure', or 'No Virologic Data at Week X'). The Snapshot algorithm treats all subjects without HIV-1 RNA data at the visit of interest, due to missing data or discontinuation of the investigational product prior to the visit window, as non-responders. Additionally, since changes in ART were not permitted in the pivotal studies, all subjects who changed ART were considered non-responders. Otherwise, virologic success or failure was determined by the last available HIV-1 RNA assessment while the subject was on treatment.

For the primary endpoint comparison, a Cochran-Mantel-Haenszel (CMH) test with strata for age (< 50 vs. ≥50 years) and baseline third agent class (PI, NNRTI, INI) was used. Adjusted estimates of the difference in the rate of responders between the two treatment arms were calculated together with two-sided 95% confidence intervals based on a stratified analysis using CMH weights. The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the 2 treatment groups.

Non-inferiority was to be concluded if the lower bound of the two-sided 95% confidence interval for the CMH adjusted difference in the proportion of patients who respond in the DTG+RPV group minus the proportion of patients who respond in the CAR group is greater than -10% for the within study analysis, and greater than -8% for the pooled analysis. The primary statistical analysis was repeated using the Per-protocol population and was compared for consistency with the results from the primary ITT-E population analysis. If both analyses would show non-inferiority the hypothesis that the antiviral effect of treatment with DTG+RPV is superior to treatment with CAR was to be tested at the two-sided 5% level of significance.

Non-inferiority margin

The non-inferiority margin of -10% applied in the pivotal studies could not be justified on a statistical basis due to the large number of comparator regimens in the study and the lack of placebo comparison data for many of the regimens. A non-inferiority margin -10% is a reasonable non-inferiority margin in order to demonstrate adequate preservation of treatment effect. In addition, data from the two studies with the same design were combined to assess non-inferiority at -8% to support regulatory assessment.

After the protocol was approved, the FDA updated their guidance on the choice of primary endpoint and associated non-inferiority margin for switch trials. Therefore, a secondary endpoint comparing the snapshot virological failure response rates between the DTG + RPV and CAR groups assessed using a NI margin of 4% was included. Given that previous switch studies have shown a snapshot virological failure rate of between 1% and 3%, this NI margin was considered stringent for this endpoint.

Assessment of homogeneity of results in subgroups

Weighted least squares chi-squared statistic according to the textbook by Fleiss JL (Wiley 1981) was used to test for homogeneity across the levels of categorical variables as one-way test with variables considered separately. Following the method proposed by Lui KJ and Kelly C (Biometrics 2000), a value of one half was added to each cell in any strata for which the stratum-specific rate estimates of response rates in the new treatment or control arm were zero. Homogeneity tests were performed as one-sided tests. Any heterogeneity found to be statistically significant was to be explored and if necessary results were to be reported for each level of the categorical variable. Investigation of heterogeneity was confined to the primary endpoint using the Week 48 Snapshot analysis. Tests of homogeneity were assessed at one-sided 10% alpha level.

Additionally, exploratory analyses for subgroup factors (age, race, gender, country, baseline CD4+ cell count, CDC center category, baseline vitamin D, baseline calcium, baseline smoking, baseline alcohol consumption, baseline BMI, duration of prior TDF expose) were performed, partly in the DEXA sub-study patients. Unadjusted difference in proportions between treatment groups and corresponding two-sided 95% CI are presented by subgroup. In case of a statistical interaction, a summary of study outcomes by subgroup is presented.

Secondary analyses

Secondary analyses of efficacy data included a repeat of the primary snapshot analysis as described above at Week 24 (conducted at the primary Week 48 analysis time point) and an analysis of the difference in the snapshot virological failures using a 4% non-inferiority margin. Confidence intervals for the difference between the treatment arms in the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 using a snapshot analysis are also presented by baseline third agent class. The proportion

of subjects without virologic (ERDF) or virologic/tolerability (TRDF) failure was estimated using the Kaplan-Meier nonparametric method based on the time to CVW or treatment related/efficacy related discontinuation (i.e., drug-related AE, protocol defined safety stopping criteria, or lack of efficacy). Subjects who had not met CVW criteria and were ongoing in the study, or who had discontinued for reasons other than those related to treatment/lack of efficacy, were censored. The estimate of the standard error used to derive CIs for the difference in proportions between treatment groups was based on Greenwood's formula (Kalbfleisch JD and Prentice RL, Wiley 1980). The estimated proportion of subjects without CVW and not discontinued due to treatment related/efficacy related reasons at Week 48 was presented by treatment group, along with estimated difference in proportions between treatment groups and its associated 2-sided 95% CI.

Interim analysis

An interim analysis was performed for the IDMC to evaluate the efficacy of DTG + RPV prior to the final analysis with a futility rule, details of assessment and operating characteristics pre-specified in the IDMC Charter. The interim futility analysis was performed approximately 9 months after "first subject first visit". The sponsor remained blinded to this analysis.

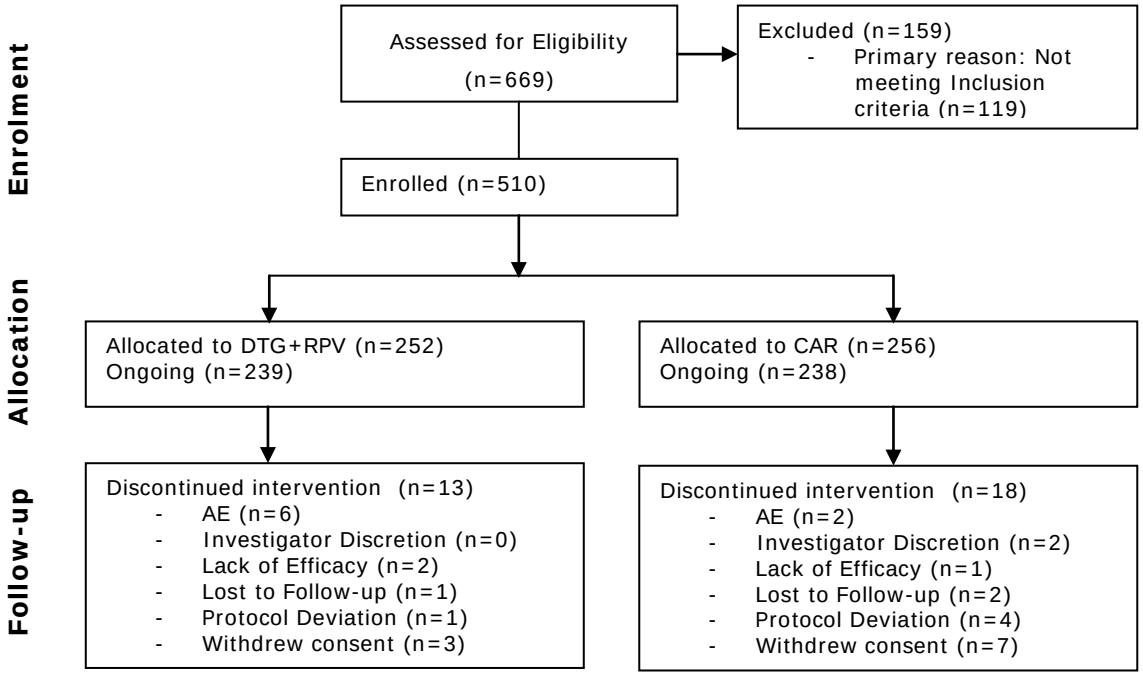
The main analysis of the pivotal studies was conducted to evaluate the primary objective of the protocol when all subjects completed their Week 48 visit. Additional analyses will be conducted when all subjects have either prematurely withdrawn from the study or completed the study by transitioning to commercial supplies.

DEXA Analyses

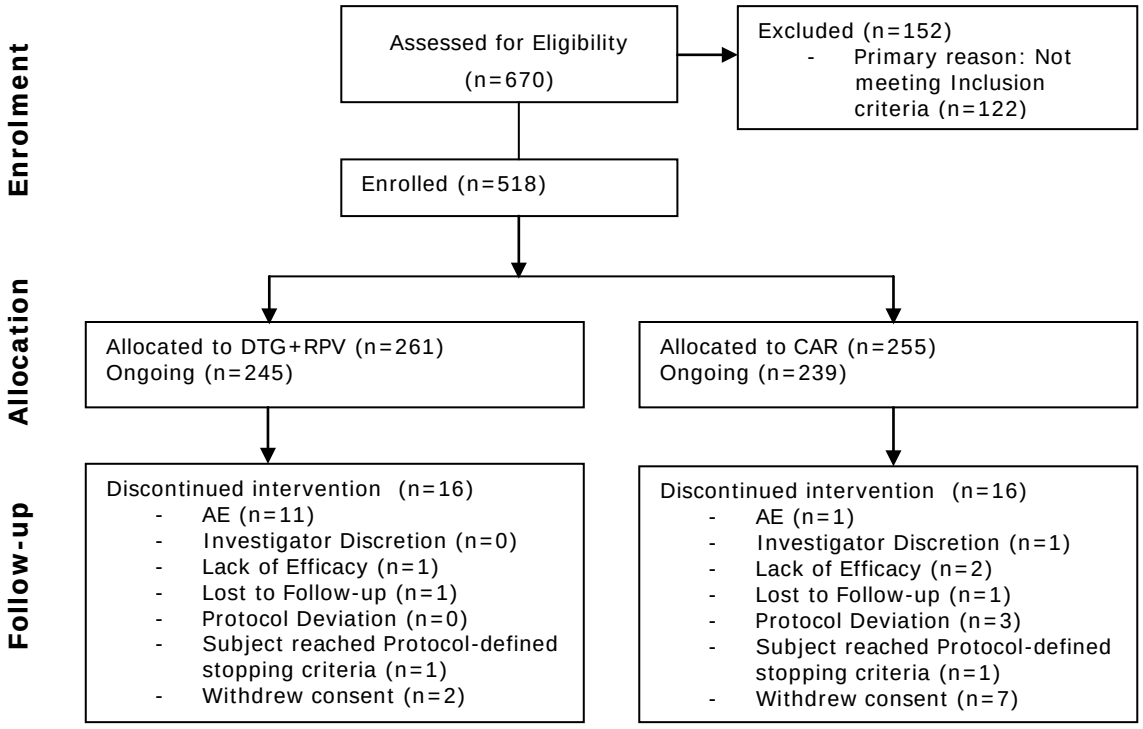
For the population in the DEXA substudy, analyses of total hip BMD assessed by areal density (g/cm^2) were performed at Week 48 and subgroup analyses for total hip BMD by subgroup were provided.

Results

Participant flow - Study 201636 (SWORD-1)



Study 201637 (SWORD-2)



Recruitment

Study 201636 (SWORD-1): First Subject First Visit: 14 April 2015, ongoing study.
Last Subject Last Visit for Week 48 analysis: 16 September 2016. The data cut-off for the Week 48 analysis was 22 November 2016.

Study 201637 (SWORD-2): First Subject First Visit: 21 April 2015, ongoing study.
Last Subject Last Visit for Week 48 analysis: 16 September 2016. The data cut-off for the Week 48 analysis was 22 November 2016.

A total of 513 subjects were randomized (1:1) to receive DTG + RPV and 511 subjects remained on their CAR. Similar proportions of subjects in each treatment group withdrew from the study (6% compared to 7%; (Table 12). The most common reason for withdrawal was adverse events (DTG + RPV: 3%; CAR: <1%). Less than 1% of subjects from both groups were withdrawn from the study due to investigator's assessment of lack of efficacy

Table 8. Summary of Subject Disposition for Studies 201636 and 201637 Pooled Data (ITT-E Population)

Number of subjects, n (%)	201636		201637		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[a]	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)
Subject 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)

Conduct of the study

Protocol amendments

There were 2 amendments to the original protocols dated 3 November 2014 for SWORD-1 and -2. Amendment No. 1 (26 February 2015) was implemented prior to enrolment of any subjects in the study and included mainly the extra stratification factor "planned participation in the Dexa substudy" and additional PK visits. 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.

Protocol deviations

In SWORD-1 and SWORD-2, 56 subjects (26 in DTG+RPV arm and 30 in CAR arm) and 58 subjects (30 in DTG+RPV arm and 28 in CAR arm) respectively were excluded from the Per Protocol Population due to “important” protocol deviations. The most common important protocol deviations were not meeting eligibility criteria and taking prohibited medications.

Baseline data

SWORD-1 and SWORD-2

Demographic and baseline characteristics

Demographic and baseline characteristics were well balanced across treatment groups and studies (Table 9 and Table 10).

Table 9. Summary of Demographic Characteristics for Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Age (y), 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

Table 10. Summary of Baseline Characteristics for Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		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 c/mL	247(98)	253 (99)	259 (99)	251 (98)	506 (99)	504 (99)
≥50 c/mL	5 (2)	3 (1)	2 (1)	4 (2)	7 (1)	7 (1)
Baseline CD4+ (log_{10} cells/mm^3)						
Median	2.786	2.805	2.785	2.798	2.786	2.805
Min., Max.	1.57, 3.18	1.98, 3.18	2.06, 3.25	2.03, 3.22	1.57, 3.25	1.98, 3.22
Hepatitis B & C Test Results						
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)

Antiretroviral Therapy at Screening

Antiretroviral therapies received by study participants at Screening constituted CAR for subjects randomized to this group on Day 1. As per the protocol for these studies, all subjects (100%) were receiving NRTIs as part of their ART regimen at screening. The most commonly reported individual NRTIs were TDF (DTG + RPV: 73%; CAR: 70%) and FTC (DTG + RPV: 69%; CAR: 67%).

In addition, 54% of subjects in both groups were receiving NNRTIs, 26% of subjects in the DTG + RPV group and 27% of subjects in the CAR group were receiving PIs, and 20% in the DTG + RPV group and 19% of subjects in the CAR group were receiving INSTIs at screening.

Furthermore, these studies limited the enrolment of subjects with prior exposure to DTG or RPV to approximately 10%. In the DTG + RPV group, 6% and 6% of subjects were receiving DTG or RPV, respectively, at Screening. Similar percentages were noted in the CAR group (8% and 6% of subjects were receiving DTG or RPV, respectively).

No patient on a regimen containing tenofovir alafenamide was included.

Numbers analysed

Efficacy analyses were conducted based on the ITT-E population, which 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 they received.

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.

The PP population was defined as subjects in the ITT-E population with the exception of 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%.

	ITT		ITT-E		PP	
	DTG+RPV	CAR	DTG+RPV	CAR	DTG+RPV	CAR
SWORD-1	254	256	252	256	226	226
SWORD-2	262	256	261	255	231	227
Pooled	516	512	513	511	457	453

Outcomes and estimation

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

Overall, 95% and 94% of subjects in the DTG + RPV group and 96% and 94% of subjects in the CAR group achieved the primary efficacy endpoint of plasma HIV-1 RNA <50 c/ml at Week 48. The analysis demonstrated that DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference for the individual studies (-4.3% and -3.9% for SWORD-1 and -2, respectively) is greater than -10%. Also the pooled analysis demonstrated that DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.0%) is greater than -8%.

The results from the PP population were consistent with those from the ITT-E (primary) population (Table 12).

Table 11. Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/ml at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (ITT-E Population)

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

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

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

Table 12. Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/ml at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (PP Population)

Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
201636				
DTG + RPV	226	217 / 226 (96%)	-0.4 (-4.0, 3.1)	-0.6 (-4.1, 2.9)
CAR	226	218 / 226 (96%)		
201637				
DTG + RPV	231	220 / 231 (95%)	-0.4 (-4.2, 3.5)	-0.4 (-4.3, 3.5)
CAR	227	217 / 227 (96%)		
Pooled Data				
DTG + RPV	457	437 / 457 (96%)	-0.4 (-3.0, 2.2)	-0.5 (-3.1, 2.1)
CAR	453	435 / 453 (96%)		

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

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

Secondary endpoints

Virologic response rates were the same between the DTG + RPV and CAR treatment groups (95%) (Table 13)

For subjects in the Snapshot category of 'No virologic data', as would be expected in open-label switch studies, there were fewer discontinuations due to AEs or death in the CAR group (3 subjects) where subjects have already taken at least 6 months of stable treatment, compared to the DTG + RPV group (17 subjects). In contrast there were fewer disconnections due for 'Other' reasons in the DTG + RPV group (7 subjects) compared with the CAR group (16 subjects). Of the 16 'Other reasons' for discontinuation in the CAR group, 5 withdrew consent, 6 had protocol deviations, 2 were lost to follow-up, 2 relocated, and 1 cited burden of travel. Of the 7 'Other reasons' for discontinuation in the DTG + RPV group, 3 withdrew consent, 2 relocated, 1 was lost to follow-up, and 1 became pregnant.

Table 13. Summary of Study Outcomes (Plasma HIV-1 RNA <50 c/ml) at Week 48 – Snapshot Analysis in Studies 201636, 201637, and Pooled Data (ITT-E Population)

Outcome n (%)	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Virologic Success	240 (95)	245 (96)	246 (94)	240 (94)	486 (95)	485 (95)
Virologic Failure	2 (<1)	2 (<1)	1 (<1)	4 (2)	3 (<1)	6 (1)
Data in window not below threshold	0	1 (<1)	0	1 (<1)	0	2 (<1)
Discontinued for lack of efficacy	2 (<1)	0	0	2 (<1)	2 (<1)	2 (<1)
Discontinued for other reason while not below threshold	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Change in ART	0	0	0	1 (<1)	0	1 (<1)
No Virologic Data	10 (4)	9 (4)	14 (5)	11 (4)	24 (5)	20 (4)
Discontinued study due to AE or Death	5 (2)	2 (<1)	12 (5)	1 (<1)	17 (3)	3 (<1)
Discontinued study for Other Reasons	5 (2)	7 (3)	2 (<1)	9 (4)	7 (1)	16 (3)
Missing data during window but on study	0	0	0	1 (<1)	0	1 (<1)

The proportion of subjects who were classified as Snapshot virological failures at Week 48 is summarized in Table 14. These results indicate that the combined use of DTG + RPV is non-inferior to CAR based on snapshot virologic failure with a non-inferiority margin of 4%. The upper bound of the 95% CI for the adjusted treatment difference (0.5%) is less than 4%.

Table 14. Analysis of Proportion of Subjects Classified as Virological Failures[a] at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (ITT-E Population)

Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion (95% CI)[b]	Adjusted Difference in Proportion (95% CI)[c]
201636				
DTG + RPV	252	2 / 252 (<1%)	0.0 (-1.5, 1.5)	0.0 (-1.3, 1.4)
CAR	256	2 / 256 (<1%)		
201637				
DTG + RPV	261	1 / 261 (<1%)	-1.2 (-2.9, 0.5)	-1.0 (-2.4, 0.5)
CAR	255	4 / 255 (2%)		
Pooled Data				
DTG + RPV	513	3 / 513 (<1%)	-0.6 (-1.7, 0.6)	-0.5 (-1.4, 0.5)
CAR	511	6 / 511 (1%)		

a. Virologic failures include subjects who had plasma HIV-1 RNA ≥ 50 c/mL at Week 48, who discontinued due to lack of efficacy, who discontinued for other reasons while not <50 c/mL, and who changed in ART.

b. Difference: Proportion on DTG - Proportion on Current ART Regimen

c. Based on Cochran-Mantel Haenszel stratified analysis adjusting for age (<50, ≥50 years old) and Baseline third agent class (PI, NNRTI, INSTI).

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

Ancillary analyses

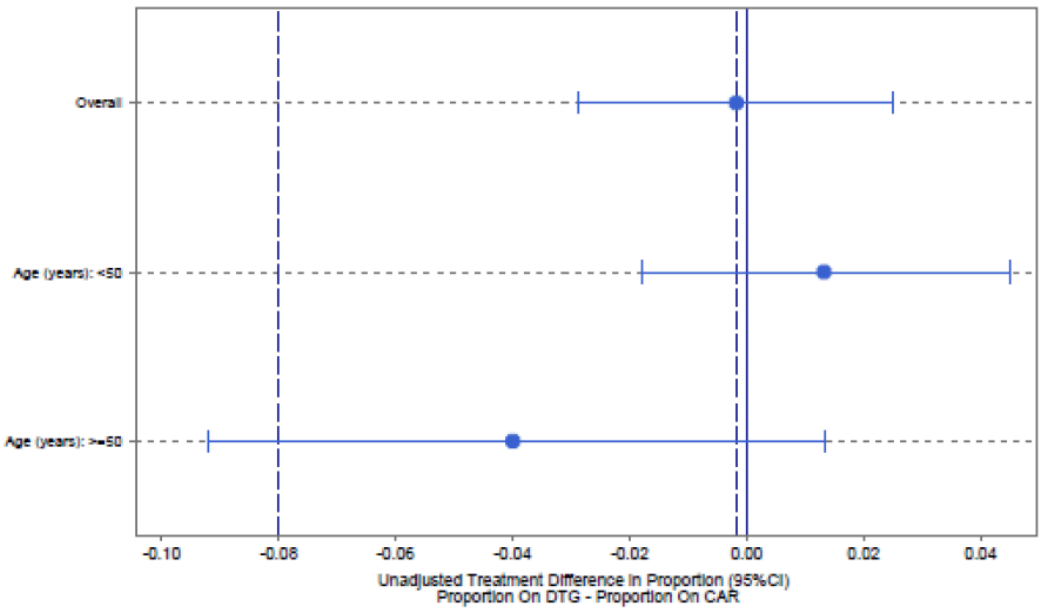
To assess the generalizability of the primary analysis results, consistency of the treatment difference was explored within subgroups. One-way homogeneity across the levels of each variable used to

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

Age Subgroup analyses

Treatment differences across age subgroups support the primary endpoint. The test for heterogeneity for an effect of age on the proportion of subjects with HIV-1 RNA <50 c/ml was statistically significant (p=0.091). This difference was driven by higher numbers of subjects in the "No Virologic Data at Week 48" category, which includes subjects who were withdrawn due to both the subgroupings of "other reasons" and "AEs leading to discontinuation" in the <50 years of age subgroup compared to the ≥50 years of age subgroup. This was not driven by a difference in virologic failure between the age groups.

Figure 6. Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/ml at Week 48 by Age Subgroups for the Pooled Data – Snapshot Analysis



Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.
The dashed reference line on the right represents the overall difference in proportion (DTG + RPV – CAR).

Table 15. Summary of Study Outcomes (<50 c/ml) at Week 48 Snapshot Analysis by Age Subgroup in the Pooled Data - Snapshot Analysis (ITT-E Population)

n (%)	<50 years		≥50 years		All Pooled Data	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
n	**366**	**369**	**147**	**142**	**513**	**511**
Virologic Success	350 (96)	348 (94)	136 (93)	137 (96)	486 (95)	485 (95)
Virologic Failure	1 (<1)	5 (1.4)	2 (1)	1 (<1)	3 (<1)	6 (1)
Data in window not below threshold	0	1 (<1)	0	1 (<1)	0	2 (<1)
Discontinued for lack of efficacy	0	2 (<1)	2 (1)	0	2 (<1)	2 (<1)
Discontinued for other reason while not below threshold	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Change in ART	0	1 (<1)	0	0	0	1 (<1)
No Virologic Data	15 (4)	16 (5)	9 (6)	4 (3)	24 (5)	20 (4)
Discontinued study due to AE or Death	11 (3)	2 (<1)	6 (4)	1 (<1)	17 (3)	3 (<1)
Discontinued study for Other Reasons	4 (1)	13 (4)	3 (2)	3 (2)	7 (1)	16 (3)
Missing data during window but on study	0	1 (<1)	0	0	0	1 (<1)

Table 16. Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by Age Subgroups in the Pooled Data - Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion % (95% CI)[a]
Age (years)	<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)	
	p-value for Test of Homogeneity[b]				0.091

a. Proportion on DTG – Proportion on CAR (unadjusted).

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

Race Subgroup analyses

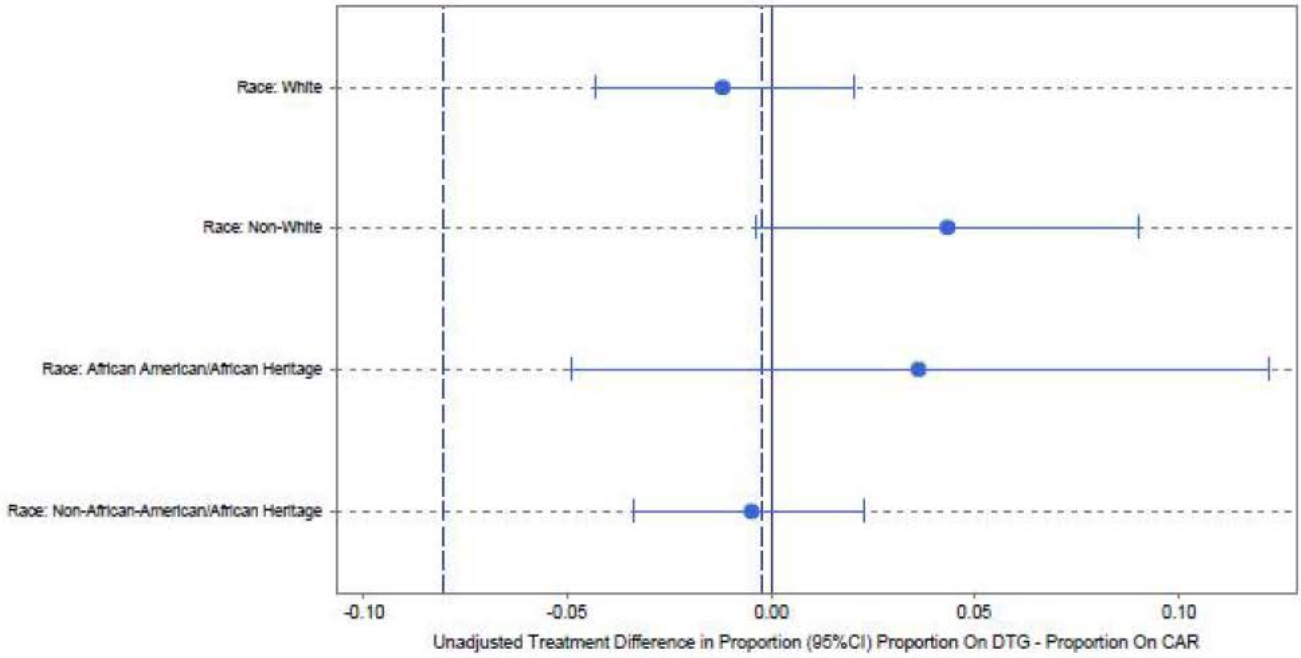
Figure 7 shows the treatment difference across race subgroup categories.

The test for heterogeneity for an effect of race for White versus Non-White subjects for the proportion of subjects with HIV-1 RNA <50 c/ml was statistically significant for the pooled analysis (p=0.058). This difference was also statistically significant for the 201637 study (p=0.06), but not for the 201636 study (p=0.592). This difference is driven by the 99% response rate in the Non-White race subgroup within the DTG + RPV treatment group.

The test for heterogeneity for an effect of race for African American/African versus Non- African American/African subjects for the proportion of subjects with HIV-1 RNA <50 c/ml was not statistically

significant for the pooled analysis (p=0.374). This difference was also not statistically significant for the individual studies.

Figure 7. Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/ml at Week 48 by Race Subgroups for the Pooled Data – Snapshot Analysis



Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.
The dashed reference line on the right represents the overall difference in proportion (DTG + RPV - CAR).

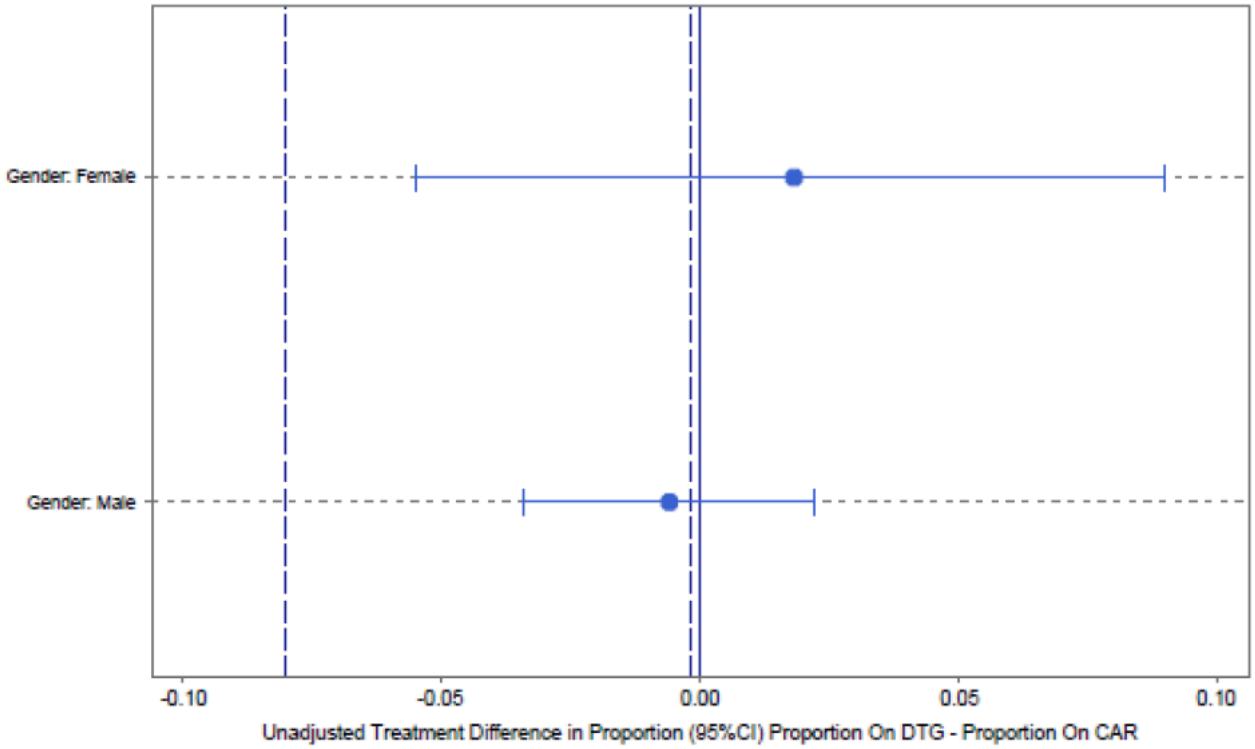
Table 17. Summary of Study Outcomes (<50 c/ml) at Week 48 Snapshot Analysis by Race Subgroup in the Pooled Data - Snapshot Analysis (ITT-E Population)

n (%)	White		Non-White		All Pooled Data	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
n	**421**	**400**	**92**	**111**	**513**	**511**
Virologic Success	**395 (94)**	**380 (95)**	**91 (99)**	**105 (95)**	**486 (95)**	**485 (95)**
Virologic Failure	**3 (<1)**	**3 (<1)**	**0**	**3 (3)**	**3 (<1)**	**6 (1)**
Data in window not below threshold	0	1 (<1)	0	1 (<1)	0	2 (<1)
Discontinued for lack of efficacy	2 (<1)	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)
Discontinued for other reason while not below threshold	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Change in ART	0	0	0	1 (<1)	0	1 (<1)
No Virologic Data	**23 (5)**	**17 (4)**	**1 (1)**	**3 (3)**	**24 (5)**	**20 (4)**
Discontinued study due to AE or Death	17 (4)	2 (<1)	0	1 (<1)	17 (3)	3 (<1)
Discontinued study for Other Reasons	6 (1)	14 (4)	1 (1%)	2 (2)	7 (1)	16 (3)
Missing data during window but on study	0	1 (<1)	0	0	0	1 (<1)

Gender Subgroup analyses

The participants were over 20% female, which was an intended goal of the studies in order to provide substantial comparative data in this demographic. The test for heterogeneity for an effect of gender on the proportion of subjects with HIV-1 RNA <50 c/ml was not statistically significant (p=0.550).

Figure 8. Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/ml at Week 48 by Gender Subgroups for the Pooled Data – Snapshot Analysis



Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.

The dashed reference line on the right represents the overall difference in proportion (DTG + RPV - CAR).

Summary of main studies

The following table summarises the efficacy results from the main studies supporting the present application.

Title: A Phase III, Randomized, Multicenter, Parallel-Group, Non-Inferiority Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Dolutegravir plus Rilpivirine from Current INI-NNRTI- or PI-based Antiretroviral Regimen in HIV-1 Infected Adults who are Virologically Suppressed			
Study identifier		201636 (SWORD-1) and 201637 (SWORD-2)	
Design		Randomized, multicenter, parallel-group, non-inferiority, switch study in patients on stable first or second regimen with no evidence of virologic non-response or failure.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks (Early switch phase) not applicable 96 weeks (late switch phase) +continuation phase till commercial

Hypothesis		H0: rg – rr ≤ -10% H1: rg – rr > -10%. Each study is designed to show that the antiviral effect of a regimen of DTG + RPV is non-inferior to standard INI-, NNRTI-, or PI-based ART regimens at Week 48. Non-inferiority can be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -10%; in the pooled analysis greater than - 8%.		
Treatments groups	Study group (DTG + RPV)			Dolutegravir 50 mg + Rilpivirine 25 mg tablets, 48 weeks (up to 148 weeks) N=513
	Control group (CAR)			Continued antiretroviral regimen, 48 weeks, N=511
Endpoints and definitions	Primary endpoint	HIV-1 RNA < 50 c/ml week 48 (ITT-E)		Proportion of subjects with plasma HIV-1 RNA < 50 copies /ml at week 48 (snapshot analysis), ITT-E population) Unadjusted and adjusted for stratification factors age and BL third agent. The Per-protocol population analyzed and compared for consistency (impact of major protocol deviations)
	Secondary endpoint	HIV-1 RNA < 50 c/ml week 48 (PP)		Proportion of subjects with plasma HIV-1 RNA < 50 copies /ml at week 48 (snapshot analysis), PP-population
	Secondary endpoint	Δ CD4 cell count by visit		Change from Baseline in CD4+ Lymphocyte Count by Visit (ITT-E Population)
	Other endpoint	HIV-1 Disease Progression		Incidence of HIV-1 Disease Progression (HIV-associated Conditions and AIDS)
Database lock		22 November 2016		

Results and Analysis

Analysis description		**Primary Analysis:** Stratified Cochran-Mantel-Haenszel test, strata for age (< 50 vs. ≥50 years) and baseline third agent class (PI, NNRTI, INI)			
Analysis population and time point description		Intent to treat- Efficacy: all randomised subjects who received at least one dose of study treatment Per protocol population At Week 48			
		Study 201636		Study 201637	
Descriptive statistics and estimate variability	Treatment group	DTG+RPV	CAR	DTG+RPV	CAR
	Number of subject	252	256	261	255
	HIV-1 RNA < 50 c/ml week 48 (ITT-E) Difference in proportion) unadjusted [adjusted]	-0.5 [-0.6]		0.1 [0.2]	
	variability (95% CI)	-4.1; 3.2		-3.9; 4.2	
	Pooled data	-0.2 (-2.9; 2.5)			
Analysis description		**Secondary analyses**			
Effect estimate per comparison	Secondary endpoint	HIV-1 RNA < 50 c/ml week 48 (PP), Pooled data	DTG+RPV	CAR	
			Difference in proportion (stratified CMH test, as for primary analysis)	-0.4	
			95% CI	-3.0; 2.2	

	Secondary endpoint	Δ CD4 cell count by visit Pooled data (descriptive)	DTG+RPV	CAR
		week 48	28	22.0
		95% CI	-55.0; 112.5	-48.0; 126.0
	Other endpoint	HIV-1 Disease Progression/HIV associated events (descriptive)	DTG+RPV	CAR
		N (disease progression)	7	1
		N (HIV associated events)	11	0

Analysis performed across trials (pooled analyses)

Since the two Phase III studies were of identical design, and results of the individual studies were for the vast majority of results very much in line with each other, pooled data is shown under summary of main studies and in Table 22. These data were included in Table 3 of the SmPC.

Table 18. Virologic Outcomes of Randomized Treatment at Week 48 (Snapshot algorithm)

	SWORD-1 and SWORD-2 Pooled Data* **	
	DTG + RPV N=513 n (%)	**CAR N=511 n (%)**
HIV-1 RNA <50 copies/mL	486 (95%)	485 (95%)
Treatment Difference*	-0.2 (-3.0, 2.5)	
Virologic non response**	<3 (1%)	6 (1%)
Reasons		
Data in window not <50 copies/mL	0	2 (<1%)
Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
Discontinued for other reasons while not <50 copies/mL	1 (<1%)	1 (<1%)
Change in ART	0	1 (<1%)
No virologic data at Week 48 window	24 (5%)	20 (4%)
Reasons		
Discontinued study/study drug due to adverse event or death	17 (3%)	3 (<1%)
Discontinued study/study drug for other reasons	7 (1%)	16 (3%)
Missing data during window but on study	0	1 (<1%)
HIV-1 RNA <50 copies/mL by baseline covariates		
	n/N (%)	n/N (%)
Baseline CD4+ (cells/ mm^3)		
<350	51 / 58 (88%)	46 / 52 (88%)
≥350	435 / 455 (96%)	439 / 459 (96%)
Baseline Third Treatment Agent Class		
INI	99 / 105 (94%)	92 / 97 (95%)
NNRTI	263 / 275 (96%)	265 / 278 (95%)
PI	124 / 133 (93%)	128 / 136 (94%)
Gender		
Male	375 / 393 (95%)	387 / 403 (96%)
Female	111 / 120 (93%)	98 / 108 (91%)
Race		
White	395 / 421 (94%)	380 / 400 (95%)
African-America/African Heritage/Other	91 / 92 (99%)	105 / 111 (95%)
Age (years)		
<50	350 / 366 (96%)	348 / 369 (94%)
≥50	136 / 147 (93%)	137 / 142 (96%)

* Adjusted for baseline stratification factors and assessed using a non-inferiority margin of - 8%.

** Non-inferiority of dolutegravir plus rilpivirine to CAR, in the proportion of subjects classified as virologic non-responders, was

demonstrated using a non-inferiority margin of 4%. Adjusted difference (95% CI) -0.6 (-1.7, 0.6).

*** The results of the pooled analysis are in line with those of the individual studies, for which differences in proportions meeting the primary endpoint of <50 copies/mL plasma HIV-1 RNA at Week 48 (based on the Snapshot algorithm) for DTG+RPV versus CAR were -0.6 (95% CI: -4.3; 3.0) for SWORD-1 and 0.2 (95% CI: -3.9; 4.2) for SWORD-2 with a preset non-inferiority margin of -10%.

N = Number of subjects in each treatment arm

CAR = current antiretroviral regimen; DTG+RPV = dolutegravir plus rilpivirine;

INI = Integrase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor;

PI = Protease Inhibitor

Clinical studies in special populations

Clinical studies in special populations have not been conducted with Juluca, the fixed dose combination tablet of DTG 50 mg and RPV 25 mg. With respect to investigation of the dual regimen DTG+RPV no upper age limit was defined for inclusion in Studies 201636 and 201637. According to the data presented the age range in these two studies was from 21 to 79 years. A detailed age distribution is displayed below.

		201636		**201637**		**POOLED**	
	Age groups	**DTG + RPV (N=252)**	**CAR (N=256)**	**DTG + RPV (N=261)**	**CAR (N=255)**	**DTG + RPV (N=513)**	**CAR (N=511)**
Controlled Trials	**Age 60-65 (Older subjects number /total number)**	14/252 (6%)	8/256 (3%)	15/261 (6%)	8/255 (3%)	29/513 (6%)	16/511 (3%)
	Age > 65-70 (Older subjects number /total number)	3/252 (1%)	5/256 (2%)	4/261 (2%)	2/255 (<1%)	7/513 (1%)	7/511 (1%)
	Age > 70-75 (Older subjects number /total number)	4/252 (2%)	4/256 (2%)	2/261 (<1%)	0/255	6/513 (1%)	4/511 (<1%)
	Age > 75 (Older subjects number /total number)	1/252 (<1%)	1/256 (<1%)	1/261 (<1%)	0/255	2/513 (<1%)	1/511 (<1%)
Non Controlled Trials		-	-	-	-	-	-

Supportive studies

Study LAI116482 (LATTE) is an ongoing Phase IIb study evaluating the utility of a 2-drug, 2-class combination of cabotegravir (CAB) + RPV once daily. Data from this study provided proof of principle for RPV combined with an INSTI as an effective 2-drug regimen for the maintenance of virologic suppression [Margolis, 2015]. A rapid and sustained response was observed across all CAB treatment

arms, with ≥ 80% of subjects achieving the primary endpoint of plasma HIV-1 RNA <50 c/ml by Week 48. In addition, data at Week 96 (72 weeks on 2- drug therapy) showed that more subjects on CAB + RPV remained suppressed (HIV-1 RNA <50 c/ml) compared to EFV +2 NRTI drugs (CAB Subtotal: 76%; EFV: 63%). While the virologic response in the CAB 60 mg arm was numerically higher than the 10 mg and 30 mg arms, the difference was driven primarily by low level viremia (data in window not below threshold) and non-virologic discontinuations (discontinuations for other reasons). Furthermore, there were fewer virologic non-responders using the Snapshot algorithm through Week 96 in the CAB arm compared to the EFV arm. These data indicate that a 2-drug regimen of RPV, in combination with an INSTI, can provide long-term efficacy.

Two other studies (SINGLE and SPRING-2) have been listed as supportive studies; a brief summary is shown in Table 23.

Table 19. Summary of Supportive SE Studies for Efficacy

Study	Study Title	SE study efficacy conclusions
ING114467 (SINGLE) (DTG)	A Phase 3, randomized, double blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects	At Week 48, 88% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 81% of participants on the single tablet regimen Atripla [difference and 95% CI; 7.4% (+2.5% to +12.3%); difference in the primary endpoint was statistically significant, p=0.003]. At Week 96, 80% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 72% of participants on the single tablet regimen Atripla [difference and 95% CI; 8.0% (+2.3% to +13.8%); difference in the primary endpoint was statistically significant, [p=0.006]. Response rates on DTG+ ABC/3TC and Atripla were generally consistent across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. At Week 144, 71% of study participants in the DTG + ABC/3TC treatment group were virologically suppressed (<50 c/mL) versus 63% of participants on the single tablet regimen of Atripla [adjusted difference and 95% CI; 8.3% (+2.0% to +14.6%); difference in the primary endpoint was statistically significant, [p=0.010]; therefore, statistical superiority at Week 144 was maintained. Differences in the Snapshot analysis were primarily driven by a lower rate of discontinuation due to AEs in the DTG + ABC/3TC treatment group. Response rates were similar between the DTG + ABC/3TC and the Atripla treatment groups across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. The longer term end-of-study data support the safety of DTG in combination with ABC/3TC once daily in an HIV infected treatment-naive patient population. The majority of subjects receiving DTG + ABC/3TC FDC who entered the continuation phase past Week 144 maintained viral suppression, based on an observed analysis. In the DTG + ABC/3TC FDC arm, antiviral response was sustained with 93% (193/207) of subjects with HIV-1 RNA <50 c/mL at Week 156 based on the observed data. The data from this completed study continue to support the use of DTG 50 mg + ABC/3TC once daily for the management of HIV infection in INSTI-naive subjects
ING113086 (SPRING-2) (DTG)	A Phase III, randomized, double blind study of the safety and efficacy of GSK1349572 50 mg once daily compared to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects	At Week 48, Data through 96 weeks support DTG 50 mg once daily for INSTI-naive subjects, and provide evidence for durable efficacy and tolerability for DTG in combination therapy. In this study, DTG has shown noninferior efficacy and a safety profile similar to RAL with no evidence of treatment emergent resistance in virologic failure. DTG administered once daily with 2 NRTIs demonstrated non-inferiority to RAL at Week 96 and was associated with good treatment response. DTG performed as well as RAL regardless of baseline viral load or background dual NRTI. DTG performed as well as RAL across demographic subgroups, including race, gender, age, HIV risk factors, Baseline CD4+ cell count and Baseline CDC category. At Week 96, DTG administered once daily with 2 NRTIs demonstrated non-inferiority to RAL at Week 96 and was associated with good treatment response. The proportion of subjects with HIV RNA <50 c/mL (81%) compared favorably with RAL (76%) through 96 weeks. DTG performed as well as RAL

		regardless of baseline viral load or background dual NRTI. DTG performed as well as RAL across demographic subgroups, including race, gender, age, HIV risk factors, Baseline CD4+ cell count and Baseline CDC category.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Studies 201636/201637

The development program for Juluca is primarily based on 2 identical pivotal Phase 3 studies (SWORD-1 and -2), and a pivotal BE study to bridge from the individual components administered in the SWORD studies to the fixed dose product intended for marketing. This is acceptable for this fixed-dose combination tablet consisting of two known active substances. No new dose response studies have been performed, which is acceptable. Clinical data from study LAI116181 showed the absence of a drug/drug interaction between DTG and RPV and hence that there is no need for a dose adjustment from approved doses when both products are used in combination.

The endpoints, including the proportion of subjects with plasma HIV-1 RNA <50 c/ml at Week 48 as primary efficacy endpoint, are considered relevant and acceptable. As the pivotal studies are switch studies, conducted in subjects who are virologically suppressed, the proportion of subjects who were classified as Snapshot virological failure at Week 48 is considered the most relevant endpoint and is therefore a main focus of the assessment. This type of study design is not specifically addressed in the CHMP guideline. CHMP, however the applicant obtained scientific advice on this matter.

Randomisation was stratified according to age (<>50 years), as the upper age group is prone to age-related risks such as CVD and might benefit from less NRTI-mediated adverse events.

Randomisation was also stratified according to class of third agent (NNRTI, PI, INSTI), which was considered appropriate. Exploratory analyses according to nucleos(t)ide backbone showed no differential outcome between the two study groups depending on nucleoside backbones used at baseline.

The primary endpoint, proportion of subjects at Week 48 with plasma HIV-1 RNA <50 c/mL, is a well-established surrogate endpoint for antiviral efficacy and is in line with the recommendations of the relevant CHMP guideline. The primary analysis population was the ITT-E population with PP-analysis for consistency. Although the ITT-population would have been the preferred analysis population, the ITT-E was acceptable, as the factual difference in patient numbers between these two populations is very small. The secondary and other exploratory efficacy endpoints were also regarded as appropriate. The study will continue for a total of 148 weeks and no comparative data versus CAR will be available after week 48, as all patients have switched to DTG+RPV thereafter.

For the primary endpoint comparison, a Cochran-Mantel-Haenszel test with strata for age (< 50 vs. ≤ 50 years) and baseline third agent class (PI, NNRTI, INI) was used. The statistical methods used for the primary analysis are considered adequate. Use of the stratified Cochran-Mantel-Haenszel test with additional analyses to assess the homogeneity of results in strata used for randomisation and subgroups was considered appropriate. Withdrawals were low and numerically similar in both treatment arms (about 6%). Withdrawal patterns showed that adverse events were the most common reason for study drop-out. The snapshot algorithm was used to determine virologic response; subjects with missing data or discontinuation of the investigational product were counted as non-responders.

Changes in ART were not permitted in the pivotal studies and all subjects who changed ART were also considered as non-responders.

The justification of the non-inferiority margin of -10% was considered acceptable. There was no formal interim analysis for efficacy. Procedures for the interim analyses for futility by an external IDMC were appropriate.

Formal hypothesis testing for the additional secondary endpoint, rate of virological failures support the conclusions from the primary analysis.

The combined Statistical Analysis Plan for the pivotal studies, covering the pivotal Week 48 analysis, a pooled analysis of studies 201636 and 201637 and a sequential analysis plan of data after the Week 48 analysis until study completion were considered appropriate. Amendments to the study protocol had no important impact on the statistical analyses and conclusions

A routine inspection of study 201636 was conducted and demonstrated the sites had a good level of GCP and protocol compliance.

Study 201674

In the relative BA study 201674 the bioavailability and the food effect of single doses of different prototype FDC DTG/RPV tablet formulations were investigated. To evaluate the food effect, PK data of different cohorts were compared. A direct comparison of the PK characteristics of the reference and test formulations under different food conditions would have been more appropriate for a reliable assessment.

Study 201676

The pivotal BE study 201676 which served as a bridge to the clinical efficacy and safety data compared the bioavailability of DTG and RPV when administered as FDC tablet with co-administration of the individual single entity products under moderate fat conditions.

Efficacy data and additional analyses

Studies 201636/201637

For both studies the point estimates for the difference in the primary endpoint were very close to zero with a narrow confidence interval and lower boundaries of up to -4.1 for the individual studies (201636) and -2.9 for the pooled analysis. Hence, non-inferiority of DTG+RPV versus CAR was proven, not exploiting the predefined non-inferiority margins.

Virological failures occurred at a very low percentage, in 3 patients in the DTG+RPV and 6 patients in the CAR-group, resulting in an adjusted difference in proportion of -0.5 (95% CI: -1.7; 0.6).

Despite the long mean duration of prior antiretroviral therapy of approximately 5 years CD4+-cell counts increased over the course of the studies in both groups and a differential effect between studies were observed. When corrected for stratification factors this difference was no longer apparent.

No subject in the CAR-group and 11 subjects in the DTG+RPV-group reported disease progression or recurrence of HIV-1 associated conditions. When disregarding the potentially non-objectively diagnosable events, i. e. constitutional symptoms and peripheral polyneuropathy, and otherwise confounded events one subject in the in the DTG+RPV group versus none in the CAR-group remain.

Further information related to this matter should be provided with the Week 100 SWORD study update and during marketing surveillance. Subgroup analyses showed no relevant difference in efficacy for gender, race or according to (prior) third line agent.

However, the dual regimen data indicated a better outcome with the dual regimen in younger age groups and in patients with less advanced disease (CDC category A or B), mainly due to more discontinuations due to adverse events in those >50 years of age and having CDC category C.

Adherence to DTG+RPV was assessed according to self-reporting and no objective measure of treatment adherence was applied. In none of the PROMs a difference between the treatment groups was observed. Hence, the anticipated benefits in terms of efficacy of the dual regimen were not substantiated with the submitted data and remain currently theoretical. As only the single entities were studied, the study was not suitable for substantiating the assumed benefit of the FDC on adherence.

A wide range of prior antiretroviral regimens was documented and no difference in efficacy was reported based on the baseline third agent used. This is considered reassuring in terms of generalizability of the results. However, the study population was highly preselected with respect to their therapeutic, virological and disease characteristics with a mean of 5 years of prior antiviral therapy, either on the first or second ARV regimen, with no ART change for virological/efficacy reasons, harbouring viruses with no evidence of any major PI, INSTI (including R263K), NRTI or NNRTI resistance mutation and being virologically suppressed for a minimum of 8 months. Further subgroup analyses according to prior ART-use and duration of virological suppression showed that 75% of the participants were on the first antiretroviral regimen and that the mean duration of use of the ART-regimen at screening was almost 4 years. Moreover, relevant comorbidities, such as CHB-infection and co-medications were excluded.

Self-reported adherence to study medications was – with intake of 98% of the doses- unusually high. It is not clear, if outside a study setting and in a less stringently selected population the regimen's efficacy would be the same.

Study 201674 and Study 201676

The data indicate a difference in the relevant PK parameters of RPV of different FDC formulations when administered after a moderate or high fat meal, particularly for the FDC "AM" which is claimed to be similar to the formulation "AW" used in the pivotal BE study 201676. For formulation "AM" mean Cmax was 20% higher and mean AUC0-t was about 22% higher after a high-fat meal compared to a moderate-fat meal, while data generated during the development of RPV SE tablets PK parameters (of the 75 mg tablet) under moderate and high fat conditions did not indicate any relevant differences and were considered comparable.

The CHMP concluded that the use of a moderate fat meal in the pivotal bioequivalence study as sufficiently sensitive and discriminatory to detect a difference between formulations.

Special populations

Children were excluded from the efficacy studies and a paediatric investigational plan is in place. While no upper age limit was set for the two SWORD studies and the oldest participant was 79 years old, only very few elderlies participated in these studies. Factually no data are available in HBV-co-infected patients. In total, only 28 patients with HCV-infection (not in immediate need of treatment) were included. Other relevant co-infection and comorbidities were either exclusion criteria or patients were

not included due to the requirement of non-permitted co-medications. This is reflected in the product information.

2.5.4. Conclusions on the clinical efficacy

Based on the submitted data, the dual combination of DTG and RPV is similarly efficacious as maintenance antiretroviral therapy in patients with stable virological suppression without known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

2.6. Clinical safety

The safety profile for DTG/RPV FDC is supported by two identical, ongoing, pivotal Phase III studies (201636 [SWORD-1] and 201637 [SWORD-2]) using DTG 50 mg + RPV 25 mg together as individual tablets. Additionally, a pivotal bioequivalence study in healthy adult volunteers (201676), a relative bioavailability study (201674) and a Phase I drug interaction study (LAI116181) were conducted. Furthermore, a dedicated DEXA sub-study was conducted (202094, ongoing, 48 week CSR completed) which enrolled subjects from the two Phase III clinical trials and is evaluating the change in bone mineral density of those subjects who have switched from a tenofovir containing regimen to DTG + RPV compared to those who remained on a tenofovir containing current regimen.

Patient exposure

Safety analyses were conducted based on the Safety Population, defined as all subjects who received at least 1 dose of study drug. The safety database consists of safety data from 1024 subjects (DTG + RPV 513; CAR 511) from the 2 identical Phase III studies 201636 and 201637 (pooled safety data are presented for those studies, cumulative through the Week 48 primary endpoint). The median time of exposure to DTG + RPV and CAR was 364 days (52 weeks). In the Early Switch Phase, a nearly equal number of patients were exposed for the whole 48 weeks of this study phase in the DTG + RPV and in the CAR group (483 (94 %) and 489 (95 %) respectively).

The safety data package is in line with recommendations outlined in Guideline on the clinical development of medicinal products for the treatment of HIV infection and is therefore considered to be adequate.

Adverse events

Any AEs were observed in 77% of subjects in the DTG + RPV group and 71% in the CAR group during the Early Switch Phase (Table 20). The majority of events reported had an intensity of Grade 1 or Grade 2 for both treatment groups (Table 21). There was a greater proportion of subjects reporting drug-related events, Grade 2-4 AEs, AEs leading to withdrawal, SAEs and drug-related SAEs in the DTG + RPV group compared with the CAR group. No drug-related fatal SAEs occurred in any subject on treatment. Imbalances in AE-rate become more obvious with increasing severity of the AEs.

Table 20. Overall Summary of Adverse Events during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any AE	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Drug-related AEs	47 (19)	5 (2)	50 (19)	4 (2)	97 (19)	9 (2)
Grade 2 to 4 AEs	72 (29)	68 (27)	76 (29)	52 (20)	148 (29)	120 (23)
Drug-related Grade 2 to 4 AEs	12 (5)	0	17 (7)	3 (1)	29 (6)	3 (<1)
AEs Leading to Withdrawal	9 (4)	2 (<1)	12 (5)	1 (<1)	21 (4)	3 (<1)
Drug-related AEs Leading to Withdrawal	5 (2)	0	9 (3)	1 (<1)	14 (3)	1 (<1)
Any SAE	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)
Drug-related SAEs	2 (<1)	0	2 (<1)	1 (<1)	4 (<1)	1 (<1)
Fatal SAEs	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Drug-related Fatal SAEs	0	0	0	0	0	0

Table 21. Summary of Adverse Events by Maximum Toxicity during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Grade 1	128 (51)	122 (48)	119 (46)	122 (48)	247 (48)	244 (48)
Grade 2	57 (23)	53 (21)	59 (23)	47 (18)	116 (23)	100 (20)
Grade 3	11 (4)	13 (5)	16 (6)	4 (2)	27 (5)	17 (3)
Grade 4	4 (2)	2 (<1)	1 (<1)	1 (<1)	5 (<1)	3 (<1)

The higher incidence of AEs in the DTG + RPV treatment group is most likely attributed to the open label and treatment switch design elements in Studies 201636 and 201637:

Firstly, it can be assumed that many AEs occur at the beginning of therapy so that subjects on stable therapy (i.e. subjects in the CAR treatment group) will report less AEs than those randomised to a new therapy regimen (i.e. subjects in the DTG + RPV treatment group). Comparing subjects stable on CAR with subjects newly switched to DTG+RPV can therefore be expected to create a bias in favour of CAR. Secondly, it must be assumed that according to study inclusion criterion, 2 subjects with relevant AEs under their previous therapy have been switched to a better tolerated treatment for at least 6 months prior to Screening. Therefore, subjects in the CAR group most likely receive a well-tolerated therapy as subjects with more severe AEs are no longer included; this condition is not given in the DTG + RPV group. Again it can be expected that this creates a bias in favour of CAR. The observation, that more serious AEs (grade 3 and 4) seem more imbalanced than less serious AEs (grade 1 and 2), supports this view.

Furthermore, most of the reported drug related events are well known and expected side effects of DTG and/or RPV and labelled in the corresponding SmPCs. The investigators were therefore aware about possible side effects of DTG and/or RPV. It is plausible, that the occurrence of those adverse

events in the DTG + RPV treatment arm will then be assessed as related to study treatment DTG + RPV by the investigators.

For a more in depth assessment of possible additive effects when using DTG and RPV in combination the Applicant provided comparison between the incidences of adverse events for DTG + RPV co-administered, and corresponding frequencies for those events for DTG and RPV given as single entities. Although it should be considered that a cross comparison between studies may be difficult e.g. because of different study populations, it can be overall concluded that based on the data provided additive side effects seem to be unlikely.

A comparison of AE incidences between the Late Switch DTG + RPV subjects and the Early Switch DTG + RPV Subjects to further support the assumption that the higher incidence of AEs in the DTG + RPV treatment group compared to CAR is most likely attributed to the open label nature and the treatment switch design, elements in Studies 201636 and 201637 will be provided post-authorisation.

The most commonly reported types of AEs occurring in ≥ 5% of subjects and also the most commonly reported more severe types of AEs (Grade 2-4) occurring in ≥ 1% of subjects were largely comparable between the DTG + RPV and CAR groups. The following most commonly reported types of AEs occurring in ≥ 5% of subjects were observed more frequently in the DTG + RPV group: headache, diarrhoea, bronchitis, arthralgia. The following most commonly reported more severe types of AEs (Grade 2-4) occurring in ≥ 1% of subjects were observed more frequently in the DTG + RPV group: Bronchitis, diarrhoea, depression, gastroenteritis and insomnia (Table 22).

Table 22. Most Common (Reported in ≥1% of Subjects in Any Treatment Group) Grade 2-4 Adverse Events by Overall Frequency during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
Preferred Term	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any Grade 2-4 event	72 (29)	68 (27)	76 (29)	52 (20)	148 (29)	120 (23)
Bronchitis	3 (1)	1 (<1)	7 (3)	2 (<1)	10 (2)	3 (<1)
Diarrhoea	5 (2)	2 (<1)	4 (2)	2 (<1)	9 (2)	4 (<1)
Headache	1 (<1)	6 (2)	5 (2)	2 (<1)	6 (1)	8 (2)
Depression	4 (2)	1 (<1)	2 (<1)	3 (1)	6 (1)	4 (<1)
Gastroenteritis	4 (2)	1 (<1)			6 (1)	2 (<1)
Insomnia	3 (1)	1 (<1)	3 (1)	1 (<1)	6 (1)	2 (<1)
Back pain	2 (<1)	6 (2)	1 (<1)	4 (2)	3 (<1)	10 (2)
Upper respiratory tract infection	1 (<1)	2 (<1)	2 (<1)	7 (3)	3 (<1)	9 (2)
Nasopharyngitis	1 (<1)	4 (2)	0	2 (<1)	1 (<1)	6 (1)

For a more detailed evaluation of all AEs observed the Applicant provided a summary of adverse events (Grade 1-4) reported in ≥1% of subjects by overall frequency in the DTG + RPV and CAR groups. Overall, it can be concluded that no new safety concerns could be identified based on these data.

Adverse Events by System Organ Class

The most commonly reported AEs in both treatment groups were from the system organ classes of infections and infestations and GI disorders. While events in the infections and infestations SOC and

musculoskeletal and connective tissue disorders occurred at similar frequencies across both treatment groups in the pooled analysis, GI-, nervous system-, skin and subcutaneous tissue- , psychiatric- , and respiratory, thoracic and mediastinal disorders events occurred at a higher frequency in the DTG + RPV treatment group (see Table 27). AEs from these SOCs are known and common side effects of the single entities DTG and/or RPV - with the exception of respiratory disorders - and therefore, no new safety concerns became obvious.

Respiratory events were very heterogeneous in nature so that no specific pattern of respiratory AEs became obvious. It can therefore be concluded that respiratory events reported more frequently in the DTG + RPV group were likely not related to study treatment. The number of subjects reporting events in other SOCs (not listed in detail here) that differed between the treatment groups (e.g., blood and lymphatic system disorders and immune system disorders) is too small to draw any conclusions.

Table 23. Summary of Adverse Events by System Organ Class during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Infections and infestations	108 (43)	115 (45)	115 (44)	119 (47)	223 (43)	234 (46)
Gastrointestinal disorders	71 (28)	56 (22)	58 (22)	26 (10)	129 (25)	82 (16)
Musculoskeletal and connective tissue disorders	35 (14)	50 (20)	43 (16)	32 (13)	78 (15)	82 (16)
Nervous system disorders	37 (15)	28 (11)	40 (15)	14 (5)	77 (15)	42 (8)
Skin and subcutaneous tissue disorders	30 (12)	22 (9)	38 (15)	23 (9)	68 (13)	45 (9)
Psychiatric disorders	34 (13)	18 (7)	27 (10)	14 (5)	61 (12)	32 (6)
General disorders and administration site conditions	28 (11)	29 (11)	21 (8)	22 (9)	49 (10)	51 (10)
Respiratory, thoracic and mediastinal disorders	23 (9)	16 (6)	22 (8)	8 (3)	45 (9)	24 (5)
Injury, poisoning and procedural complications	23 (9)	23 (9)	18 (7)	26 (10)	41 (8)	49 (10)
Reproductive system and breast disorders	12 (5)	16 (6)	9 (3)	10 (4)	21 (4)	26 (5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (3)	10 (4)	11 (4)	7 (3)	18 (4)	17 (3)
Renal and urinary disorders	5 (2)	5 (2)	10 (4)	4 (2)	15 (3)	9 (2)

With respect to GI disorders, the largest differences occurred for AEs of flatulence, abdominal distention, and constipation. For nervous system disorders, subjects from the DTG + RPV reported a higher incidence of AEs of headache and dizziness. For skin and subcutaneous tissue disorders, 12 (2%) subjects in the DTG + RPV group versus 3 (<1%) subjects in the CAR group reported rash. For psychiatric disorders, insomnia, depression, and abnormal dreams were reported at higher rates for the DTG + RPV group. For respiratory, thoracic and mediastinal disorders, the largest difference occurred for the preferred terms of rhinitis allergic, oropharyngeal pain, and catarrh.

Overall, the observed events in the DTG + RPV group are known, common and expected side effects for DTG and RPV and the study population. It can therefore be concluded that no new or unexpected side effects were detected.

Drug-Related Adverse Events

Table 24 gives an overview of the most common drug-related AEs (reported in ≥1% of subjects in any treatment group) during the Early Switch Phase. As already mentioned, drug-related AEs were clearly more frequently reported for the DTG + RPV group compared with the CAR group in the Early Switch phase (97 (19%) vs. 9 (2%)). No individual drug-related adverse event was reported in more than 2% of subjects. For both treatment groups the highest proportion of subjects reported a drug-related AE related to GI disorders, followed by psychiatric disorders and nervous system disorders. The majority of drug-related AEs were classified as Grade 1 in either treatment group. The most common drug-related AEs in the DTG + RPV group were headache, diarrhoea, abdominal distension, nausea. Also the more severe drug-related AEs Grade 2–4 were observed more frequently in the DTG + RPV group than in the CAR group (29, 6% vs. 3, <1%). The most common Grade 2-4 drug related AEs in the DTG+RPV group were depression (4 events) and a sampling of gastrointestinal events (Table 29). There was no pattern of drug related Grade 2-4 AEs highlighting any specific SOC.

For a more detailed evaluation of all drug-related AEs observed the Applicant provided a summary of drug-related adverse events (Grade 1-4) reported in ≥1% of subjects by overall frequency in the DTG + RPV and CAR groups. Overall, it can be concluded that no new safety concerns could be identified based on these data:

No new types of drug related adverse drug reactions were observed during the Early Switch Phase for the safety population as most of the reported drug related events are well known and expected side effects of DTG and RPV labelled in the corresponding SmPCs. The most likely explanations for the imbalances with regard to drug-related AEs between the 2 treatment groups are already discussed above (drug-related AEs observed are common and expected AEs form the single substances so it is plausible that the occurrence of those adverse events will be assessed as related to study treatment DTG + RPV by the investigators).

Table 24. Most Common Drug-Related Adverse Events (Reported in >=1% of Subjects in Any Treatment Group) by Preferred Term during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	47 (19)	5 (2)	50 (19)	4 (2)	97 (19)	9 (2)
Headache	5 (2)	0	6 (2)	0	11 (2)	0
Diarrhoea	4 (2)	1 (<1)	4 (2)	0	8 (2)	1 (<1)
Abdominal distention	5 (2)	0 (0)	2 (<1)	0	7 (1)	0
Nausea	4 (2)	0 (0)	3 (1)	0	7 (1)	0
Insomnia	3 (1)	1 (<1)	3 (1)	0	6 (1)	1 (<1)
Dizziness	2 (<1)	1 (<1)	4 (2)	0	6 (1)	1 (<1)
Flatulence	1 (<1)	0	5 (2)	0	6 (1)	0
Abnormal dreams	3 (1)	0	3 (1)	0	6 (1)	0
Anxiety	3 (1)	1 (<1)	2 (<1)	0	5 (<1)	1 (<1)
Fatigue	5 (2)	0	0	0	5 (<1)	0
Depression	3 (1)	0	2 (<1)	0	5 (<1)	0
Abdominal pain upper	2 (<1)	0	3 (1)	0	5 (<1)	0

Table 25. Summary of All Drug-Related Grade 2-4 Adverse Events by Overall Frequency during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	12 (5)	0	17 (7)	3 (1)	29 (6)	3 (<1)
Depression	2 (<1)	0	2 (<1)	0	4 (<1)[a]	0
Asthenia	1 (<1)	0	2 (<1)	0	3 (<1)	0
Diarrhoea	2 (<1)	0	1 (<1)	0	3 (<1)	0
Dyspepsia	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Abdominal distension	1 (<1)	0	1 (<1)	0	2 (<1)	0
Anxiety	1 (<1)[b]	0	1 (<1)	0	2 (<1)	0
Headache	0	0	2 (<1)	0	2 (<1)	0
Insomnia	1 (<1)	0	1 (<1)	0	2 (<1)	0
Abnormal dreams	0	0	1 (<1)	0	1 (<1)	0
Alopecia	0	0	1 (<1)	0	1 (<1)	0
Anhedonia	0	0	1 (<1)	0	1 (<1)	0
Constipation	0	0	1 (<1)	0	1 (<1)	0
Depressed mood	0	0	1 (<1)	0	1 (<1)	0
Dizziness	0	0	1 (<1)	0	1 (<1)	0
Drug-induced liver injury	1 (<1)[c]	0	0	0	1 (<1)	0
Eosinophilic pneumonia acute	0	0	1 (<1)[d]	0	1 (<1)	0
Erectile dysfunction	1 (<1)	0	0	0	1 (<1)	0
Pancreatitis acute	1 (<1)[e]	0	0	0	1 (<1)	0
Photosensitivity reaction	0	0	1 (<1)	0	1 (<1)	0
Rash	0	0	1 (<1)	0	1 (<1)	0
Rash pruritic	1 (<1)	0	0	0	1 (<1)	0
Renal failure	0	0	1 (<1)	0	1 (<1)	0
Suicidal ideation	0	0	1 (<1)[f]	0	1 (<1)	0
Tremor	0	0	1 (<1)[g]	0	1 (<1)	0
Vision blurred	1 (<1)	0	0	0	1 (<1)	0
Vitamin D deficiency	0	0	1 (<1)	0	1 (<1)	0
Hyperglycaemia	0	0	0	1 (<1)	0	1 (<1)
Suicide attempt	0	0	0	1 (<1)[h]	0	1 (<1)

Note: Only On-treatment events are considered.

Note: All drug-related events reported as Grade 3 or 4 are footnoted below; all other events listed are Grade 2.

a. Grade 3 depression was reported in 2 subjects (Study 201636) [see Section 2.1.6.3] and in subject (Study201637)

b. Grade 4 anxiety (one subject in Study 201636)

c. Grade 3 drug-induced liver injury (one subject in Study 201636)

d. Grade 3 eosinophilic pneumonia acute (one subject in Study 201637)

e. Grade 4 pancreatitis acute (one subject in Study 201636)

f. Grade 3 suicidal ideation (one subject in Study201637)

g. Grade 3 tremor (one subject in Study201637)

h. Grade 4 suicide attempt (one subject in Study201637)

Adverse events of special interest (AESIs)

The following AESIs have been determined for DTG + RPV based on non-clinical and/or clinical safety data for the SEs: Hypersensitivity, Hepatobiliary Disorders, Psychiatric Disorders Including Depression and Suicidality, Drug Resistance, Skin and Subcutaneous Disorders, Gastrointestinal Disorders, Renal Disorders, Musculoskeletal and Connective Tissue Disorders, and Grade 3 to 4 Lipase Elevations.

Nervous system disorders were not predefined as AESI, although events from this SOC are common, known and expected side effects of the single entities. This is considered acceptable because adverse events subsumed under this SOC (e.g. headache, dizziness) are less serious events which do not require any special monitoring.

The numbers of **hypersensitivity reactions** were low with no major differences in both treatment groups.

The numbers of events in the **hepatobiliary disorders** SOC were low with overall no major differences in both treatment groups (DTG + RPV 5 (<1%); CAR 2 (<1%)). The AEs observed from this SOC were variable in nature and no meaningful AE pattern could be detected. In the DTG+RPV group 2 events of drug-induced liver injury (DILI) (both of them Grade 3) occurred; DILI in one subject was the only hepatobiliary event considered drug-related to study treatment DTG + RPV. According to the information given, it is reasonable to conclude that the DILI event in one of the subjects seem to be not related to study treatment but to acetaminophen.

Independent of the events of hepatobiliary disorders observed in the SWORD studies, the Applicant completed the routine review of hepatobiliary disorders for DTG containing products on 2nd February 2018. As a result, the Applicant updated the company core datasheet for DTG containing products with the addition of 'acute hepatic failure' as an rare adverse reaction. Based on the submitted data of severe liver disorders observed with DTG containing regimens it cannot be ruled out that the DTG-containing regimen may be the likely causative agent for the small number of severe liver dysfunction events. Therefore, the addition of 'acute hepatic failure' as a rare adverse reaction in the Juluca SmPC/PIL is appropriate.

Psychiatric AEs were overall reported more frequently in the DTG + RPV treatment group (DTG + RPV 61 subjects, 12%; CAR 32 subjects, 6%). Insomnia, depression, anxiety, and abnormal dreams were the most commonly reported AEs from this SOC in the DTG + RPV group - the majority of them were considered Grade 1 or 2. Related to psychiatric disorders also drug-related AEs and AEs leading to withdrawal were reported more frequently in the DTG + RPV treatment group (drug related: DTG + RPV 26 subjects (5%) vs. CAR 2 (<1%); withdrawals: 9 (2%) vs. 1 (<1%), see Tables 30 and 31). Psychiatric AEs were the most common observed SOC leading to withdrawal in the DTG + RPV group. The majority of the drug-related events were Grade 1.

The incidence of AEs relating to depression was higher in the DTG + RPV treatment group (22 subjects (4%) vs. 8 (2%)); all events were single occurrences in both treatment groups. Six AEs relating to depression were considered drug-related in the DTG + RPV treatment group.

The reporting rate for AEs relating to suicidal behaviors was overall low and comparable across the treatment groups (DTG + RPV 4 [<1%], CAR 3 [<1%]) and all events relating to suicidal behaviors in the DTG + RPV group were single occurrences. One event in the DTG + RPV group (Grade 3 suicidal ideation in one subject with past history of depression) was considered drug-related and led to withdrawal. Events of suicidal ideation and behavior were (additionally to the AE/SAE forms) also identified via the Possible Suicide Related Adverse Events (PSRAE) forms and the electronic Columbia Suicidality Severity Rating Scale (eC-SSRS). Seven additional cases were identified herewith. All events in the context of suicidal behaviors were reported as recovered or recovered with sequelae. None of the events resulted in completed suicide.

Overall, it can be concluded that the psychiatric AE profile of co-administered DTG + RPV is consistent with the psychiatric AE profile of the single entities DTG and RPV. No new types of psychiatric AEs were reported. Reassuringly, in the pivotal studies treatment with DTG+RTV did not lead to increased suicidality as compared to control treatment. The higher incidences of any psychiatric AEs in the DTG + RPV group can most likely be explained by the already mentioned facts (switch design elements in studies 201636 and 201637 where subjects in the CAR treatment group receive a well-tolerated

therapy in contrast to subjects in the DTG + RPV treatment group which are randomized to new therapy regimen; psychiatric side effects observed in DTG + RPV arm are known, expected and labeled AEs for the single entities DTG and/or RPV and therefore, the occurrence of these events will be assessed as related to DTG + RPV by the investigators).

However, use of both single entities is known to be associated with neuropsychological AEs. Moreover, it is noticed that there are several publications in literature reporting a higher rate of DTG discontinuations due to neuropsychological events (including headache, insomnia, suicidal ideation) than would have been expected based on clinical trial data (e.g. de Boer AIDS 2016 30:2831-2834, Bonfanti AIDS 2017 31:455-457, Borghetti AIDS 2017 31:457-459). Depression (including suicidal ideation and behaviours particularly in patients with a pre-existing history of depression or psychiatric illness) is listed as important identified risk in the DTG+RPV RMP and will be followed closely post marketing. For a more in-depth assessment of the psychiatric AEs, a comparison between the incidences of psychiatric AEs observed in the two pivotal studies with the incidences of psychiatric AEs observed in the pivotal studies with the single entities DTG and RPV was provided. In addition, the Applicant was requested to provide more detailed information on baseline characteristics related to (the history of) psychiatric disorders for the study population included in the SWORD vs the single entity Phase III studies. Based on all data provided, there is no indication that the combination of DTG+RPV results in an additive / supra-additive risk for psychiatric ADRs.

Table 26. Summary of Drug-Related Adverse Events from the Psychiatric disorders SOC and Maximum Toxicity for the DTG + RPV and CAR group - Early Switch Phase – POOLED

Treatment: DTG +RPV (N=513)					
	Maximum toxicity				
System organ class Preferred term	Grade 1	Grade 2	Grade 3	Grade 4	Total
Psychiatric disorders					
Any event	16 (3%)	6 (1%)	3 (<1%)	1 (<1%)	26 (5%)
Abnormal dreams	5 (<1%)	1 (<1%)	0	0	6 (1%)
Insomnia	4 (<1%)	2 (<1%)	0	0	6 (1%)
Anxiety	3 (<1%)	1 (<1%)	0	1 (<1%)	5 (<1%)
Depression	1 (<1%)	2 (<1%)	2 (<1%)	0	5 (<1%)
Anhedonia	0	1 (<1%)	0	0	1 (<1%)
Depressed mood	0	1 (<1%)	0	0	1 (<1%)
Libido increased	1 (<1%)	0	0	0	1 (<1%)
Nervousness	1 (<1%)	0	0	0	1 (<1%)
Nightmare	1 (<1%)	0	0	0	1 (<1%)
Sleep disorder	1 (<1%)	0	0	0	1 (<1%)
Suicidal ideation	0	0	1 (<1%)	0	1 (<1%)
Treatment: CAR (N=511)					
	Maximum toxicity				
System organ class Preferred term	Grade 1	Grade 2	Grade 3	Grade 4	Total
Psychiatric disorders					
Any event	1 (<1%)	0	0	1 (<1%)	2 (<1%)
Anxiety	1 (<1%)	0	0	0	1 (<1%)
Insomnia	1 (<1%)	0	0	0	1 (<1%)
Suicide attempt	0	0	0	1 (<1%)	1 (<1%)

Table 27. Summary of Adverse Events from the Psychiatric Disorders SOC Leading to Withdrawal/Permanent Discontinuation of Study Drug for the DTG+RPV and CAR group – Early and Late Switch Phase

System organ class Preferred term	**SWORD 1** **DTG + RPV** **(252)**	**SWORD 2** **DTG + RPV** **(261)**	**POOLED** **DTG + RPV** **(513)**
Psychiatric disorders			
Any event	4 (2%)	5 (2%)	9 (2%)
Anxiety	2 (<1%)	2 (<1%)	4 (<1%)
Depression	1 (<1%)	2 (<1%)	3 (<1%)
Insomnia	1 (<1%)	1 (<1%)	2 (<1%)
Depressed mood	0	1 (<1%)	1 (<1%)
Panic attack	1 (<1%)	0	1 (<1%)
Suicidal ideation	0	1 (<1%)	1 (<1%)
System organ class Preferred term	**SWORD 1** **CAR** **(238)**	**SWORD 2** **CAR** **(239)**	**POOLED** **CAR** **(477)**
Psychiatric disorders			
Any event	1 (<1%)	0	1 (<1%)
Abulia	1 (<1%)	0	1 (<1%)
Confusional state	1 (<1%)	0	1 (<1%)

It is not possible to quantify the risk of developing **clinical resistance** to DTG + RPV as the database is too small to draw any conclusion.

With regard to **skin and subcutaneous disorders SOC**, there was a difference of AE rates related to AESI rash in the DTG + RPV group compared with CAR group (pooled analysis) in Studies 201636 and 201637. However, serious rash was not observed, including any reports of Stevens Johnson syndrome, TEN, or erythema multiforme. Overall, no major imbalances in drug-related AEs and no serious adverse events in the skin and subcutaneous disorders SOC were observed.

GI events and also drug related GI disorders were reported more frequently in the DTG + RPV treatment group (any GI event: 25% vs. 16%; drug-related: 7% vs. <1%). The most commonly reported events in both treatment groups were diarrhea and dyspepsia and the most commonly reported drug-related AEs in the DTG + RPV treatment group were diarrhea (8 subjects, 2%), abdominal distension, nausea (each 7 subjects, 1%), and flatulence (6 subjects, 1%). There were 3 SAEs related to GI events reported in the DTG + RPV group: acute pancreatitis (questionable diagnosis according to the case narrative (further information can be found below in section “Drug-Related Serious Adverse Events”)), gastrointestinal hemorrhage (considered not related by the investigator which is endorsed according to case narrative: endoscopic examinations revealed no obvious source of bleeding; possible cause for the event of GI bleeding is “rare” ibuprofen use for chronic back pain) and gastroesophageal reflux (not related, most likely caused by underlying disease according to the case narrative).
Altogether, the most commonly reported AEs in the DTG + RPV treatment group are well known and expected side effects of the single entities which is a plausible explanation for the imbalances of GI events in the 2 treatment groups (as discussed already above).

The incidences of events in the **renal disorders** SOC were low in both treatment groups with a slightly higher number of events reported in the DTG + RPV group (DTG + RPV 15 (3%); CAR 9 (2%)); the majority of renal events were classified as Grade 1 for both treatment groups. One event of renal failure in a subject (considered drug-related, but the subject’s medical history could also result in an increase of creatinine) and 1 event of acute renal impairment in a subject were reported in the DTG + RPV group. As both subjects had a Grade 1 creatinine elevation only, the diagnoses of renal failure and renal impairment are not fully plausible. However, it is reassuring that both events of mild increases in creatinine were reversible so that a chronic renal impairment can be excluded. It is agreed that the other events subsumed under renal disorders SOC were most likely not related to DTG/RPV. Overall,

data submitted so far give no hints for relevant renal adverse effects for DTG + RPV compared with CAR.

The incidence of all adverse events from the **musculoskeletal and connective tissue disorders** SOC was comparable in both treatment groups whereas drug related AEs were more frequently observed in the DTG + RPV group (all Grade 1). However, the reported events (arthralgia, musculoskeletal pain) are known and expected side effects of DTG and/or RPV; this is most likely the reason for the observed imbalance with regard to AEs from the musculoskeletal and connective tissue disorders SOC. No new types of events related to musculoskeletal and connective tissue disorders were observed.

There were only minimal and therefore no clinically significant differences in changes in **lipid profile** between the 2 groups.

Serious adverse events

The incidence of subjects developing any SAE (DTG + RPV 27 subjects, 5%; CAR 21 subjects, 4%) and the incidence of drug-related SAEs (DTG + RPV 4, <1%; CAR, <1%) was similar between treatment groups during the Early Switch Phase. In the Late Switch Phase additional 14 subjects reported a total of 18 SAEs; according to the data submitted it is reasonable that none of which were considered related to study treatment. According to Table 32, the most frequently reported SAE during the Early Switch Phase was pneumonia (3 subjects in the DTG + RPV group, none in the CAR group) and suicide attempt (reported in 1 subject each for the DTG + RPV and CAR groups). All other SAEs were reported in 1 subject each.
Overall, the incidence of SAEs was low in both treatment groups. The reported SAEs were highly variable in nature and no meaningful pattern could be detected. There were some numerical imbalances for certain types of SAEs, but due to the low number of affected patients, firm conclusions cannot be drawn.

Table 28. Summary of All Serious Adverse Events by Preferred Term during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	210636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)
Pneumonia	1 (<1)	0	2 (<1)	0	3 (<1)	0
Suicide attempt[a]	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Abscess limb	0	0	1 (<1)	0	1 (<1)	0
Acute kidney injury	0	0	1 (<1)	0	1 (<1)	0
Alcohol poisoning	0	0	1 (<1)	0	1 (<1)	0
Cholecystitis chronic	0	0	1 (<1)	0	1 (<1)	0
Depression	0	0	1 (<1)	0	1 (<1)	0
Drug-induced liver injury	1 (<1)	0	0	0	1 (<1)	0
Eosinophilic pneumonia acute	0	0	1 (<1)	0	1 (<1)	0
Facial bones fracture	0	0	1 (<1)	0	1 (<1)	0
Gastroenteritis	1 (<1)	0			1 (<1)	0
Gastrointestinal haemorrhage	0	0	1 (<1)	0	1 (<1)	0
Gastrooesophageal reflux disease	0	0	1 (<1)	0	1 (<1)	0
Haemarthrosis	0	0	1 (<1)	0	1 (<1)	0
Headache	0	0	1 (<1)	0	1 (<1)	0
Hodgkin's disease mixed cellularity stage unspecified	1 (<1)	0	0	0	1 (<1)	0
Kaposi's sarcoma	0	0	1 (<1)	0	1 (<1)	0
Lymphogranuloma venereum	0	0	1 (<1)	0	1 (<1)	0
Orchitis	0	0	1 (<1)	0	1 (<1)	0
Pancreatitis acute	1 (<1)	0	0	0	1 (<1)	0
Panic attack	1 (<1)	0	0	0	1 (<1)	0

Periorbital cellulitis			1 (<1)	0	1 (<1)	0
Plasmablastic lymphoma	1 (<1)	0	0	0	1 (<1)	0
Pulmonary sepsis	0	0	1 (<1)	0	1 (<1)	0
Renal colic	0	0	1 (<1)	0	1 (<1)	0
Rotavirus infection	0	0	1 (<1)	0	1 (<1)	0
Tibia fracture	0	0	1 (<1)	0	1 (<1)	0
Vertigo	1 (<1)	0	0	0	1 (<1)	0
Wrist fracture	1 (<1)	0	0	0	1 (<1)	0
Anal fistula	0	1 (<1)	0	0	0	1 (<1)
Breast cancer	0	1 (<1)	0	0	0	1 (<1)
Bronchitis	0	1 (<1)	0	0	0	1 (<1)
Drug hypersensitivity	0	0	0	1 (<1)[b]	0	1 (<1)[b]
Fibula fracture	0	0	0	1 (<1)	0	1 (<1)
Foreign body	0	0	0	1 (<1)	0	1 (<1)
Hepatitis C	0	1 (<1)	0	0	0	1 (<1)
Influenza	0	1 (<1)	0	0	0	1 (<1)
Intervertebral disc protrusion	0	1 (<1)	0	0	0	1 (<1)
Jarisch-Herxheimer reaction	0	0	0	1 (<1)[b]	0	1 (<1)[b]
Joint injury	0	0	0	1 (<1)	0	1 (<1)
Keratitis	0	0	0	1 (<1)	0	1 (<1)
Lung neoplasm malignant	0	1 (<1)	0	0	0	1 (<1)
Non-cardiac chest pain	0	1 (<1)	0	0	0	1 (<1)
Peritonsillar abscess	0	1 (<1)	0	0	0	1 (<1)
Proctitis	0	1 (<1)	0	0	0	1 (<1)
Pulmonary embolism	0	0	0	1 (<1)	0	1 (<1)
Rectal abscess	0	1 (<1)			0	1 (<1)
Retinal detachment	0	0	0	1 (<1)	0	1 (<1)
Thyroglossal cyst infection	0	1 (<1)	0	0	0	1 (<1)
Toxic encephalopathy	0	1 (<1)	0	0	0	1 (<1)
Tympanic membrane perforation	0	0	0	1 (<1)	0	1 (<1)

a. There was 1 subject (Study 201636) with a Grade 4 event of suicidal ideation that was classified by the site as non-serious and not related to drug; this event is not included in the above table, however, the event was later determined by the site to be a suicide attempt.
b. The events of drug hypersensitivity and Jarisch-Herxheimer reaction occurred in the same subject and were reported for the same reaction in this subject.

Drug-Related Serious Adverse Events

Four subjects in the DTG + RPV group experienced drug-related SAEs (compared to 1 in the CAR group): acute pancreatitis, DILI, depression, and acute eosinophilic pneumonia (drug-related SAE in the CAR group: suicide attempt). No drug-related SAEs were reported with an onset during the Late Switch Phase. Narratives are provided for all observed drug related SAEs; only a short summary of the cases together with a short discussion of each event will be presented here:

- (SAE - Pancreatitis acute): Past medical history of fatty food and alcohol intake, including a significantly higher alcohol and fatty food intake than usual reported for the week prior to the SAE.
  According to the narrative, the diagnosis of 'acute pancreatitis' is very questionable as the patient had only an isolated increase of lipase with no increase of amylase, only slight abdominal pain on one single day and no findings in an abdomen CT examination.

- SAE – Depression: Past history of depression. Onset at Day 214 of Grade 3 depression that was considered serious, related to study drug, and led to withdrawal. 27 days later subject was hospitalized due to depressive disorder with suicidal tendencies, and DTG and RPV were discontinued. The outcome of the depression was not recovered/not resolved at the time of the Week 48 analysis cut-off date although there was improvement as evidenced by the result of the MADRS.
  Depression and suicidal ideation are known and labeled ADRs of DTG and RPV.

- SAE – Eosinophilic pneumonia acute: Onset of Grade 3 eosinophilic pneumonia acute on Day 195. Subject was hospitalized. After 3 days clinical and radiological improvement of the process. The outcome of eosinophilic pneumonia acute was not recovered/not resolved, but the subject was discharged from the hospital with clinical and radiological improvement and continued on corticoids treatment. DTG and RPV were discontinued.
  As this is a single case it cannot be concluded that there is a causal relationship between DTG/RPV treatment and the event of eosinophilic pneumonia cannot be considered conclusively proven.

- SAE - Drug-induced liver injury: Current history of drug related liver disease at baseline. On Day 34 after the first dose of DTG + RPV, subject developed severe Grade 3 drug-induced liver injury (ALT 466 IU/L [Grade 3], AST 696 IU/L [Grade 4], bilirubin 38 µmol/L [Grade 2]). Subject reported right hypochondrium pain (persistent, not colic), associated with choluria, and no other symptoms of hepatitis. DTG and RPV were discontinued 3 days later when laboratory results became available. ALT, AST, and bilirubin had returned to within the normal range at a subsequent Follow-up on study Day 45. According to the Applicant, this case does not meet criteria for serious hepatotoxicity as bilirubin increased <2 x ULN and direct bilirubin was <35%. This conclusion seems to be in contradiction to the fact that the event of 'Drug-induced liver injury' in this subject was reported and submitted as serious hepatotoxicity by the Applicant. However, according to the data submitted the event was obviously not serious since the limits for bilirubin and direct bilirubin failed to meet the protocol defined criterion for serious hepatotoxicity. Furthermore, it is reassuring that this event was reversible.

Hepatobiliary disorders are already labelled in the SmPC of DTG and RPV. The possible risk of hepatotoxicity should be further monitored during post marketing period. Apart from the DILI event reported in the SWORD studies, the Applicant performed a routine review of hepatobiliary disorders observed during therapy with DTG containing regimen. Based on the submitted data of severe liver disorders observed with DTG containing regimens, 'acute hepatic failure' was added in section 4.8 of the Juluca SmPC as a rare adverse reaction.

In conclusion a slightly higher number of serious drug-related AEs was observed for the DTG + RPV treatment group, but it must be noted that the incidence of serious drug-related AEs overall could be considered as low for both treatment groups (DTG + RPV: 4 subjects; CAR: 1 subject (<1% of subjects in each group)). The drug related SAEs reported were very heterogeneous in nature and always single events, which are partly to be expected on the basis of the known safety profile of the single entities DTG and RPV, and partly to be explained by predisposing conditions. Overall, it can be concluded that new safety concerns were not observed.

Deaths

In both treatment groups one death each were reported at the time of the cut-off date for the Week 48 analysis; both occurred in the Early Switch Phase. One subject in the DTG + RPV group died due to an AE of Kaposi's sarcoma and 1 subject in the CAR group died due to an AE of lung neoplasm malignant. Neither event was considered related to study treatment by the investigator. The Applicant provided

case narratives for each of the subject's death, confirming that the fatalities were most likely not related to treatment. Overall, no imbalances for mortality were observed.

Laboratory findings

Liver Chemistry

Hepatobiliary AEs in the Early Switch Phase are discussed already above in section 'Adverse events of special interest (AESIs)'.
In 9 subjects elevations of ALT >3 x ULN were observed in the DTG + RPV group during the Early Switch Phase and 1 subject in the Late Switch Phase. Six of the elevations in the Early Switch Phase and the elevation in the Late Switch Phase were due to other causes; the explanations given in the submitted documents for these increases are plausible. One subject was diagnosed with drug-induced liver injury (discussed above), and two further subjects were withdrawn from the studies after switching to DTG + RPV in the Late Switch Phase due to elevations in transaminases with no alternative diagnoses established. It can be concluded from data provided that increases in ALT and AST in these both subjects are most likely related to treatment with DTG + RPV. No further action is required because increased transaminases are labelled as a very common ADR in the Juluca PIL.
In the DTG + RPV group bBilirubin increased to a maximum of Grade 2.
Grade 1 to 4 increases of AST were observed in both treatments groups during the early switch phase with a higher incidence in the DTG+RPV group. AST-elevations were single episodes only with spontaneous resolution and most likely be chance findings. The clinically more relevant Grade 2-4 AST-elevations were more frequently reported in subjects on CAR. "Increases in transaminases" is labelled in the Juluca SmPC. No further action is required.
Overall it can be concluded that increases in aminotransferases are known and very common side effects of both, DTG and RPV. Altogether, no new risk with regard to the liver chemistries and no increased risk of hepatic toxicity for DTG + RPV compared with CAR could be detected.

Renal Function

Renal disorders AEs in the Early Switch Phase are discussed already above in section 'Adverse events of special interest (AESIs)'.
Ten (2%) subjects in the DTG + RPV group had Grade 1 maximum post-baseline emergent elevations in creatinine; there were no Grade 2 to Grade 4 elevations. The increases in serum creatinine became evident at Week 4 (the earliest time point assessed) and remained stable through Week 48. Initial and afterwards stable creatinine increase is a known effect of DTG. This is not considered clinically relevant but should be labelled in the SmPC. Consistent with the creatinine increase, the mean change from Baseline in estimated GFR from CKD-EPI creatinine equation showed a small decrease in the DTG + RPV group. CKD-EPI GFR using cystatin C showed no clinical relevant change from Baseline in the DTG + RPV group, confirming that DTG + RPV had no effect on glomerular filtration rate, but only reduced creatinine clearance. Urine albumin/creatinine ratio and protein/creatinine ratio showed only little change in either treatment group up to Week 48 confirming there was no adverse effect on renal tubular function. Additionally, several other renal biomarkers – beside creatinine and cystatin C - were evaluated to further assess for any impact of study treatment on renal function. There was a decrease in the median urine retinol binding protein and the median urine beta-2-microglobulin concentration in both treatment groups with a slightly higher decrease the DTG + RPV group.
Altogether, no safety concerns with regard to the renal chemistries and no increased risk of renal toxicity for DTG + RPV compared with CAR could be detected.

Creatine Phosphokinase increase

During the Early Switch Phase 29 subjects in the DTG + RPV group had CPK increases; 3 of which Grade 4. All events were classified as exercise related. Neither event was considered serious or related to study treatment.

Lipase increase

Post-baseline emergent lipase elevations were observed more frequently in the CAR group (DTG + RPV 51 subjects, 10%), CAR 73, 14%) - most of them considered Grade 1 or 2 and asymptomatic. In the DTG + RPV group 2 increases in lipase up to Grade 4 were reported. The Grade 4 increases were isolated lipase elevations, asymptomatic, not associated with other symptoms and reversible despite continued study medication DTG + RPV. These data are reassuring and no consequences are necessary.

Lipid Parameters

A small proportion of subjects in both treatment groups had treatment-emergent cholesterol and triglycerides elevation of Grade 2 or higher at Week 48. Grade 4 lipid elevation was not observed in the DTG + RPV group. Overall, there were no meaningful differences in the measured lipid parameters (total cholesterol, LDL cholesterol and triglycerides) between the 2 treatment groups. Also the total cholesterol/HDL ratio was similar between the 2 groups. Increases in lipid parameters are known from RPV (total cholesterol (fasted) and LDL cholesterol). No new safety concern was detected. The changes in lipids are not relevantly different between baseline and Week48 when subjects who were using lipid modifying agents were excluded.

Hematology

The Applicant presented a tabulated summary of maximum post-baseline emergent hematological alterations observed during the Early Switch Phase for the safety population. Overall, there were only few post-baseline alterations with regard to hematological parameters in the DTG + RPV and CAR group. The maximum intensity of post-baseline emergent hematology alterations was comparable across the two treatment groups. A significant higher number of subjects in the DTG + RPV group had platelets alterations Grade 1 which is not considered clinically relevant.

Vital Signs

Vital signs measurements were recorded at Baseline only. This is considered acceptable as effects on blood pressure and/or heart rate are not expected from the single substances.

Cardiac Evaluations

A 12-lead ECG was performed at Screening visit only. This is acceptable, because based on data from the TQT studies with the single entities DTG and RPV and based on the results of the DDI study LAI116181 between both drugs it can be concluded that the doses used in the SWORD studies are not associated with a risk for QTc prolongation after combined administration of RPV with DTG.

Cardiovascular Biomarkers

Cardiovascular biomarkers in blood were assessed and included C-reactive protein, d-dimer, fatty acid binding protein-2, glucose, HOMA-IR (insulin resistance), IL-6, oxidized LDL cholesterol, soluble CD14, soluble CD163, soluble vascular cell adhesion molecule-1, and insulin. There was no obvious pattern in changes from Baseline to Week 48 and no major differences between the 2 treatment groups for these biomarkers.

Bone Evaluations

A dedicated, ongoing Phase III DEXA substudy was conducted as part of the 2 pivotal studies (201636 [SWORD-1] or 201637 [SWORD-2].

Title: An Evaluation of Bone Mineral Density in HIV-1-Infected Adult Subjects Switching from a Tenofovir-Containing Antiretroviral Therapy Regimen to a Dolutegravir Plus Rilpivirine Regimen

Primary Objective:

- To evaluate the change in bone mineral density (BMD) assessed by areal density in total hip at 48 weeks following switch of subjects from an antiretroviral therapy (ART) regimen containing Tenofovir disoproxil fumarate (TDF) to dolutegravir plus rilpivirine (DTG + RPV) once daily compared with continued therapy with the TDF-containing regimen.

Secondary Objectives:

- To evaluate the change in BMD assessed by areal density in lumbar spine at 48 weeks following switch of subjects from an ART regimen containing TDF to DTG + RPV once daily compared with continued therapy with the TDF-containing regimen.
- To evaluate the change in BMD assessed by areal density in lumbar spine and total hip over time following switch of subjects from an ART regimen containing TDF to DTG + RPV OD.
- To evaluate the change in BMD in lumbar spine and total hip assessed by T-scores and Z-scores at 48 weeks following switch of subjects from an ART regimen containing TDF to DTG + RPV once daily compared with continued therapy with the TDF-containing regimen.
- To evaluate the change in BMD assessed by T-scores and Z-scores in lumbar spine and total hip over time following switch of subjects from an ART regimen containing TDF to DTG + RPV once daily.
- To assess the effect of baseline third agent class on BMD in lumbar spine and total hip over time following switch to the DTG + RPV once daily.

Study Design: This sub-study (202094 [DEXA sub-study]) was an open-label, parallel-group sub-study of the 2 identical pivotal, Phase III, randomized, multicentre, parallel-group, non-inferiority studies, 201636 and 201637 (SWORD-1 and SWORD-2), evaluating the efficacy, safety, and tolerability of switching to DTG + RPV from current integrase strand transfer inhibitor (INSTI)-, non-nucleoside reverse transcriptase inhibitor (NNRTI)-, or protease inhibitor (PI)-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed.
This sub-study evaluated any change from baseline in the BMD in the 'total hip', which included the femoral neck, trochanter, and intertrochanter areas and the lumbar spine, which includes the first lumbar vertebra (L1) to the fourth lumbar vertebra (L4), in subjects at 3 time points over 148 weeks following the switch from a triple ART regimen containing TDF to the NRTI–sparing 2-drug regimen of DTG + RPV.

Number of subjects: Study 202094 could recruit up to 165 eligible subjects with a goal of approximately 150 evaluable subjects including approximately 75 evaluable subjects from each of the DTG + RPV and current antiretroviral regimen (CAR) treatment groups across both parent studies (201636 [SWORD-1] and 201637 [SWORD-2]). At of the data cutoff for Week 48 (22 November

2016), this sub-study enrolled 102 subjects, who were included in the analyses.

Study Population: Diagnosis and key inclusion criteria included HIV-1 infected subjects screened and eligible for either parent study (201636 or 201637) and received a TDF-containing ART regimen. The main exclusion criteria were subjects with less than 3 vertebra in the LI to L4 range suitable for BMD measurement, bilateral hip replacement, uncontrolled thyroid disease, male hypogonadism, endocrine diseases, history of fragility fractures, severe osteoporosis, BMI <18 kg/m2 or ≥ 40 kg/m2, vitamin D deficiency, and current use of tamoxifen or bone-related treatment.

Treatment administration: Study 202094 recruited eligible subjects from the early switch DTG + RPV treatment group and from the late switch group who continued their CAR through to Week 52 across either of the parent studies (201636 or 201637). Subjects participating in this sub-study had DEXA scans performed at Day 1 and at study Weeks 48. Subjects in study 202094 received at least 48 weeks of therapy with DTG + RPV or CAR in the parent study. Subjects who withdrew early prior to the last scheduled visit had a DEXA scan performed at their Withdrawal Visit.

Criteria for evaluation: The primary endpoint was the percent change from Baseline at Week 48 in total hip BMD as assessed by areal density (g/cm2). The secondary endpoints for this study included the percent change from Baseline at Week 48 for lumbar spine BMD, change in lumbar spine BMD and total hip BMD over time as assessed by areal density (g/cm2), and change in total hip and lumbar spine BMD as assessed by T-scores and Z-scores. In addition, these secondary endpoints were also assessed by Baseline third agent.

Efficacy Results: No efficacy assessments were conducted as a part of this sub-study

Safety Results:

Changes from Baseline in Total Hip BMD and in Lumbar Spine BMD at Week 48 Assessed by Areal Density were greater for subjects in the DTG + RPV group compared with the CAR group (there was almost no change in the mean BMD in the total hip in the CAR group). An analysis of the difference between the treatment groups from Baseline to Week 48 using an ANCOVA model yielded a p-value of 0.014 for total hip BMD and a p-value of 0.039 for lumbar spine BMD for the DTG + RPV. The Applicant wasrequested to perform the main analysis with covariable BMD at baseline and factors treatment, age and third agent class.

Results from the analysis of the secondary endpoints of both total hip and lumbar spine BMD assessed as T-scores and Z-scores were consistent with and supportive of the primary analysis. Analysis by Baseline third agent (INSTI, NNRTI, or PI) for the changes from Baseline at Week 48 in total hip and lumbar spine BMD assessed by areal density, T-scores, and Z-scores were also supportive of the primary and secondary endpoint results.

For subjects in both treatment groups, FRAX score results showed little change from Baseline at Week 48 in the 10-year probability of hip fracture (-0.08% and 0.03%, respectively) or 10-year probability of osteoporotic fracture (-0.12% and -0.04%, respectively).

Analysis of treatment differences in total hip BMD at Week 48 across demographic subgroups (age, gender, and race) and Baseline characteristics (Baseline BMI and CD4+ lymphocyte count) produced results that were supportive of the primary result, although the number of subjects in several of the defined sub-populations was too small to make comparisons across subgroups. Of note, there was no evidence of a gender effect in changes in BMD from Baseline to Week 48 noted for either treatment group.

Marked decreases in each of the 3 bone biomarkers examined (bone specific alkaline phosphatase [BSAP], Procollagen type 1-N-propeptide [P1NP], and osteocalcin) was observed for the DTG + RPV group compared with the CAR group; all of which were demonstrated to be statistically significant. Type 1 collagen cross-linked C-telopeptide (CTX) bone biomarker results were not available at the time

of this report. For bone-specific alkaline phosphatase and osteocalcin there was a significant interaction between treatment group and Baseline third agent class.

Overall, the results of this DEXA study show that DTG + RPV, compared to control, numerically increased bone mineral density and decreased bone turnover. It is reassuring that BMD is not decreased, i.e. BMD does not give rise to a safety concern. On the other hand, the data are not considered sufficient to claim any beneficial effect on bone metabolism, bone stability and fracture rate. The long-term clinical effects of these changes are therefore unknown.

Safety in special populations

No specific clinical study was performed with DTG+RPV in paediatric subjects, elderly subjects, subjects with renal insufficiency or hepatic impairment, or subjects co-infected with HIV-1 and hepatitis B or C. No adequate and well-controlled studies of DTG+RPV have been conducted in pregnant women. No human experience of acute overdose with the administration of DTG+RPV is available. The waiver of studies in special populations with the FDC RPV and DTG is considered acceptable as - according to current knowledge - there is no evidence for additional toxicities after co-administration of DTG and RPV and sufficient data are available with respect to safety in special population for the single entities DTG and RPV.

Regarding paediatrics, the PDCO agreed to the proposed paediatric investigation plan for Juluca (EMEA-001750-PIP01-15) and has agreed on an open-label, randomized, active controlled non-inferiority study to evaluate the maintenance of Efficacy and Safety of dual therapy, Dolutegravir (DTG) plus Rilpivirine (RPV), in anti-retroviral therapy (ART)-experienced HIV-1-Infected Children, from 6 to less than 18 years of age who are virologically suppressed on their current anti-retroviral (ARV) regimen (Study 3 in the PIP, completion is deferred to Dec 2022).

As there were hardly any **elderly** subjects enrolled in the SWORD studies (aged 65 years or older (n=18 in the DTG+RPV groups of both studies pooled, n=13 in the CAR groups)), safety in the elderly population cannot be reliably assessed and is included as missing information in the RMP.

In the 201636 and 201637 pooled analysis, there was no significant difference noted in the number of AEs reported post baseline between males (77%) and females (78%) in the DTG + RPV group. Events occurring in subjects <50 (76%) years and ≥50 (80%) years in the DTG + RPV group were similar. Some difference was observed in the number of AEs reported between races in the DTG + RPV group; however the majority of subjects were white and there were relatively small numbers in the other groups. There seemed to be more discontinuations due to AEs or death in the DTG+RPV vs CAR group in subjects over 50 years old.

Table 29. Summary of Adverse Event Categories by Age group – Early Switch Phase – Pooled – DTG + RPV

MedDRA Terms	Age <=65 N=498 n (%)	Age 66-70 N=7 n (%)	Age 71-75 N=6 n (%)	Age >75 N=2 n (%)
Total AEs	381 (77)	7 (100)	6 (100)	1 (50)
Serious AEs – Total	27 (5)	0	0	0
- Fatal	1 (<1)	0	0	0
- Hospitalization/prolong existing hospitalization	25 (5)	0	0	0
- Life-threatening	1 (<1)	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	1 (<1)	0	0	0
AE leading to drop-out	21 (4)	0	0	0
Psychiatric disorders	60 (12)	0	1 (17)	0
Nervous system disorders	75 (15)	0	2 (33)	0
Accidents and injuries	27 (5)	1 (14)	0	0
Cardiac disorders	2 (<1)	0	0	0
Vascular disorders	10 (2)	1 (14)	0	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	215 (43)	3 (43)	4 (67)	1 (50)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	21 (4)	0	0	0
<other AE appearing more frequently in older patients>				

Table 30. Summary of Adverse Event Categories by Age group – Early Switch Phase – Pooled – CAR

MedDRA Terms	Age <=65 N=499	Age 66-70 N=7	Age 71-75 N=4	Age >75 N=1
Total AEs	358 (72)	4 (57)	1 (25)	1 (100)
Serious AEs – Total	21 (4)	0	0	0
- Fatal	1 (<1)	0	0	0
- Hospitalization/prolong existing hospitalization	17 (3)	0	0	0
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	3 (<1)	0	0	0
AE leading to drop-out	3 (<1)	0	0	0
Psychiatric disorders	32 (6)	0	0	0
Nervous system disorders	41 (8)	1 (14)	0	0
Accidents and injuries	37 (7)	1 (14)	0	0
Cardiac disorders	2 (<1)	0	0	0
Vascular disorders	12 (2)	0	0	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	231 (46)	3 (43)	0	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	14 (3)	1 (14)	0	0
<other AE appearing more frequently in older patients>				

Gender, Age, and Race

No safety concern regarding gender and age was observed.

As the majority of subjects in studies 201636 and 201637 were white, no meaningful conclusion can be drawn regarding differences in white and black race and Asians.

Hepatic Impairment

Overall, only few patients with mild or moderate hepatic impairment were included in studies 201636 and 201637 (in the DTG + RPV group 29 subject with chronic hepatitis C at Baseline and 1 subject with ALT ≥3xULN at Baseline); all patients in the SWORD studies were Child- Pugh A. There was no evidence of any adverse effect following the switch to DTG + RPV in this patient population. Overall, no safety concern could be identified in patients with mild and moderate hepatic impairment. However, due to the limited number of patients with hepatic impairment enrolled in the SWORD studies, a final conclusion on the safety profile in this patient population is not possible. The SmPC states that Juluca should be used with caution in patients with moderate hepatic impairment.

Renal Impairment

138 (27%) subjects with mild renal impairment (CAR 131 (26%)) and 6 (1%) subjects with moderate renal impairment (CAR 4 (<1%)) were enrolled into the DTG + RPV treatment arms in the SWORD studies; no subjects with severe renal impairment were enrolled. Overall, it can be concluded that the safety profile in patients with mild renal impairment is not different compared to the safety profile in

patients without renal impairment. Due to the low number of patients with moderate renal impairment enrolled in the pivotal studies no adequate conclusions can be drawn from the data provided. Patients with severe renal impairment were excluded from SWORD studies.

Pregnancy and Lactation

The Applicant provided a comprehensive summary of pregnancy outcomes from clinical trials and post-marketing use of Dolutegravir (DTG) including latest data from the Antiretroviral Pregnancy Registry (APR). The submitted data indicate an increased rate of congenital anomalies, spontaneous abortion, and still birth after exposure to DTG based regimen in pregnant women.
Overall, the MAHs of DTG and RPV are committed to continuously generate data related to pregnancy. Accordingly, the risk of congenital anomalies, spontaneous abortion and still birth after administration of Juluca in pregnant women should be further evaluated during post-marketing. The absence of adequate and well-controlled studies of the DTG/RPV FDC in pregnant or breastfeeding women is addressed in the RMP as missing information and use of Juluca during pregnancy is not recommended.

Immunological events

The Applicant did not include a discussion of immunological events. Immunosuppression is not described for the single entities DTG or RPV; therefore, immunosuppressive effects are not expected for the FDC DTG + RPV either.

Safety related to drug-drug interactions and other interactions

In study LAI116181 only AEs Grade 1 - with the exception of 3 Grade 2 AEs – were observed. No new safety signals were detected from study.

Discontinuation due to AEs

Table 35 shows that 21 (4%) subjects in the DTG + RPV group and 3 (<1%) subjects in the CAR group experienced AEs leading to withdrawal/permanent discontinuation of study drug during the Early Switch Phase. All AEs leading to withdrawal had an incidence of <1%. AEs leading to withdrawal were most frequently reported from the psychiatric disorders (DTG + RPV, 9; CAR, 1) and GI disorders (DTG + RPV, 7) SOCs. During the Late Switch Phase, an additional 6 subjects discontinued due to AEs (1 randomized to DTG + RPV at Baseline and 5 who switched to DTG + RPV at Week 52).

Baseline ART third-agent class (PI, INSTI, or NNRTI) did not seem to influence withdrawals in the DTG + RPV treatment group as a similar number of subjects reported AEs leading to withdrawal/ permanent discontinuation of study treatment during the Early Switch Phase - irrespective of their prior baseline ART third-agent class (7 of 133 (5%) subjects from a PI-containing regimen, 8 of 275 (3%) subjects from a NNRTI-containing regimen, and 6 of 105 (6%) subjects from an INSTI-containing regimen).

Overall, the incidences of the treatment discontinuations were not balanced across the both treatment groups with a higher incidence of withdrawals in the DTG + RPV group.

As already discussed, this is most likely explained by the switch design elements of the SWORD 1 and 2 studies and by the fact, that most of the AEs leading to withdrawal are known and expected side effects of the SEs. Therefore, it is plausible that the investigators will assess the occurrence of these events as related to study treatment with DTG and RPV – where applicable with the consequence of a

treatment withdrawal. Overall, no safety concern can be deduced based on the data submitted with regard to discontinuation due to AEs.

Table 31. Summary of Adverse Events Leading to Withdrawal/Permanent Discontinuation of Study Drug by SOC - Early Switch Phase

System organ class Preferred term	**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)**
Any event	9 (4%)	2 (<1%)	12 (5%)	1 (<1%)	21 (4%)	3 (<1%)
Psychiatric disorders						
Any event	4 (2%)	0	5 (2%)	1 (<1%)	9 (2%)	1 (<1%)
Anxiety	2 (<1%)	0	2 (<1%)	0	4 (<1%)	0
Depression	2 (<1%)	0	2 (<1%)	0	3 (<1%)	0
Insomnia	2 (<1%)	0	1 (<1%)	0	2 (<1%)	0
Depressed mood	0	0	1 (<1%)	0	1 (<1%)	0
Panic attack	2 (<1%)	0	0	0	1 (<1%)	0
Suicidal ideation	0	0	1 (<1%)	0	1 (<1%)	0
Suicidal attempt	0	0	0	1 (<1%)	0	1 (<1%)
Gastrointestinal disorders						
Any event	3 (1%)	0	4 (2%)	0	7 (1%)	0
Abdominal distention	1 (<1%)	0	1 (<1%)	0	2 (<1%)	0
Dyspepsia	0	0	2 (<1%)	0	2 (<1%)	0
Gastrointestinal hemorrhage	0	0	1 (<1%)	0	1 (<1%)	0
Pancreatitis acute	1 (<1%)	0	0	0	1 (<1%)	0
Peptic ulcer	1 (<1%)	0	0	0	1 (<1%)	0
Neoplasms benign, malignant and unspecified						
Any event	2 (<1%)	2 (<1%)	1 (<1%)	0	3 (<1%)	2 (<1%)
Breast cancer	0	1 (<1%)	0	0	0	1 (<1%)
Hodgkin disease	1 (<1%)	0	0	0	1 (<1%)	0
Kaposi sarcoma	0	0	1 (<1%)	0	1 (<1%)	0
Lung neoplasm malign	0	2 (<1%)	0	0	0	1 (<1%)
Plasmablastic lymphoma	1 (<1%)	0	0	0	1 (<1%)	0
Nervous system disorders						
Any event	0	0	2 (<1%)	0	2 (<1%)	0
Headache	0	0	1 (<1%)	0	1 (<1%)	0
Tremor	0	0	1 (<1%)	0	1 (<1%)	0
Hepatobiliary disorders						
Any event	1 (<1%)	0	0	0	1 (<1%)	0
Drug-induced liver injury	1 (<1%)	0	0	0	1 (<1%)	0
Respiratory, thoracic and mediastinal disorders						
Any event	0	0	1 (<1%)	0	1 (<1%)	0
Eosinophilic pneumonia acute	0	0	1 (<1%)	0	1 (<1%)	0

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The phase III studies 201636 (SWORD-1) and 201637 (SWORD-2) used DTG 50 mg + RPV 25 mg together as individual tablets. Additionally, a pivotal bioequivalence study in healthy adult volunteers (201676) was conducted to confirm that the DTG/RPV FDC tablet is equivalent to DTG and RPV given as two separate tablets together. Also a relative bioavailability study (201674) was conducted with different FDC formulations encompassing also investigation of a food effect. A Phase I drug interaction study (LAI116181) has evaluated the pharmacokinetics and safety of DTG and RPV in healthy adult subjects. An ongoing DEXA sub-study (202094) which enrolled subjects from the 2 Phase III clinical trials is evaluating the change in bone mineral density of those subjects who have switched from a tenofovir containing regimen to DTG + RPV compared to those who remained on a tenofovir containing current regimen.

The safety database consists of safety data from 1024 subjects (DTG + RPV 513; CAR 511) from studies 201636 and 201637. The median time of exposure of 364 days (52 weeks) to DTG + RPV and CAR was in line with recommendations outlined in the Guideline on the clinical development of medicinal products for the treatment of HIV infection. Overall, the safety data package provided is appropriate for an adequate safety evaluation.

A greater proportion of subjects in the DTG + RPV group compared with those in the CAR group reported any AEs, drug-related AEs, AEs leading to withdrawal, and SAEs. Imbalances in AE rate become more obvious with increasing severity of the AEs.

The impact of the switch design on the comparative safety, i.e. incidence of AEs is a plausible explanation for the imbalances observed:

Firstly, it can be assumed that many AEs occur at the beginning of therapy so that subjects on stable therapy (i.e. subjects in the CAR treatment group) will report less AEs than those randomised to a new therapy regimen (i.e. subjects in the DTG + RPV treatment group). Comparing subjects stable on CAR with subjects newly switched to DTG+RPV can therefore be expected to create a bias in favour of CAR. An analysis of the timing of occurrence of adverse events relative to the start of DTG+RPV / CAR treatment shows a shorter median time to onset in the DTG + RPV group compared to the CAR group. This observation reinforce the assumption that the higher incidence of AEs in the DTG + RPV treatment group vs CAR group is mainly due to the fact that subjects in the DTG+RVP group were not familiar with the adverse events of this treatment while the subjects on the CAR arm were already on their regimen for at least 6 months and thereby somewhat selected for tolerating the treatment.

Secondly, it must be assumed that according to study inclusion criterion 2 subjects with relevant AEs under their previous therapy have been switched to a better tolerated treatment for at least 6 months prior to screening. Therefore, subjects in the CAR group most likely receive a well-tolerated therapy as subjects with more severe AEs are no longer included; this condition is not given in the DTG + RPV group. Again it can be expected that this creates a bias in favour of CAR. The observation, that more serious AEs (grade 3 and 4) seem more imbalanced that less serious AEs (grade 1 and 2), supports this view.

Furthermore, most of the reported drug related events are well known and expected side effects of DTG and/or RPV and labelled in the corresponding SmPCs. The investigators are therefore aware about possible side effects of DTG and/or RPV. It is plausible, that the occurrence of those adverse events in the DTG + RPV treatment arm will then be assessed as related to study treatment DTG + RPV by the investigators.

A comparison between the incidences of adverse events for DTG + RPV co-administered, and corresponding frequencies for those events for DTG and RPV given as single entities was proposed to

evaluate possible additive effects when using DTG and RPV in combination. Although it should be considered that a cross comparison between studies may be difficult e.g. because of different study populations, it can be overall concluded that based on the data provided additive side effects seem to be unlikely.

A comparison of AE incidences between the Late Switch DTG + RPV subjects and the Early Switch DTG + RPV subjects to further support the assumption that the higher incidence of AEs in the DTG + RPV treatment group compared to CAR is most likely attributed to the open label and treatment switch design elements in Studies 201636 and 201637 will be submitted upon availability in 2Q2018.

The most commonly reported types of AEs were largely comparable between the DTG + RPV and CAR groups. AEs were most commonly reported from the system organ classes of infections and infestations, GI disorders, nervous system disorders, skin and subcutaneous tissue disorders, psychiatric disorders, and respiratory, thoracic and mediastinal disorders. No difference was seen in the incidence of AEs from the infections and infestations SOC in the 2 treatment groups. The types of AEs reported and subsumed under the SOCs with imbalances are overall known and expected side effects of the single entities DTG and/or RPV or can be considered as not drug-related. It can therefore be concluded that no new adverse reaction became obvious.

AEs leading to withdrawal were most frequently reported from the system organ class psychiatric disorders and GI disorders.

No new types of drug related adverse events were observed; most of the reported drug related events are well known and expected side effects of the single entities labelled in the corresponding SmPCs.

The AESIs that have been determined for co-administered DTG + RPV are considered adequate and sufficient based on non-clinical and/or clinical safety data for DTG and RPV. No relevant new safety concerns with regard to hypersensitivity, hepatobiliary disorders, psychiatric disorders including depression and suicidality, drug resistance, skin and subcutaneous disorders, gastrointestinal disorders, renal disorders, musculoskeletal and connective tissue disorders, and Grade 3 to 4 lipase elevations were identified as a result of the special monitoring.

The psychiatric AE profile (including depression and suicidality) for DTG + RPV was comparable to the known safety profile for the single entities.

According to the data submitted so far, the incidence of SAEs was low in both treatment groups. The reported SAEs were highly variable in nature and no meaningful pattern could be detected. There were some numerical imbalances for certain types of SAEs, but due to the low number of affected patients, firm conclusions cannot be drawn.

The incidence of serious drug-related AEs overall was low for both treatment groups (again with a slightly higher number of events in the DTG + RPV group). The events were very heterogeneous in nature and single events each, partly to be expected on the basis of the known safety profile of the single entities DTG and RPV, and partly to be explained by predisposing conditions. Overall, no new safety concerns were observed.

No imbalances for mortality were observed between the 2 treatment arms with a low number of deaths occurred. The fatalities were most likely not related to treatment.

No major differences were observed overall in post-baseline emergent toxicities between the DTG + RPV and CAR group in the clinical chemistry laboratory parameters. Reassuringly, there seems to be no increased risk of renal toxicity or hepatic toxicity for DTG + RPV compared with CAR.

The Applicant provided additional data to include ‘acute hepatic failure’ as a rare adverse reaction in the PI of dolutegravir containing ARVs. Based on the submitted data of severe liver disorders observed

with DTG containing regimens it cannot be ruled out that the DTG-containing regimen may be the likely causative agent for the small number of severe liver dysfunction events observed. Therefore, the addition of 'acute hepatic failure' as a rare adverse reaction in the Juluca SmPC/PIL was considered appropriate.

Only few post-baseline alterations with regard to haematological parameters were observed in the DTG + RPV and CAR group. The maximum intensity of post-baseline emergent haematological alterations was overall comparable across the two treatment groups.

The results of this DEXA study show that DTG + RPV, compared to control, numerically increased bone mineral density and decreased bone turnover. It is reassuring that BMD is not decreased, i.e. BMD does not give rise to a safety concern. On the other hand, the data are not considered sufficient to claim any beneficial effect on bone metabolism, bone stability and fracture rate. The long-term clinical effects of these changes are therefore unknown.

There was no evidence for an increased risk of renal toxicity or hepatic toxicity for DTG + RPV compared with CAR.

2.6.2. Conclusions on the clinical safety

Based on safety data provided it can be concluded that the safety profile of DTG taken in combination with RPV seems to be consistent with the established safety profiles of the single agents and no additional risks or safety issues due to combination therapy could be identified.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns The safety profile of DTG taken in combination with RPV is consistent with the safety profile of the single entities, and no additional risks or safety issues due to combination therapy have been identified.	
Important identified risks	**DTG, RPV** • Depression (including suicidal ideation and behaviours particularly in patients with a pre-existing history of depression or psychiatric illness) • Drug resistance **Identified risk for DTG, potential risk for RPV** • Hepatotoxicity **DTG** • Hypersensitivity • Interaction with dofetilide or pilsicainide
Important potential risks	**DTG, RPV** • Severe or serious rash (DAIDS Grade 3/4) **DTG** • Renal disorders • Rhabdomyolysis • Pancreatitis **RPV** • QT interval prolongation • Blood cortisol decreased
Missing information	• Use in the elderly (>65 years) • Use in pregnancy and breast feeding

	• Use in children and adolescents (<18 years) • Long term safety

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
A Prospective Observational Cohort Study to Monitor and Compared the Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir (with or without Abacavir) and other Integrase Inhibitors (with or without Abacavir) Ongoing	To investigate the risk of HSR, hepatotoxicity and serious rash (DAIDS category 3 or 4)	HSR Hepatotoxicity Serious rash	Final protocol submission	June 2014
			Study start	June 2014
			Study completion (data collection completion)	June 2019
			Final report	2Q2020 (extended time to allow for bio specimen collection from suspected HSR cases)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study 200336: A Prospective Interventional Pharmacokinetic and Safety Study of DTG/ABC/3TC in Pregnant Women Ongoing	To investigate the use of DTG during pregnancy	Use in pregnancy	Protocol effective	23 December 2013
			Study start	16 January 2015
			Final report	End of study CSR anticipated 2022
Study 201636 (SWORD 1) / Study 201637 (SWORD 2): A Phase III, randomized, multicenter, parallel-group, noninferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus rilpivirine from current INI-, NNRTI-, or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed. Ongoing	These studies are designed to demonstrate the non-inferior antiviral activity of switching to DTG + RPV once daily compared to continuation of CAR up to 48 weeks. These studies will also characterize the long-term antiviral activity, tolerability and safety of DTG + RPV through Week 148.	Long term safety	Protocol effective	03 November 2014
			Study start dates	April 2015
			Final reports	End of study CSRs anticipated December 2021
Antiretroviral Pregnancy Registry (APR) Ongoing	Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.	Use in pregnancy	A registry interim report is prepared semi-annually summarising the aggregate data.	Data from the APR will be presented in the PBRER.
Real-world evidence for effectiveness of Two Drug Regimen, Antiretroviral therapy with integrase inhibitors plus a reverse transcriptase inhibitor (COMBINE-2) Planned	To evaluate the effectiveness and safety of DTG-based 2-drug regimens (DTG/RPV or DTG/3TC)	Drug resistance	Protocol submission	June 2018

Risk minimisation measures

Routine risk minimisation activities are considered sufficient for management of risks with the DTG/RPV FDC.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Applicant seeks the following therapeutic indication for Juluca:

„JULUCA is indicated 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 6 months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor (see section 5.1)."

HIV-infection has become a manageable chronic disease. In the EU several drugs of different drug classes are approved for antiretroviral therapy of HIV-1 infected patients, for both patients not previously treated (naïve) and patients in need of a change in therapy.

For many years the proportion of subjects at Week 48 with plasma HIV-1 RNA < 50 copies/mL, has been a well-established surrogate endpoint for antiviral efficacy and, hence, prognosis of HIV-1 infection and disease.

3.1.2. Available therapies and unmet medical need

Current treatment guidelines recommend a combination of 2 nucleos(t)ide reverse transcriptase inhibitors plus an agent from a different class, i.e. a triple combination regimen. These NRTI-based regimens have been shown to be effective and largely tolerated, however have been associated with long-term toxicities, such as lactic acidosis or bone and kidney changes. Use of NRTI-sparing regimens has hence been postulated to improve the overall tolerability and hence long-term therapeutic success.

In addition, over the past years one focus of drug development has become co-formulation of all active substances to form single tablet, once daily, antiretroviral regimens.

Two nucleos(t)ide-free regimens are currently recommended by learned societies (EACS 2017), both encompassing the INSTI raltegravir and the boosted PI darunavir. These regimens require twice daily dosing of raltegravir and a fixed dose combination tablet of the INSTI and the PI+booster are not available. These regimens are not considered “preferred” by the learned society and are recommended only in patients with favourable virological and immunological baseline characteristics. These regimens are thus not widely used.

Improved tolerability, safety, and simple dosing regimens are important drivers of good adherence and hence lessen the risk of development of drug resistance.

3.1.3. Main clinical studies

For confirmation of the efficacy of the applied product the Applicant submitted four key studies:

- A drug-drug interaction and food interaction study with DTG and RPV as single entities and different fixed dose formulations (see Study no. 201674),
- A bioequivalence study between DTG and RPV as single entities versus the fixed dose combination under fed conditions with moderate fat meal (see Study no. 201676) and
- Two identically designed efficacy and safety studies with DTG and RPV as dual regimen and administered as single entities (Study 201636 and 21637), comprising a total of 1024 virologically suppressed patients with 513 patients in the investigational arm. These studies were designed as so-called “switch studies” with the control arm randomised to continuing on the baseline antiretroviral regimens and statistical testing for non-inferiority. For methodological issues (many different regimens in the control arm) studies were not blinded. After 48 weeks patients from the control arm were switched to DTG+RPV. The studies are ongoing and their overall duration will be 148 weeks.

3.2. Favourable effects

No relevant DDI between DTG and RPV was observed, which is supportive for combining the two active substances.

As for the single entities an increase in exposure, Cmax and AUC, was seen when the FDC was administered with a meal. Bioequivalence of DTG and RPV as single entities and as FDC was shown under moderate-fat meal conditions.

The primary efficacy analyses of the Phase III studies (201636/201637) as well as for the pooled data demonstrated that DTG plus RPV administered ad single entities is non-inferior to CAR, with more than 94% of subjects in both arms achieving the primary endpoint of < 50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm.

Point estimates for the difference were very close to zero with narrow confidence intervals, the worst estimates (for study 201636) down to -4.1, i.e. much less than the predefined margin of -10% for the individual studies. For the pooled analyses the point estimate was -0.2 (-3.0; 2.5), adjusted for baseline stratification factors with the unadjusted analysis showing almost identical results.

Virological failures occurred only at very low numbers in both groups, with only 1 of these subjects in the DTG + RPV arm having genotypic substitution K101K/E mixture in RT. This subject was noted as non-adherent and viral load decreased from first measurement to confirmatory visit and further down to < 50 c/ml upon withdrawal.

Increases in CD4+-cell counts from baseline to week 48 were noted in both groups.

In addition, secondary analyses were supportive for comparative efficacy of DTG+ RPV versus CAR.

3.3. Uncertainties and limitations about favourable effects

The patient population of the studies was highly preselected in terms of numbers/duration of prior antiretroviral therapy, comorbid conditions, co-medications and absence of relevant resistance mutations. Moreover, patients had been on their first or second therapy for a mean of about 5 years. The available data question the generalizability of the study results to a wider target population. The approved indication reflects a selected patient population in terms of prior durability of viral suppression and presence of resistant mutations.

Differences in terms of rate of virological suppression, transient increases in viral load and slow virological re-suppressions as well as clear differences in terms of CD4+-cell counts between the two study groups were not reported. However, one subject in the DTG+RPV group versus none in the CAR-group experienced disease progression. Further information related to disease progression and occurrence of HIV-1 associated conditions is requested with the Week 100 SWORD study update and during marketing surveillance.

Information regarding occurrence of resistant minority variants will be provided post-authorisation.

The Applicant claims fewer long-term toxicities and better adherence as the major advantages of the dual regimen with DTG+RPV. However, so far, no such advantage is evident.

Persistence of HIV replication in sanctuary sites can occur despite undetectable viraemia in plasma, and this could be more pronounced with dual than with triple therapy. As viral replication in sanctuary sites has been associated with persistent systemic inflammation and immune activation, as well as with accelerating neurocognitive dysfunction, this may have potential consequences on the long term. Long-term data will be provided post-authorisation.

3.4. Unfavourable effects

The safety data package for this application consists of safety data of 1024 subjects (DTG + RPV 513; CAR 511) from the two ongoing Phase III studies 201636 and 201637.

Adverse events related to the GI tract were more frequently reported with DTG + RPV (129 subjects, 25% vs. 82 subjects, 16% in the comparator group). While diarrhoea and dyspepsia were the most commonly reported AEs in both treatment groups, differences were seen for flatulence, abdominal distention and constipation.

Nervous system disorders (mainly headache and dizziness) were also more frequently observed with DTG + RPV than with comparator (77 subjects, 15% vs 42 subjects, 8%).

Less frequently, psychiatric side effects were observed in response to DTG + RPV (61 subjects, 12% vs. 32 subjects, 6%), mainly consisting of depression, suicidal ideation and behaviour, insomnia and abnormal dreams. Psychiatric AEs lead most commonly to withdrawal in the DTG + RPV group.

All these AEs described above are well known from the individual single entities and are therefore expected.

Furthermore, a higher rate of AEs subsumed under respiratory, thoracic and mediastinal disorders (45 subjects, 9% vs. 24 subjects, 5%) were observed. However, events in the Respiratory, thoracic and mediastinal disorders SOC were very heterogeneous in nature so that no specific pattern of respiratory AEs became obvious. It was concluded that respiratory events described in the DTG + RPV group were likely not related to study treatment.

An early small increase of mean serum creatinine levels which remained stable over time was observed in subjects in the DTG + RPV group; this is a known effect of DTG.

In addition, ADRs not observed in the pivotal studies with DTG + RPV but listed in the corresponding SmPCs from the single entities are included in the Juluca SmPC (e.g. hypersensitivity, decreased white blood cell count, immune reconstitution syndrome, increased pancreatic amylase).

3.5. Uncertainties and limitations about unfavourable effects

Based on all safety data submitted it is reasonable to conclude that the safety profile of the combined administration of DTG and RPV seems to be consistent with the established safety profiles and the current labelling of the single agents. No additional risks or safety issues were identified.

3.6. Effects Table

Table 32. Effects Table for Juluca for the treatment of HIV-1 infections in virologically suppressed adults (cut-off 22nd November 2016)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint of studies 201636/ 201637	Proportion of patients with HIV-1 RNA in plasma at week 48, (Snapshot Analysis for Studies 201636, 201637, and Pooled Data (ITT-E Population))	%	DTG+RPV **Study -36** 95% *Difference* -0.5 (adj: -0.6) **Study -37** 94% *Difference* 0.1 (adj (0.2) **Pooled data** *Difference* -0.2	CAR 96% (95% CI: -4.1;3.2) 94% (95% CI: -3.9;4.2) (95% CI: -2.9,2.5)	- Questionable generalisability of results to wider target population Strength of evidence regarding internal validity only : strong	See section 2.5.2 and 2.5.3
Unfavourable Effects						
Imbalance in AEs rates	Higher incidence of AEs in the DTG + RPV group compared to CAR in the 2 pivotal Phase III studies Any AEs drug-related AEs	Sub-jects, % Sub-jects, %	395 77 97 19 21	364 71 9 2 3	Most likely explainable by study design. ADRs in DTG + RPV group in general in line with known safety profile of the single substances. However, possible additive effects should be further discussed.	Section 2.6 and 2.6.1

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The favourable effects shown in the efficacy studies 201636 and 201637 are reassuring regarding the good performance of the dual nucleos(t)ide free regimen consisting of DTG 50 mg and RPV 25 mg as compared to continuation of a so far efficacious (and well-tolerated) nucleos(t)ide containing antiretroviral regimen. While the study results appear to be quite robust with respect to their internal validity, the external validity of the study results is unclear:

Stringent patient selection criteria hamper the generalizability of the study results to a wider target population.

The unfavourable effects seen in studies 201636 and 201637 do not raise a major concern with respect to the safety of the dual treatment regimen consisting of DTG 50 mg and RPV 25 mg. The overall safety profile of the combination appears comparable to what is known from the single entities. Clarification was sought on individual aspects regarding the differential AE-rates between test and reference treatment.

No efficacy and safety data have been obtained with the fixed dose combination tablet Juluca.

A bioequivalence study (201676) was submitted as bridge for efficacy and safety, which confirmed bioequivalence between the single entities and the FDC in moderate fat conditions. A potential differential food effect for the FDC as compared to the SEs with higher mean exposures after a high-fat as compared to moderate-fat meal was observed for the FDC. However, the CHMP concluded that the use of a moderate fat meal in the pivotal bioequivalence study is sufficiently sensitive and discriminatory to detect a difference between formulations.

3.7.2. Balance of benefits and risks

The clinical programme as such is appropriate for confirmation of efficacy and safety of the combination of DTG and RPV as a dual antiretroviral regimen – as single entities as well as a fixed dose combination. However, additional concerns were identified with respect to efficacy/safety of Juluca, which will be addressed post-authorisation.

3.8. Conclusions

The overall benefit-risk of Juluca is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Juluca is favourable in the following indication:

Juluca is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.