Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for emtricitabine / rilpivirine / tenofovir alafenamide fumarate

Proprietary Product Name: Odefsey

Sponsor: Gilead Sciences Pty Ltd

First round report: 27 January 2016
Second round report: 20 May 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviations	Meaning
3TC	lamivudine
ABC	abacavir
ACTH	adrenocorticotropic hormone
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	efavirenz / emtricitabine / tenofovir disoproxil fumarate (coformulated; Atripla)
ATV	atazanavir
AZT	zidovudine
BHIVA	British HIV Association
BMD	bone mineral density
BMI	body mass index
CD4	cluster determinant 4
CDC	Centres for Disease Control and Prevention
CG	Cockcroft-Gault
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula for calculating glomerular filtration rate

Abbreviations	Meaning
CLcr	creatinine clearance
CMH	Cochran-Mantel-Haenszel
COBI, C	cobicistat (Tybost)
CSR	clinical study report
C-telopeptide	type 1 collagen C-telopeptide
CV	coefficient of variation
DHHS	Department of Health and Human Services
DHEAS	dehydroepiandrosterone sulphate
DRV, D	darunavir
EACS	European AIDS Clinical Society
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
eGFRCG	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
eGFRCKD-EPI	Creatinine estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration serum creatinine equation
eGFRcreat	estimated glomerular filtration rate for creatinine as calculated by the Modification of Diet in Renal Disease formula
EQ VAS EQ	visual analogue scale
ETR	etravirine
EVG, E	elvitegravir (Vitekta)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEPO4	fractional excretion of phosphate

Abbreviations	Meaning
FEUA	fractional excretion of uric acid
FTC, F	emtricitabine (Emtriva)
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HDL	high-density lipoprotein
HIV, HIV-1	human immunodeficiency virus, type 1
HIVTSQ	HIV Treatment Satisfaction Questionnaire
INSTI	integrase strand-transfer inhibitor
IAS-USA	International Antiviral Society of the United States of America
ISE	Integrated Summary of Efficacy
ITT	intent-to-treat
ITT-SS	intent-to-treat population using the snapshot analysis
LDL	low-density lipoprotein
LH	luteinizing hormone
LOCF	last observation carried forward
LPV/r	ritonavir-boosted lopinavir
LSM	least-squares mean
m	module
M = E	missing = excluded
M = F	missing = failure
M = LOCF	missing = last observation carried forward
MH	Mantel-Haenszel
M-MASRI	Modified Medication Adherence Self-Report Inventory
N or n	number of subjects in a population (N) or subset (n)
NCEP	National Cholesterol Education Program

Abbreviations	Meaning
NNRTI	nonnucleoside reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
NVP	nevirapine
OLE	open label extension
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PEP	postexposure prophylaxis
P-gp	P-glycoprotein
PI	protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PP-SS	per protocol population using the snapshot analysis
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PT	preferred term
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAM	resistance-associated mutation
RAP	resistance analysis population
RBP	retinol binding protein

Abbreviations	Meaning
RT	reverse transcriptase
RNA	ribonucleic acid
ROW	Rest of World
RPV	rilpivirine
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
SF-36	Short Form-36
SF-36v2	Version 2 of the Short Form-36
SOC	system organ class
STB	elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate (coformulated; Stribild)
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TLOVR	time to loss of virologic response
TmP/GFR	renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
TVD	emtricitabine / tenofovir disoproxil fumarate (coformulated; Truvada)
UACR	urine albumin to creatinine ratio
UPCR	urine protein to creatinine ratio
VF	virologic failure

Abbreviations	Meaning
VFres	virologic failure based on resistance criteria
VFss	virological failure according to snapshot analysis

1. Introduction

This is a submission to register a Fixed Dose Combination (FDC) tablet consisting of emtricitabine (FTC, F), rilpivirine (RPV, R) and tenofovir alafenamide fumarate (TAF).

1.1. Drug class and therapeutic indication

F/R/TAF has been developed for the treatment of HIV-1 infection for once-daily oral administration. The FDC is a combination of one nucleoside reverse transcriptase inhibitor (emtricitabine or FTC or F) and one non-nucleoside reverse transcriptase inhibitor (rilpivirine RPV or R) and one nucleotide reverse transcriptase inhibitor (tenofovir alafenamide fumarate or TAF).

There is no currently approved indication for this FDC. ODEFSEY is proposed to be indicated as a complete regimen for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of ODEFSEY and with plasma HIV-1 RNA ≤ 100,000 copies/mL at the start of therapy.

It should be noted that the sponsor states the indication does not include the condition that HIV-1 RNA should be ≤ 100,000 copies/mL. This is in conflict with the above indication statement contained in the PI.

1.2. Dosage forms and strengths

Emtricitabine/rilpivirine/tenofovir alafenamide fumarate(F/R/TAF) fixed-dose combination (FDC) tablets are an immediate-release tablet dosage form containing 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV), and 25 mg of tenofovir alafenamide (TAF, GS-7340). F/R/TAF tablets are grey, capsule-shaped, film-coated tablets debossed with “GSI” on one side and “255” on the other. F/R/TAF tablets are 15 mm long and 7 mm wide.

F/R/TAF tablets are packaged in 75 mL white, high density polyethylene (HDPE) bottles containing three grams of silica gel desiccant and a polyester coil. Each bottle contains 30 tablets and is capped using a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminium-faced liner.

The following dosage forms and strengths are currently registered.

Emtricitabine (EMTRIVA F/FTC) is approved for treatment of HIV-1 infection when used in combination with other antiretroviral agents. Emtriva AUST Rs 96426, 96427; registration was granted on 21st December 2004. FTC is also approved as a component of TRUVADA (TDF/FTC, AUST R 107072), ATRIPLA (TDF /FTC/efavirenz, AUST R154491). Emtriva is also one component of the FDC Stribild which was granted registration on February 7, 2013. FTC and TAF are components of the investigational FDCs Descovy (F/TAF 200/10 mg and 200/25 mg) and Genvoya E/C/F/TAF (150/150/200/10 mg). An application for Genvoya E/C/F/TAF was submitted and accepted for evaluation on 27 February 2015.

The F/R/TAF FDC contains components that are either approved products or are anticipated to become registered for the treatment of HIV-1 infection. RPV and FTC are components of EVIPLERA (F/R/TDF, AUST R 176537). RPV is marketed as a single agent in Australia by Janssen as Edurant.

The submission proposes registration of the following dosage forms and strengths: ODEFSEY is a fixed dose combination of antiretroviral drugs FTC 200mg, RPV 25mg, and TAF 25mg.

1.3. Dosage and administration

The following dosage forms are registered for administration: Emtricitabine (FTC/F) 200mg and Rilpivirine (RPV) 25mg as separate tablets for oral administration. FTC can be administered with or without food. It is recommended that RPV is administered with a meal. TAF is currently not approved. TAF is not available as a single agent.

In adults and paediatric patients 12 years of age and weighing ≥ 35 kg the proposed dosage for ODEFSEY is one tablet taken orally once daily with food. There is no particular time of day recommended for dosing.

No data are available on which to make a dose recommendation for children <12 years of age or weighing <35 kg.

1.3.1. Elderly

No dose adjustment is required for elderly patients. In clinical trials of Genvoya: 80 of the 97 patients enrolled aged 65 years and over received FTC+TAF given with EVG+COBI as a fixed-dose combination tablet. No differences in safety or efficacy have been observed between elderly patients and those between 12 and less than 65 years of age. However, there have been no studies conducted in older patients taking FTC/TAF with other anti-retroviral combinations.

1.3.2. Missed Doses

If a dose of ODEFSEY is missed by less than 12 hours, the missed dose should be taken as soon as possible. If the dose of ODEFSEY was missed by more than 12 hours, the next dose should be taken at the next regularly scheduled time.

1.3.3. Hepatic Impairment

No dose adjustment of ODEFSEY is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of ODEFSEY in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, ODEFSEY is not recommended for use in patients with severe hepatic impairment

1.3.4. Renal Impairment

No dose adjustment of ODEFSEY is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/min. The safety of ODEFSEY has not been established in adult patients with estimated creatinine clearance that declines below 30 mL/min or in paediatric patients with renal impairment. No data are available to make dose recommendations in paediatric patients with renal impairment.

2. Clinical rationale

Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. For ART-naive HIV-1 infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI).

The success of potent and well tolerated ART means that morbidity and mortality in the HIV infected population is increasingly driven by non-AIDS associated co-morbidities. Clinical attention has become more focused on the optimisation of tolerability, long term safety, and adherence to potent ART regimens. A medical need remains for new, effective therapies that take into consideration the non HIV co-morbidities, demographics of the aging HIV infected population, ARV resistance, and regimen simplification. Chronic kidney disease is important, since observational studies have demonstrated a relationship between kidney disease and progression to AIDS and

death. Moreover, HIV associated nephropathy, present in up to 30% of patients, is a common cause of ESRD requiring dialysis and potential transplantation. ART with proven efficacy and safety in the both elderly and young patients is important; however there are limited data and treatment options are available in both populations. The elderly have increased risks for co-morbidities, including those related to renal function and bone mineralisation. There are specific and complex challenges for the treatment of adolescents, especially related to adherence, and who also represent the population that will require ART for the longest time.

Given the duration for which a newly diagnosed person with HIV-1 may take an ART regimen throughout his or her lifetime, the F/RPV/TAF (Odefsey) tablet, may provide the potential for the longevity of treatment that optimises tolerability, long-term safety, and durable efficacy. For HIV-infected patients, Odefsey, with its substitution of Truvada for TAF may have advantages over the existing marketed product containing Truvada/FTC and RPV (Eviplera); specifically less proteinuria, less need for renal monitoring, and less impact on bone mineralisation relative to F/TDF/RPV treatment. The relatively low dose of TAF (25 mg vs TDF 300 mg) that is used in Odefsey could allow HIV-infected, virologically suppressed patients to convert from the TDF-based Eviplera regimen with possible renal and bone safety advantages.

> *Comment: The rationale for developing HIV-1 therapies that have long-term effectiveness, while minimising non-HIV related co-morbidities, is an essential goal to improve long-term HIV management.*

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier is based on a bioequivalence study (GS-US-366-1159) that is intended to provide the 'pharmacokinetic bridge' between the FTC and TAF components of Odefsey and the FTC/TAF components of Genvoya (E/C/F/TAF), although the dose of TAF in Odefsey is 25mg, whereas the dose in Genvoya is 10mg, albeit boosted with 150mg of Cobicistat. The clinical data in the submitted dossier is, to a greater extent, comparable to that in the Genvoya dossier.

As noted by the sponsor there are no data available in this marketing submission on the use of Odefsey in the target population of patients with HIV-1 infection. The only data in this dossier are derived from healthy adult subjects who were administered Odefsey in Phase 1 bioequivalence studies. There are no clinical data on adolescent subjects who are either healthy or who have HIV-1 infection. All other data are based on evidence from the Genvoya submission, which is not approved at this time.

The submission contains the following clinical information:

- Two clinical pharmacology studies, including two that provided pharmacokinetic data and none that provided pharmacodynamic data. The pharmacokinetic studies are GS-US-366-1159 which is a Phase 1 two way cross-over study comparing the bioequivalence of FTC/TAF administered as Genvoya (E/C/F/TAF) with FTC/TAF administered as Odefsey (F/RPV/TAF) and secondly RPV administered as a single tablet, compared with RPV administered as Odefsey). The second PK study is a phase 1 study, GS-US-366-1651, describing the PK of Odefsey under fed and fasted conditions, both in healthy subjects. A third study is included, GS-US-366-1689, which is a phase 1 study to determine the possible drug interactions between Odefsey and the combination of Ledipasvir/Sofosbuvir.
- No population pharmacokinetic analyses.
- No pivotal efficacy/safety studies. The dossier for Genvoya is included, but these data are specifically for the combination of E/F/C/TAF at a TAF dose of 10 mg. There are no

bioequivalence studies comparing the 10mg TAF dose with the 25mg dose used in the Odefsey FDC, except as Genvoya, which also contains EVG and COBI.

- No dose-finding studies.
- There are two post-marketing reports of cumulative clinical experience with Eviplera as related to skin reactions and weight gain. Eviplera is a different FDC to Odefsey as it contains 300mg TDF compared with the 25mg of TAF in Odefsey.

3.2. Paediatric data

The submission included paediatric data related to clinical studies on Genvoya, not specifically on Odefsey. The Genvoya data are provided on HIV-infected treatment naive adolescents 12 years old or greater (GS-US-292-0106). There are no bioequivalence or clinical data for Odefsey in adolescents. This is especially relevant in relation to the recommended use of Odefsey 200mg/25/25mg as there are no bioequivalence studies presented in the dossier to enable determination of the relationship of the 10mg TAF boosted with 150mg Cobicistat dosage as used in the Genvoya study GS-US-292-0106.

3.3. Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice. All of the studies were conducted under a United States Investigational New Drug Application (IND) and in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, consent form, study subject information sheets, and advertisement were submitted by each investigator to a duly constituted Institutional Review Board for review and approval before study initiation. All subjects provided written informed consent after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	Bioequivalence † - Single dose	GS-US-366-1159
	Food effect	GS-US-366-1651
PK interactions	Ledipasvir/Sofosbuvir	GS-US-366-1689

† Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Physicochemical characteristics of the active substance

4.2.1.1. FTC (GS-9019, GS-9036, FTC, F)

Empirical Formula

C8H10FN3O3S; Formula Weight: 247.24; Emtricitabine contains two chiral centres at the C-2 and the C-5 positions of the 1,3-oxathiolane ring. Emtricitabine is produced as the 2R, 5S-enantiomer, designated as the cis-(-)-enantiomer. The pKa of Emtricitabine is 2.65.

Three polymorphs of Emtricitabine have been observed. Emtricitabine (FTC) Form I is the commercial FTC drug substance. FTC may exist in three crystalline forms. Form I is the most thermodynamically stable form at temperatures below 130°C and is the only form isolated from the commercial synthetic process. Form II is a metastable form and has only been produced after heating Form I above its melting point of about 155°C. Upon cooling, Form II converts to Form III. Form III has only been observed following heating and cooling cycles, and has never been isolated by crystallization from organic solvents. FTC Form I is not hygroscopic and absorbs less than 0.03% water at a relative humidity of 90% at 25°C. FTC is a free base with one ionisable moiety in the pH range of 2-10. FTC exhibits a pKa of2.7 as determined by potentiometric titration. FTC exhibits pH-dependent solubility over a physiological pH range.

The intrinsic solubility of FTC free base is 106 mg/mL (pH 7) and is enhanced under acidic conditions to greater than 750mg/mL at pH 2.3. FTC undergoes hydrolysis in aqueous solution, and to a smaller degree, in the solid-state after exposure to humidity and heat. Two main hydrolytic degradants are (2R, 5S)-5-fluoro-1-[2(hydroxymethyl)-1, 3-oxathiolane-5-yl]-2, 4(1H,3H)-pyrimidinedione (FTU) and 5-fluorocytosine (5-FC). FTU is the major degradation product under acidic conditions, whereas cyclic-FTU degradation also requires cyclization through nucleophilic addition to the uracil ring before or after hydrolysis. The two observed cyclic-FTU diastereomers are designated cyclic-FTU1 (GS-9237 or cFTU1) and cyclic-FTU2 (GS-492127 or cFTU2). Cyclic-FTU is not formed in the FTC drug substance.

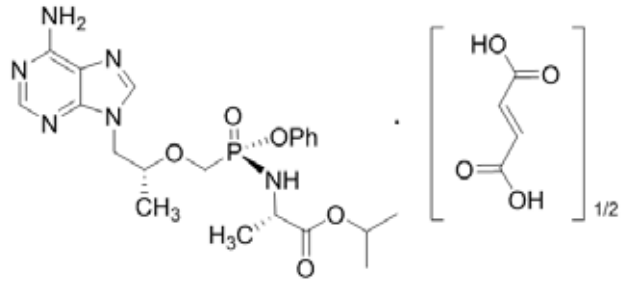
Susceptibility of FTC to oxidation was evaluated in aqueous solution containing 1%v/v hydrogen peroxide. Under these conditions, FTC oxidizes to form FTC-sulphoxide. FTC-sulphoxide has not been observed in FTC drug substance stored under recommended storage or accelerated stability conditions. In the solid state, FTC exhibits excellent chemical stability when stored up to 36months at the long-term condition of 25°C/60%RH and up to 6 months at 40°C/75%RH. FTC is not sensitive to light. FTC is nearly completely absorbed with an oral bioavailability of 93%.It is therefore deemed a high-permeability drug substance. FTC is considered to be a BCS Class 1 compound with high solubility across the physiologic pH range and high permeability observed in human clinical studies.

4.2.1.2. TAF

Empirical Formula

C21H29O5N6P; Formula Weight: 476.5; Tenofovir alafenamide is a prodrug of TFV. Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C. After absorption, TAF is converted to TFV intracellularly, which is phosphorylated to the active metabolite, tenofovir diphosphate (TFV-DP), which competes with natural 2'-deoxyadenosine triphosphate (dATP) for incorporation by the HIV-1 or HBV reverse transcriptase (RT) and, once incorporated, results in chain-termination.

Figure 1: TAF chemical compound



Stereochemistry

TAF fumarate has three chiral centres. The chiral centre at the propyloxy side chain is in the R-configuration. The absolute stereo-configuration of the carbonylethylamino substituent is derived from the amino acid L-alanine, which has the S-configuration at the alpha-carbon. The remaining stereocentre is located at the phosphorus atom and is in the Sp configuration.

Polymorphism

TAF fumarate consists of tenofovir alafenamide free base and a half-molar equivalent of fumaric acid. TAF fumarate is isolated as an unsolvated anhydrous polymorph (Form I). Form I has been determined as the thermodynamically most stable form and is the only polymorph identified as relevant to the designed crystallization process. A tetrahydrofuran solvate (Form II) has been identified through a stable form screen. Form II desolvates under drying conditions to generate Form I. Tenofovir diphosphate is a very weak inhibitor of mammalian DNA polymerases α, β, δ, ε, and mitochondrial DNA polymerase γ.

Tenofovir alafenamide is metabolized by hydrolases including carboxyl esterase 1 and cathepsin A (Cat A) and has minimal interaction with typical xenobiotic metabolizing enzymes. Unlike tenofovir disoproxil fumarate (TDF, Viread), TAF is relatively stable in human plasma (t½ ~75 minutes), but rapidly converts to TFV inside cells. Because TAF is more stable in plasma than the TDF, higher levels are achieved in HIV-target cells. In HIV-target cells, including lymphocytes and macrophages, TAF is metabolized by Cat A, providing enhanced delivery of TFV. During clinical studies, administration of TAF resulted in subsequent formation of 4-fold (3-7-fold at 90% confidence interval) higher intracellular levels of TFV-DP in peripheral blood mononucleated cells (PBMCs) and 90% lower circulating levels of TFV relative to TDF.

4.2.1.3. Rilpivirine hydrochloride (RPV HCl)

Rilpivirine hydrochloride (RPV HCl) polymorph A is the commercial RPV drug substance. Three polymorphic forms (A, B and C) of RPV HCl were isolated in a polymorph screening study, as well as a hydrate form D. RPV HCl is capable of forming solvates with certain solvents. Polymorph A is the most thermodynamically stable of the polymorphic forms and is the form of the drug substance produced by the commercial process. Melting of polymorph A, with decomposition, commences at 250°C. RPV HCl polymorph A is not hygroscopic and absorbs up to approximately 0.2% water at 95% relative humidity. The water uptake is reversible and no hysteresis is found. RPV has one ionisable moiety in the pH range of 2-10. RPV exhibits a pKa of 5.6 for the pyrimidine moiety. RPV HCl is practically insoluble in aqueous media, with solubilities ranging from <0.02µg/mL to 20µg/mL over the pH range 1.2 to 6.6. RPV is lipophilic with a partition coefficient (Log P) of 4.86 determined at pH 7.0. RPV (R314585) is not prone to degradation in suspensions at low pH (0.1N HCl) or in water. Some degradation is observed in 0.1N NaOH suspensions.

Base-catalysed hydrolysis of the nitrile moieties yielded the amides R399558 and R401371. Additionally, isomerization of RPV yielded the Z-isomer R289932. RPV HCl is stable when stored up to 48 months at the long-term storage condition of 30°C/65% RH and up to 6 months at the accelerated condition of 40°C/75% RH, when protected from light. No stability related changes were observed in appearance, assay, water content, polymorphism and microbiological purity

during storage of the drug substance over a 48month period. Photostability studies of RPV HCl drug substance were conducted according to ICH Q1B guidelines. Impurity R600649 is observed at levels of 0.20% –0.26%, T002592 (GS-9639) is observed at the level of 2 ppm, and a slight increase in the Z-isomer impurity R289932 (0.03% 0.06%) is observed. RPV is prone to oxidation in 0.3% hydrogen peroxide solution at 60°C, with formation of R419763.

Oxidative ring opening of the diamino pyrimidinyl-ring results in D015553, which can undergo ring closure to form D015554. An increase of T002592 (GS-9639) was also observed under oxidative conditions (up to 2620 ppm after 4days at 60°C). The above mentioned degradation products are not considered potential degradation products in the drug substance and/or drug product given they have not been observed in the solid state under accelerated and long-term storage conditions.

The permeability of RPV was evaluated using Caco-2 monolayers. Steady-state permeation coefficient values for RPV were in the range 10 to 13 × 10-6 cm/s and 15 to 27 × 10-6 cm/s, for absorptive and secretory transport, respectively. Permeability appeared to be practically concentration-independent from 3 to 100μM, supporting a major role for passive trans-cellular permeation in trans-epithelial RPV movement. Based on these observations, RPV HCl is considered to be a BCS Class 2 compound with low solubility across the physiological pH range and high permeability.

4.3. Pharmacokinetics in healthy subjects

4.3.1. Absorption

4.3.1.1. Sites and mechanisms of absorption

FTC

Single- and multiple-dose PK studies have shown that FTC is rapidly and extensively absorbed after oral administration. Plasma FTC concentrations were measurable at the earliest sampling time (15 minutes post dose) and reached a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1200 mg) and then followed an apparent multi-exponential decay. Greater than 85% of an oral dose of FTC is absorbed with little first-pass elimination prior to reaching the systemic circulation, resulting in a high absolute bioavailability value.

TAF

TAF is transported by P-glycoprotein (P-gp) and subject to metabolism by esterases expressed in the intestine. Inhibition of P-gp by COBI reduces P-gp–mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed. Cumulative results from Studies GS-US-292-0103, GS-US-292-0101, and GS-US-311-0101 indicate that TAF exposure following a 10-mg dose (either as a single agent co-administered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg alone. Cobicistat inhibits P-gp and therefore increases serum exposure to TAF, thus justifying the use of the 10mg TAF dosage in the presence of cobicistat.

RPV

The transepithelial permeability of RPV was intermediate in human colon carcinoma-derived (Caco-2) cells. Passive transcellular diffusion is proposed as a mechanism for RPV intestinal absorption. Rilpivirine was not a substrate of P-glycoprotein (P-gp). Rilpivirine showed P-gp inhibitory properties with an apparent 50% inhibitory concentration (IC50) of 9.2 μM (3.4 μg/mL). Therefore, inhibition of transepithelial permeation of P-gp substrates by RPV cannot be excluded.

After oral administration of TMC278 base, the absolute oral bioavailability of RPV was 32%, 54%, 31%, and 24% to rats, rabbits, dogs and monkeys, respectively. Adding CA in the formulation administered to rats and dogs usually increased the exposure showing that the absorption of RPV is pH-dependent in these species as in humans.

After oral administration of RPV (base and HCl forms), peak plasma concentrations were generally reached rapidly followed by a decline at lower dose levels, whereas at higher dose levels, the plasma profiles showed a plateau until at least 8 hours in all species. Across the dose range studied and species including humans, plasma concentrations of RPV increased dose-proportionally or more often less than dose-proportionally, due to low solubility. At very high dose levels in animals, no further increase in exposure was seen.

FTC/RPV/TAF

With respect to potential drug interactions within the combination that could affect absorption, FTC and RPV show high passive permeability and absorption is unlikely to be affected when administered with TAF. While TAF is an efflux substrate in the intestine, absorption is unlikely

to be affected by FTC as intestinal efflux transport is not inhibited by FTC. Inhibition of P-gp by RPV observed in vitro is unlikely to be clinically relevant as RPV did not affect plasma exposure to P-gp substrates including digoxin and TAF in clinical drug interaction studies.

Although formal nonclinical studies of the absorption kinetics of the FTC/RPV/TAF FDC have not been conducted, clinical studies on the combination have been performed on healthy adults to determine food effect.

4.3.2. Bioavailability

4.3.2.1. Absolute bioavailability

Bioavailability of TAF

Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (~ 40%). TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine. Inhibition of P-gp by a boosting agent (e.g., COBI or RTV) reduces P-gp-mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. Cumulative results from Study GS-US-366-1159, GS-US-292-0103, and GS-US-292-0101, indicated that TAF exposure following administration of TAF 10 mg with a boosting agent (either as a single agent co-administered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg without a boosting agent, including following administration of the FTC/RPV/TAF FDC.

As TAF is not metabolized by CYP enzymes except for weak metabolism observed for CYP3A4 in vitro, CYP inducers are not expected to have a relevant effect on TAF PK; however, most CYP inducers are also P-gp inducers, and co-administration with P-gp inducers may decrease the absorption of TAF. Co-administration with a moderate CYP3A and P-gp inducer (i.e., EFV) resulted in slightly lower TAF exposure (14% to 22%), and co-administration with a weak CYP3A and P-gp inducer (i.e. RPV) resulted in no change to TAF exposure. As such, minimal effect on TAF exposure is expected upon co-administration of F/TAF with a moderate or weak CYP3A/P-gp inducer. Co-administration of F/TAF with potent CYP3A/P-gp inducers is not recommended.

Bioavailability of RPV (TMC278)

Trial TMC278-C117 (not included in the dossier) investigated the relative oral bioavailability of TMC278 administered as the Phase III tablet compared to the Phase IIb tablet (TMC278-C117). The Phase III tablet, administered as 4 × 25-mg tablets or 1 × 150-mg tablet, was compared to the Phase IIb tablet administered as 1 × 100-mg tablet or 3 × 50-mg tablets, respectively. In each comparison, the exposure to TMC278 using the Phase III tablet was comparable to the exposure using the Phase IIb tablet. It is therefore concluded that data obtained for TMC278 using the Phase IIb tablet should be consistent with those obtained using the Phase III tablet. Furthermore, the exposure to TMC278 at a dose of 25 mg once daily was shown to be generally comparable for the Phase IIb tablet and the Phase III tablet in clinical trials in healthy subjects (TMC278-C151, and TMC278-C152 and TMC278-C130, respectively; not included in this dossier) and in HIV-1 infected subjects (Phase IIb trial C204 and Phase III trials, respectively; not included in this dossier). Both registrational Phase

III trials with TMC278 at the recommended dose of 25 mg once daily were performed with the TMC278 25-mg Phase III tablet.

Bioavailability of FTC

In Study FTC-110, the relative bioavailability of the commercial oral solution formulation (Formulation C-1) and the commercial capsule formulation (200 mg; Formulation B) were investigated in healthy subjects compared with that of an intravenous solution (from which the absolute bioavailability of FTC was derived in the same study). The bioequivalence of the capsule and oral solution were also assessed.

The geometric mean AUCinf ratios indicate that the relative bioavailability (in comparison with the intravenous solution) of the capsule was 93% (90% CIs: 87% to 99%), whereas the relative bioavailability for the oral solution was 75% (90% CIs: 70% to 80%). Based on AUCinf ratios, the relative bioavailability of the capsule formulation compared with oral solution was 124% (90% CIs: 117% to 133%).

At 93%, the relative bioavailability of the capsule is high, indicating excellent absorption via the oral route. The lower bioavailability of the solution compared with the capsule was unexpected and difficult to explain, although the magnitude of the difference (approximately 24%) between the 2 oral formulations is considered unlikely to be of any clinical importance. Furthermore, data for the FTC oral solution are not directly relevant to the present application, which concerns a combination tablet formulation.

4.3.2.2. Bioavailability relative to an oral solution or micronised suspension

Not applicable as there is no oral solution of Odefsey.

4.3.2.3. Bioequivalence of clinical trial and market formulations

There have been no clinical trials of Odefsey in the target population of HIV-1 infected patients. The Phase 1 bioequivalence studies utilised the same formula as proposed for the marketing formulation.

4.3.2.4. Bioequivalence of different dosage forms and strengths

No dose ranging studies of Odefsey have been conducted.

4.3.2.5. Bioequivalence to relevant registered products

This section is presented by the sponsor as the pivotal bioequivalence data to support extrapolation of the clinical and safety of Odefsey as related to Genvoya and Edurant. However, this section of the assessment specifies bioequivalence to relevant registered products and Genvoya is currently not registered. While Edurant is a registered product, it is not administered as a single agent. It is most commonly administered as FTC/TDF/RPV (Eviplera). A submitted bioequivalence study by the sponsor is summarised in this section and comments are provided.

4.3.3. Study GS-US-366-1159

A Phase 1, Randomized, Open-Label, Single-Dose, Three-Way, Six-Sequence, Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine, Rilpivirine and Tenofovir Alafenamide from a Fixed Dose Combination of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (200/25/25 mg) Relative to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination and Rilpivirine (25 mg).

4.3.3.1. Objectives

The primary objectives of this study were as follows:

- To evaluate the bioequivalence of emtricitabine (F; FTC) and tenofovir alafenamide (TAF) administered as elvitegravir (EVG; E)/cobicistat (COBI; C)/FTC/TAF (E/C/F/TAF)

(150/150/200/10 mg) fixed-dose combination (FDC) tablet or as FTC/rilpivirine [RPV]/TAF (200/25/25 mg) FDC tablet.

- To evaluate the bioequivalence of RPV administered as a 25-mg tablet or as FTC/RPV/TAF (200/25/25 mg) FDC tablet

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of single oral doses of FTC, RPV, and TAF administered as FTC/RPV/TAF, RPV, and E/C/F/TAF.

4.3.3.2. Study Design

This was a randomized, open-label, single-dose, 3-way, 6-sequence, crossover study to determine the bioequivalence of FTC and TAF, administered as E/C/F/TAF FDC tablet or as FTC/RPV/TAF FDC tablet, and the bioequivalence of RPV administered as RPV single tablet or as FTC/RPV/TAF FDC tablet. Following screening and Day −1 procedures, subjects were randomized 1:1:1:1:1:1 to 1 of 6 treatment sequences (1 [ABC], 2 [ACB], 3 [BAC], 4 [BCA], 5 [CAB], or 6 [CBA]) and received a single dose of 1 of the following treatments (A, B, or C) on Days 1, 15, and 29:

- Treatment A: Single dose of FTC/RPV/TAF (200/25/25 mg) FDC tablet administered orally under fed conditions
- Treatment B: Single dose of RPV 25-mg tablet administered orally under fed conditions
- Treatment C: Single dose of E/C/F/TAF (150/150/200/10 mg) FDC tablet administered orally under fed conditions

Subjects were admitted to the study clinic on Day –1 and remained confined to the clinic until Day 35 (treatment sequences 1 and 3) or Day 43 (treatment sequences 2 and 4–6). Subjects received follow-up a phone call 7 (± 2) days after discharge from the study clinic (Day 42 [± 2 days] (treatment sequences 1 and 3) or Day 50 [± 2 days] (treatment sequences 2 and 4–6).

4.3.3.3. Study Population

Healthy males and nonpregnant, nonlactating females aged 18 to 45 years, inclusive, with a body mass index (BMI) of ≥ 19 and ≤ 30 kg/m^2, no significant medical history, creatinine clearance (ie, estimated glomerular filtration rate calculated using the Cockcroft Gault formula [eGFRCG]) ≥ 70 mL/min, and in good general health as determined by the investigator at the screening evaluation.

4.3.3.4. Pharmacokinetic Results

Statistical comparisons of the plasma FTC, RPV, and TAF PK parameters AUC_{last}, AUC_{inf}, and C_{max} are presented below.

Table 2: Study GS-US-366-1159: Statistical Comparisons of Pharmacokinetic Parameter Estimates Between Test and Reference Treatments (All PK Analysis Set).

FTC PK Parameter	N	Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	95	9381.9 (21.7)	96	10159.4 (21.5)	92.24	90.84, 93.67
AUC_{inf} (h•ng/mL)	95	9603.2 (21.6)	96	10387.1 (21.5)	92.37	90.93, 93.83
C_{max} (ng/mL)	95	1608.6 (26.5)	96	1583.8 (23.8)	100.81	97.52, 104.21
RPV PK Parameter	**N**	**Test Mean (CV%)**	**N**	**Reference Mean (CV%)**	**GLSM Ratio (Test/Reference) (%)**	**90% CI (%)**
FTC/RPV/TAF (200/25/25 mg) (Test) vs RPV (25 mg) (Reference)						
AUC_{last} (h•ng/mL)	95	3698.6 (34.9)	95	3373.4 (40.0)	111.70	106.31, 117.38
AUC_{inf} (h•ng/mL)	95	3843.1 (36.2)	95	3540.7 (43.0)	110.51	105.82, 115.42
C_{max} (ng/mL)	95	121.4 (26.1)	95	108.0 (28.7)	113.52	108.40, 118.89
TAF PK Parameter	**N**	**Test Mean (CV%)**	**N**	**Reference Mean (CV%)**	**GLSM Ratio (Test/Reference) (%)**	**90% CI (%)**
FTC/RPV/TAF (200/25/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	95	250.0 (43.4)	96	238.4 (36.5)	102.85	98.18, 107.75
AUC_{inf} (h•ng/mL)	82	263.6 (42.0)	85	247.4 (36.1)	103.85	98.27, 109.74
C_{max} (ng/mL)	95	198.0 (57.7)	96	191.5 (48.2)	100.78	91.63, 110.85

The GLSM ratios and corresponding 90% CIs of AUClast, AUCinf, and Cmax for FTC, RPV, and TAF were contained within the 80% to 125% boundary criteria specified for bioequivalence.

4.3.3.5. Safety Results

Safety was comparable between the 3 study treatments. No deaths, serious AEs, AEs leading to premature study drug discontinuation, or pregnancies were reported. All AEs were Grade 1 in severity.

Overall, the most frequently reported AEs were constipation, nausea, and headache.

All but 1 Grade 3 laboratory abnormalities were occult blood on urinalysis in female subjects (5 of 8 subjects had confirmed menses; no event was considered clinically important). One subject had Grade 3 amylase and Grade 4 lipase without clinical symptoms. No laboratory abnormality was considered clinically important.

No clinically relevant changes in median values for hematology and chemistry parameters were observed during this study.

No clinically relevant changes in vital sign measurements were observed during this study.

4.3.3.6. Conclusions according to the sponsor

- The FTC and TAF components of the FTC/RPV/TAF (200/25/25 mg) FDC are bioequivalent to the E/C/F/TAF (150/150/200/10 mg) FDC.
- The RPV component of the FTC/RPV/TAF (200/25/25 mg) FDC is bioequivalent to RPV 25-mg tablet (Edurant).
- FTC, RPV, and TAF administered as FTC/RPV/TAF (200/25/25 mg) FDC, RPV (25 mg), and E/C/F/TAF (150/150/200/10 mg) FDC were generally safe and well-tolerated in healthy volunteers.

Comment: It is unclear why the sponsor has not used Descovy and Eviplera as the references for Odefsey bioequivalence study. Genvoya is unlicensed and it is also a different FDC than Odefsey as it contains a boosting agent (Cobi) and an Integrase inhibitor (Evg) and the TAF

dosage is 10mg, not 25 mg as in Odefsey. Data in Module 5 are not provided on the bioequivalence of 10mg TAF to TAF 25mg, although this was determined in the Descovy dossier GS-US-311-1473. Descovy contains the same dose of TAF (25mg) as in Odefsey, when intended for use without a boosting agent. Moreover, the RPV component of Odefsey should be evaluated with Eviplera as this is both licensed and has the equivalent components to Descovy and Odefsey (TDF at 300mg and TAF at 25mg).

4.3.3.7. Influence of food

This is the second of two studies submitted by the sponsor that utilise Odefsey FDC in a bioequivalence study.

Study GS-US-366-1651

A Phase 1 Study to Determine the Effect of Food on the Pharmacokinetics of Emtricitabine, Rilpivirine and Tenofovir Alafenamide (TAF) Administered as the Emtricitabine/Rilpivirine/Tenofovir Alafenamide (F/R/TAF) Fixed Dose Combination (FDC) Tablet in Healthy Volunteers

Objectives

The primary objective of this study was as follows:

- To evaluate the effect of food on the pharmacokinetics (PK) of emtricitabine (FTC), rilpivirine (RPV), and tenofovir alafenamide (TAF) when administered as FTC/RPV/TAF fixed-dose combination (FDC)

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of administration of the FTC/RPV/TAF FDC under fed and fasted conditions

Study Design

This was a randomized, open-label, single-dose, 2-period, crossover, food-effect study. Two cohorts of subjects were enrolled to assess the effect of moderate-fat food (Cohort 1: Treatments A and B) and the effect of high-calorie, high-fat food (Cohort 2: Treatments A and C), on the PK of a single-dose FTC/RPV/TAF (200/25/25 mg) FDC tablet.

Following screening and Day –1 assessment, eligible subjects were randomized (1:1) within each cohort to 1 of 2 treatment sequences (AB or BA in Cohort 1; AC or CA in Cohort 2) and received a single dose of study drug on Days 1 and 11. The study treatments were as follows:

- Treatment A (fasted): Single-dose FTC/RPV/TAF (200/25/25 mg) FDC tablet, administered orally under fasted conditions in the morning (Cohorts 1 and 2)
- Treatment B (fed, moderate-fat): Single-dose FTC/RPV/TAF (200/25/25 mg) FDC tablet, administered orally under fed conditions (approximately 600 kcal, approximately 27% fat) in the morning (Cohort 1 only)
- Treatment C (fed, high-calorie, high-fat): Single-dose FTC/RPV/TAF (200/25/25 mg) FDC tablet, administered orally under fed conditions (approximately 800-1000 kcal, approximately 50% fat) in the morning (Cohort 2 only)

Subjects were admitted to the study center on Day –1 and remained confined until Day 21. Subjects received a follow-up telephone call on Day 25 to 30.

Study Population

Healthy males or healthy non-pregnant, non-lactating females, aged 18 to 45 years, inclusive, and with a body mass index (BMI) of ≥ 19 and ≤ 30 kg/m^2, no significant medical history, and a normal renal function (estimated glomerular filtration rate [eGFR] ≥ 70 mL/min calculated using the Cockcroft-Gault method [$eGFR_{CG}$]).

Pharmacokinetic Results

FTC, RPV, and TAF plasma PK parameters (FTC and RPV: AUCinf, AUClast, and Cmax; TAF: AUClast and Cmax), and the statistical comparisons of these parameters following the administration of a single dose of FTC/RPV/TAF under fasted conditions and fed conditions (moderate-fat or high-calorie, high-fat food), are presented below.

Table 3: Study GS-US-366-1651: Statistical Comparisons of Pharmacokinetic Parameter Estimates Between Test (Moderate-Fat or High-Fat) and Reference Treatments (FTC, RPV, and TAF PK Analysis Sets).

FTC PK Parameter Mean (%CV)	FTC/RPV/TAF Fasted (N = 30)	FTC/RPV/TAF Fed, Moderate-Fat (N = 30)	GLSM Ratio (%) (90% CI) Moderate-Fat vs. Fasted
AUC_{inf} (h•ng/mL)	10687.7 (15.2)	9750.2 (17.1)	90.96 (88.53,93.45)
AUC_{last} (h•ng/mL)	10498.2 (15.6)	9530.0 (17.1)	90.57 (88.28,92.92)
C_{max} (ng/mL)	2276 (23.8)	1734 (25.6)	75.96 (70.10,82.31)
RPV PK Parameter Mean (%CV)	**FTC/RPV/TAF Fasted (N = 30)**	**FTC/RPV/TAF Fed, Moderate-Fat (N = 30)**	**GLSM Ratio (%) (90% CI) Moderate-Fat vs. Fasted**
AUC_{inf} (h•ng/mL)	2891.4 (55.0)	3175.6 (40.1)	112.73 (103.35,122.97)
AUC_{last} (h•ng/mL)	2451.0 (37.5)	2851.9 (37.6)	115.80 (107.42,124.83)
C_{max} (ng/mL)	65.5 (35.8)	91.5 (36.9)	139.17 (124.04,156.14)
TAF PK Parameter Mean (%CV)	**FTC/RPV/TAF Fasted (N = 30)**	**FTC/RPV/TAF Fed, Moderate-Fat (N = 30)**	**GLSM Ratio (%) (90% CI) Moderate-Fat vs. Fasted**
AUC_{last} (h•ng/mL)	223.8 (34.9)	325.1 (33.4)	144.82 (133.13,157.54)
C_{max} (ng/mL)	386 (45.6)	306 (45.7)	77.49 (65.54,91.62)

FTC PK Parameter Mean (%CV)	FTC/RPV/TAF Fasted (N = 30)	FTC/RPV/TAF Fed, High-Fat (N = 30)	GLSM Ratio (%) (90% CI) High-Fat vs. Fasted
AUC_{inf} (h*ng/mL)	11214.0 (16.9)	9827.0 (18.3)	87.55 (84.76,90.42)
AUC_{last} (h*ng/mL)	11008.2 (16.8)	9605.9 (18.0)	87.20 (84.48,90.00)
C_{max} (ng/mL)	2107 (27.7)	1551 (23.2)	74.48 (69.50,79.82)
RPV PK Parameter Mean (%CV)	**FTC/RPV/TAF Fasted (N = 30)**	**FTC/RPV/TAF Fed, High-Fat (N = 30)**	**GLSM Ratio (%) (90% CI) High-Fat vs. Fasted**
AUC_{inf} (h•ng/mL)	2158.0 (42.8)	3579.2 (32.4)	172.39 (149.29,199.06)
AUC_{last} (h•ng/mL)	2014.4 (41.5)	3352.2 (30.6)	173.24 (149.10,201.28)
C_{max} (ng/mL)	55.8 (43.3)	108.1 (27.5)	206.67 (179.08,238.51)
TAF PK Parameter Mean (%CV)	**FTC/RPV/TAF Fasted (N = 30)**	**FTC/RPV/TAF Fed, High-Fat (N = 30)**	**GLSM Ratio (%) (90% CI) High-Fat vs. Fasted**
AUC_{last} (h•ng/mL)	201.1 (40.4)	311.7 (42.4)	153.46 (139.10,169.31)
C_{max} (ng/mL)	316 (45.4)	230 (58.1)	69.12 (56.61,84.41)

4.3.3.8. Safety Results

Adverse events were reported in 8 of 60 subjects (13.3%) following FTC/RPV/TAF administered under fasted conditions, 1 of 30 subjects (3.3%) following FTC/RPV/TAF administered under fed conditions (moderate-fat food), and 4 of 30 subjects (13.3%) following FTC/RPV/TAF administered under fed conditions (high-calorie, high-fat food).

One subject had AEs that were considered by the investigator as related to study drug (nausea, vomiting, and dizziness); these occurred after dosing on the day of administration of FTC/RPV/TAF under fed conditions (high-calorie, high-fat food), and all resolved on the same day without treatment.

No deaths or SAEs were reported, and no subjects discontinued due to an AE. All AEs were Grade 1 (mild).

None of the AEs was reported by more than 1 subject in any treatment group.

4.3.3.9. Conclusions

The overall conclusions of this study are as follows:

- Overall TAF exposure (AUClast) increased by approximately 45% and 53% (moderate-fat and high-calorie, high-fat conditions, respectively) when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed compared with fasted conditions.
- Overall FTC exposure (AUCinf) decreased by approximately 9% and 12% (moderate-fat and high-calorie, high-fat conditions, respectively) when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed compared with fasted conditions.
- Overall RPV exposure (AUCinf) increased by approximately 13% and 75% (moderate-fat and high-calorie, high-fat conditions, respectively) when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed compared with fasted conditions.
- Single doses of the FTC/RPV/TAF FDC tablet, administered under fed and fasted conditions, were generally well tolerated in this study.

Dose proportionality

Not applicable

Bioavailability during multiple-dosing

No additional repeat-dose pharmacokinetic studies were considered warranted with the combination of FTC, RPV, and TAF With respect to potential drug interactions within the combination that could affect absorption, FTC and RPV shows high passive permeability and absorption is unlikely to be affected when administered with TAF. While TAF is an efflux substrate in the intestine, absorption is unlikely to be affected by FTC as intestinal efflux transport is not inhibited by FTC. Inhibition of P-gp by RPV observed in vitro is unlikely to be clinically relevant as RPV did not affect plasma exposure to P-gp substrates including digoxin and TAF in clinical drug interaction studies. Although formal nonclinical studies of the absorption kinetics of the FTC/RPV/TAF FDC have not been conducted, clinical studies on the combination have been performed.

Effect of administration timing

Dosing should occur with a meal, but not dependent on time of day.

4.3.4. Distribution

4.3.4.1. Volume of distribution

The distribution of Odefsey into compartments other than plasma (e.g., cerebrospinal fluid or genital tract secretions) has not been clinically evaluated in humans. The dissolution profile for the commercial tablet formulation of FTC/RPV/TAF showed that greater than 75% of FTC and TAF were dissolved within 30 minutes and greater than 75% RPV was dissolved within 60 minutes.

4.3.4.2. Plasma protein binding

- FTC: The protein binding of FTC was very low (< 5%) in mouse, rabbit, monkey, and human plasma.

- RPV: Rilpivirine was extensively bound to plasma proteins in all species and the plasma protein binding was found to be concentration independent. Plasma protein binding values ranged between 99.08% and 99.97% (TMC278-NC112). Rilpivirine was extensively bound to human albumin (99.5% at the physiological protein concentration of 4.3% and irrespective of the RPV concentration) and to lesser extent to α1-acid glycoprotein (48.8% at the physiological protein concentration of 0.07% and a TMC278 concentration of 1 µg/mL). The rank order of blood to plasma concentration ratio in all species was monkey > dog > rat > man > guinea pig > rabbit > mouse and ranged from 0.96 to 0.58. The distribution of RPV to red blood cells (RBCs) is limited in all species.
- TAF and TFV: Since TAF is highly unstable in rodent plasma due to hydrolytic cleavage by plasma esterases, the extent of TAF binding to plasma was determined in dog and human plasma in vitro. In vitro protein binding of TAF was moderate in dog and human plasma with the percent unbound values of 48.0% and 46.8%, respectively. These in vitro values were higher than those observed in multiple human ex vivo studies with the mean percent unbound TAF ranging from 14% to 23% in all subjects. Since the ex vivo results should be more clinically relevant than the in vitro values, percent unbound TAF of 20% was used for the assessments for potential drug interactions. The protein binding of TFV was very low (< 10%) in the plasma and serum of humans and all other species examined.

4.3.4.3. Erythrocyte distribution

Not applicable

4.3.4.4. Tissue distribution

FTC

The tissue distribution of [14C] FTC was characterized in rats and cynomolgus monkeys after a single oral dose of 200 mg/kg (TOX092 and TOX063, respectively). Emtricitabine was widely distributed in the body, with measurable concentrations found in all tissues within 1 hour following oral administration. Tissue concentrations generally declined in parallel with plasma concentrations, with no indication of accumulation in any tissue examined. Virtually no radioactivity remained in the body at 72 hours after dosing. The highest concentrations of FTC were found in the kidneys and liver. Concentrations in CNS tissues were 2% to 10% of the concentration in plasma.

RPV

The tissue distribution of RPV in rats has been studied using QWBA following single oral administration of [^{14}C] TMC278 (40 mg/kg). Studies were performed in pigmented Long Evans rats and pregnant female Sprague Dawley rats. Distribution to placenta and foetuses was examined in the latter study. In rats, tissue distribution of [^{14}C] TMC278 base and its metabolites after a single dose was rapid and extensive. The highest concentrations of radioactivity were measured in the liver, adrenal gland, brown fat, and kidney. There was no evidence of undue retention and there were no indications of irreversible binding of RPV and its metabolites to melanin.

After a single oral dose of 150 mg [^{14}C]TMC278 in healthy adults, the blood-to-plasma ratios of total ^{14}C-radioactivity were time-independent, with values ranging between 0.65 and 0.75, indicating that TMC278 and its metabolites were not distributed to blood cells to any significant extent. The distribution of TMC278 into compartments other than plasma (e.g., cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

TAF and TFV

Following oral administration of [^{14}C] TAF to mouse, rat, and dog, [^{14}C] TAF-derived radioactivity was widely distributed to most of the tissues in all species. Consistent with high hepatic extraction, high levels of radioactivity were observed in the liver; high radioactivity was also measured in the kidney. Low levels of radioactivity were observed in brain and testis in mouse. No melanin binding

was observed in rats. Distribution trends in the pigmented uveal tract of the eye and pigmented skin suggested that [14C] TAF-related radioactivity was not selectively associated with melanin-containing tissues in the pigmented mouse. Distribution studies in dogs showed 5.7 to 15-fold higher ^{14}C-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [^{14}C]-TAF relative to [^{14}C]-TDF. The concentration of TAF in dogs was relatively high also in lungs, thyroid, spleen, skeletal muscle, bone marrow, and some other tissues relative to TDF. Since the clinical TAF dose is >10-fold less than TDF, accumulation of TAF and/or its metabolites in these tissues should be similar (or less) to that with TDF.

Following single intravenous administration of [^{14}C]TFV in male rats, the highest concentrations of radioactivity were found in the kidney, liver, urine, and large intestine and trace amounts were observed in bone or bone marrow.

FTC/RPV/TAF

Drug interactions between FTC, RPV, and TAF that affect distribution would not be expected from the data available. While plasma protein binding is high for RPV and moderate for TAF, the binding was very low for FTC and TFV. Therefore, interactions through binding displacement would not be anticipated.

4.3.5. Metabolism

4.3.5.1. Interconversion between enantiomers

Not applicable

4.3.5.2. Sites of metabolism and mechanisms / enzyme systems involved

No studies have been conducted utilising the Odefsey FDC. Individual components have been assessed with the sponsor assuming the FDC will have the same metabolic pathways as the individual components.

TAF

The biotransformation of TAF was studied in mice, rats, dogs, and humans. Endogenous purine metabolites including hypoxanthine, xanthine, allantoin, and uric acid were observed in all species, including humans. TFV accounted for a majority of drug-related material in plasma, urine, and faeces from all species, except for human plasma in which uric acid was the predominant metabolite, accounting for 73.9% of the total AUC over 96 hours. The major metabolite in rat bile was M18, which accounted for 63% of total radioactivity recovered in bile. M18 and its oxidized metabolite, M16, were the major metabolites in dog bile accounted for 29% and 38% of total radioactivity recovered in bile. Various oxidative metabolites were found in dog bile. No metabolites unique to human were observed. Following oral dosing of mice, rats, and dogs with [^{14}C]TAF, the majority of radiolabel was recovered in the faeces or urine in all species. The elimination of a large amount of radioactivity in bile of bile duct-cannulated dogs indicates that biliary excretion is a major route of elimination of [^{14}C]TAF-derived radioactivity in dogs. Total recovery of radiolabel was high for all species.

The major enzyme involved in intracellular conversion of TAF to TFV in PBMCs is cathepsin A (CatA), which is a high-capacity and low-affinity pathway not readily inhibited by other xenobiotics

TAF has a distinct metabolism profile designed to maximize both antiviral potency and clinical safety. Inside cells, TAF is converted by intracellular enzymes to form the pharmacologically active metabolite TFV-DP. Due to increased plasma stability and activation by CatA, as compared with TDF, TAF is more efficiently loaded into PBMCs (including lymphocytes and other HIV-target cells) and macrophages, which results in greater concentrations of TFV-DP in PBMCs and lower exposure of TFV to the systemic circulation and undesired tissues, including the kidney and bone.

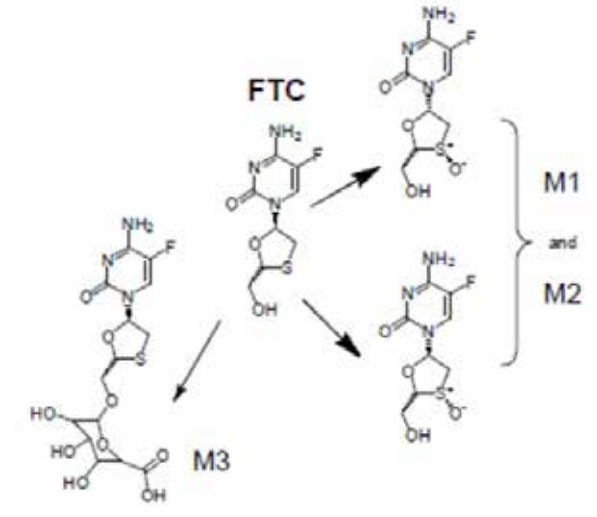
In contrast to PBMCs, TAF is primarily hydrolysed by carboxylesterase 1 in primary hepatocytes. Of the HIV PIs (DRV, ATV, LPV, and RTV), the boosting agent COBI, and HCV PIs (telaprevir, boceprevir, TMC-435, BI-201355, MK-5172, GS-9256, and GS-9451), the HCV PIs telaprevir and boceprevir, which are known to inhibit CatA, were the only ones that changed the antiretroviral effect of TAF in primary CD4+ T lymphocytes (reduced 23-fold and 3-fold, respectively). These data support the co-administration of the tested therapeutic PIs, with the exception of telaprevir or boceprevir, in combination with TAF, without negatively affecting its clinical pharmacology and intracellular conversion to TFV.

Emtricitabine and TFV are analogues of 2 different nucleosides, cytosine and adenosine, respectively, and do not share a common intracellular metabolism pathway. In experiments where both FTC and TFV were incubated together at concentrations higher than achieved in the plasma (10 μM), the intracellular phosphorylation of FTC and TFV to their active intracellular anabolites was not affected.

FTC

Emtricitabine is not subject to significant metabolism by CYP enzymes. Generation of a minor (~1%) sulphoxide metabolite (M1 and/or M2) was catalysed by CYP3A4, and inhibitor studies suggested that at least one other enzyme, possibly flavin-containing monooxygenase, may play a role (15396 v1). A minor direct glucuronide metabolite, M3, was also detected.

Figure 2: Oxidative Metabolism of FTC



RPV

The in vitro metabolism of TMC278 was studied in human hepatocytes and liver subcellular fractions of humans and various animal species. A major metabolic pathway of TMC278, representing the main in vitro biotransformation, was aromatic hydroxylation at the pyrimidinyl moiety, followed by glucuronidation. Another major metabolic pathway was aliphatic hydroxylation at 1 of the methyl groups of the cyanoethenyl-2,6-dimethylphenyl moiety, followed by dehydration to form a tricyclic metabolite. Aliphatic hydroxylation in combination with glucuronidation was also observed. The mercapturic acid biosynthesis route was a minor pathway, as was the release of the nitrile group followed by reduction/oxidation, resulting in the formation of an alcohol metabolite and a carboxylic acid metabolite. *N*-glucuronidation at the pyrimidinyl moiety of TMC278 also occurred. All TMC278 metabolites that were identified in human test systems were also found in at least 1 animal species.

4.3.5.3. Non-renal clearance

TAF

TAF is eliminated following metabolism to its major metabolite TFV. TAF and TFV have a median plasma t1/2 of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Renal excretion of intact TAF is a minor pathway with less than ≤ 2% of the dose eliminated in urine.

RPV

A mass balance study (Study C119) showed that most of the [14C] TMC278-related radioactivity from a single 150-mg dose administered as 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 TMC278 accounted for a mean of 25.5% of the dose in faeces.

FTC

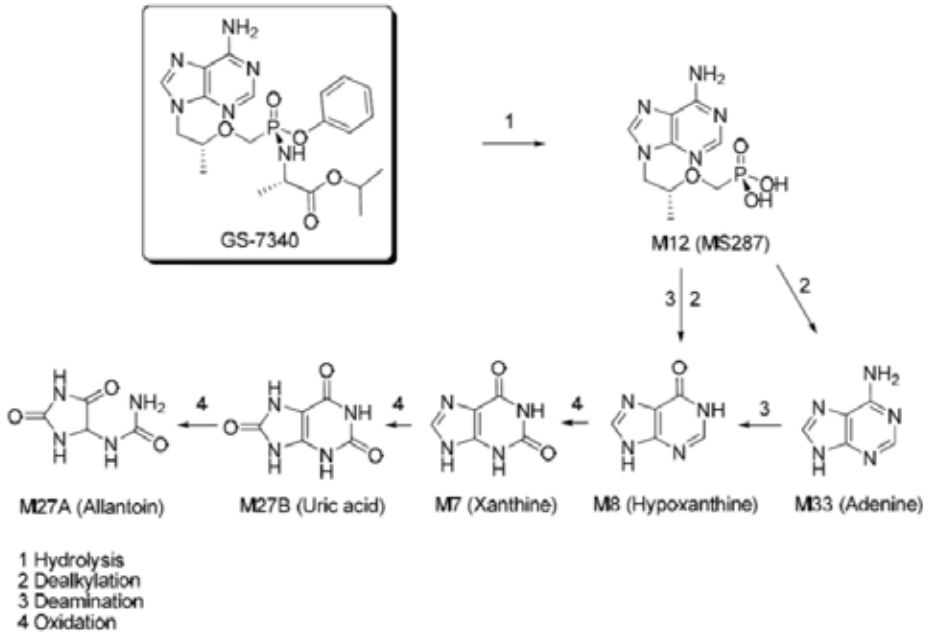
Following administration of [^{14}C] FTC, complete recovery of the FTC dose was achieved in urine (~86%) and faeces (~14%).

4.3.5.4. Metabolites identified in humans

No metabolites unique to humans were observed.

Active metabolites

Figure 3: Proposed Biotransformation Pathway of TAF in Humans.



M12 = TFV

Pathways are proposed based on general knowledge of metabolism and do not imply definitive pathways. Direct experimentation was not performed.

RPV

TMC278 was extensively metabolized, with more than 15 metabolites detected. The most abundant metabolite in faeces, which was derived from oxidation of TMC278 at the 5-position of the pyrimidinyl moiety, accounting for a mean of 16.1% of the dose. Three other metabolites each accounted for 2.2% to 3.0% of the dose. Metabolite carboxylic acid on the cyanoethenyl moiety resulted from methyl hydroxylation at the dimethyl phenyl moiety. Further dehydration of

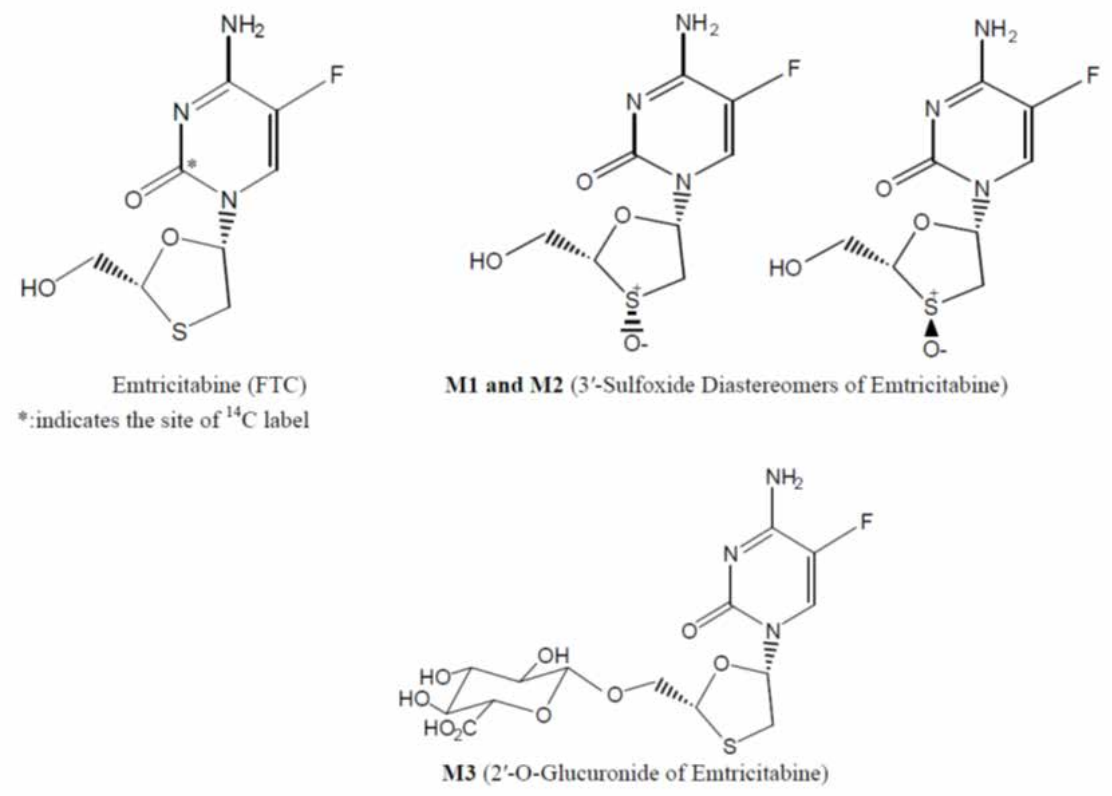
hydroxymethyl TMC278 resulted in a tricyclic metabolite (0.6%), which in turn was further oxidized or transformed to a carboxylic acid metabolite (1.6%). Two other minor metabolites were unknown, and accounted for 0.3% and 0.5% of the dose.

In urine, apart from the carboxylic acid metabolite (0.03%), the other metabolites were phase-2 metabolites (glucuronides or glutathione derived conjugates) including 2 glycine conjugates and a mercapturic acid conjugate. In total, these glutathione derived metabolites accounted for 1.2 % of the dose. The other metabolites were an *N*-glucuronide of TMC278 (0.6 %), and 2 glucuronides of hydroxylated metabolites (0.3% and 0.6%). 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 TMC278 (≤ 10.2% of the sample radioactivity), the tricyclic metabolite (≤ 9.7% of the sample radioactivity), and hydroxymethyl TMC278 (≤ 5.1% of the sample radioactivity) (NC157). Other metabolites (glucuronides of hydroxymethyl TMC278 and hydroxylated TMC278) were only traceable by liquid chromatography/tandem mass spectrometry (LC/MS/MS).

FTC

FTC is primarily eliminated from the plasma via renal excretion as unchanged drug (approximately 65% of an oral dose and approximately 73% of an IV dose). Metabolism is a minor route of elimination. In a mass balance study with [$_{14}$C] FTC, an average of 65% to 70% of an oral FTC dose was excreted in urine as unchanged drug, accounting for >80% of the total radioactivity present in urine (Study FTC-106). Approximately 13% of an oral dose was recovered in the urine (12.9%) and in faeces (0.01%) as metabolites. Three putative metabolites were isolated, with structures tentatively identified by mass spectrometry (Figure 4).

Figure 4: Putative Metabolites of FTC.



4.3.6. Other metabolites

Not applicable

4.3.6.1. Pharmacokinetics of metabolites

As discussed above

4.3.7. Consequences of genetic polymorphism

Not applicable

4.3.8. Excretion

4.3.8.1. Routes and mechanisms of excretion

TAF

TAF is eliminated following metabolism to its major metabolite TFV. TAF and TFV have a median plasma $t_{1/2}$ of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Renal excretion of intact TAF is a minor pathway with less than ≤ 2% of the dose eliminated in urine. In clinical PK studies, the pharmacologically active metabolite, TFV-DP, has a $t_{1/2}$ of 150 to 180 hours within PBMCs.

FTC

The plasma FTC $t_{1/2}$ was approximately 10 hours. Following FTC dosing, the steady-state mean intracellular $t_{1/2}$ of FTC-TP (the active drug moiety) in PBMCs was 39 hours. FTC is primarily excreted by the kidney by both glomerular filtration and active tubular secretion.

RPV

A mass-balance study showed that most of the [^{14}C] TMC278-related radioactivity from a single 150-mg dose administered as 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 TMC278 accounted for a mean of 25.5% of the dose in faeces. Only trace amounts (< 1%) of unchanged TMC278 were detected in urine.

4.3.8.2. Mass balance studies

TAF

Mass balance was determined in Study GS-US-120-0109 (not provided in Module 5), available in the Descovy assessment dossier. The primary objective of this study was to determine the mass balance of TAF following administration of a single, oral dose of radiolabeled carbon-14 ([^{14}C])TAF.

This was an open-label, Phase 1, mass balance study conducted at a single study centre in the United States to evaluate the PK, metabolism, and excretion of TAF following administration of a single, oral dose of radiolabeled [^{14}C]TAF in healthy subjects.

A total of 8 subjects were planned to be enrolled to obtain 6 evaluable subjects. Eight subjects were enrolled, completed study drug administration, and included in the safety and PK analysis sets. Six subjects completed the study, and 2 subjects withdrew consent. All subjects were men, and most (7 subjects [87.5%]) were white. The median age was 29 years (range: 19 to 45 years). The median BMI was 25.9 kg/m2 (range: 22.6 to 29.3 kg/m2), and the median eGFRCG was 117.5 mL/min (range: 87.7 to 198.2 mL/min).

The results of this mass balance study confirmed that TAF was extensively metabolised in urine and faeces. The total mean ± SD recovery of [14C]-radioactivity in faeces plus urine was 84.4% ± 2.45% (N = 7), with the percentage of radioactive dose recovered from faeces at 47.2% ± 4.62% (N = 7) and the percentage of radioactive dose recovered from urine at 36.2% ± 5.62% (N = 8). The predominant species detected in faeces and urine was TFV, accounting for 99% of the radioactivity recovered in faeces, and 86% of the radioactivity recovered in urine. All other metabolites detected in the faeces and urine were in trace amounts, with no values exceeding 2% of the administered radioactive dose. Only 1.41% ± 0.561% of the total radioactive dose was identified in urine as TAF, suggesting very low renal TAF clearance. No radioactive TAF was detected in faeces.

There were 2 concentration peaks present in the plasma [14C]-radioactivity time profile. At the first maximal plasma radioactivity concentration around 2 hours postdose, the predominant species was TAF, accounting for 72.6% of the total [14C]-radioactivity quantified. At the second maximal plasma radioactivity concentration around 24 to 48 hours postdose, the predominant species was uric acid, accounting for 97.6% of the total [14C]-radioactivity quantified. Over the 96-hour period following TAF administration, the predominant species circulating in plasma was uric acid, which accounted for 73.9% of the total [14C]-radioactivity AUC over the 96-hour period; TAF and TFV AUC represented 1.8% and 1.5% of the total [14C]-radioactivity AUC, respectively.

In addition to TFV and uric acid, additional low quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine. They are identical to the endogenous products of purine metabolism and should not cause any safety risk.

FTC

In vitro studies indicate that FTC is not an inhibitor of human CYP450 enzymes. Following administration of [^{14}C]FTC, complete recovery of the FTC dose was achieved in urine (~86%) and faeces (~14%). The biotransformation of FTC includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable. The plasma FTC $t_{1/2}$ was approximately 10 hours. Following FTC dosing, the steady-state mean intracellular $t_{1/2}$ of FTC-TP (the active drug moiety) in PBMCs was 39 hours. FTC is primarily excreted by the kidney by both glomerular filtration and active tubular secretion.

RPV

In vitro experiments indicate that RPV primarily undergoes oxidative metabolism mediated by the CYP 3A system. The terminal elimination half-life of RPV is approximately 45 hours.

A mass balance study (Study C119) showed that most of the [^{14}C]TMC278-related radioactivity from a single 150-mg dose administered as 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 TMC278 accounted for a mean of 25.5% of the dose in faeces. Only trace amounts (< 1%) of unchanged TMC278 were detected in urine.

4.3.8.3. Renal clearance

Emtricitabine and TFV are almost exclusively eliminated by renal excretion. While TFV is a substrate for OAT1, OAT3, and MRP4, none of these transporters was inhibited by FTC. TAF and TFV have a median plasma $t_{1/2}$ of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

Rilpivirine is predominantly excreted in faeces. Therefore, interactions within the components of the FTC/RPV/TAF FDC during excretion are unlikely.

4.3.8.4. Intra- and inter-individual variability of pharmacokinetics

Not applicable.

4.4. Pharmacokinetics in the target population

The FDC, Odefsey, has not been administered to the target population of either adults or adolescents with HIV-1 infection.

4.4.1. Pharmacokinetics in other special populations

The FDC, Odefsey, has not been administered to other special populations.

4.4.1.1. Pharmacokinetics in subjects with impaired hepatic function

The FDC, Odefsey has not been administered to subjects with impaired hepatic function.

4.4.1.2. Pharmacokinetics in subjects with impaired renal function

The FDC, Odefsey, has not been administered to subjects with impaired renal function.

TAF

An open-label study was performed to evaluate the PK of TAF and its metabolite TFV in non–HIV-infected subjects with severe renal impairment (defined as subjects with eGFRCG between 15 mL/min and 29 mL/min [inclusive] who were not on dialysis) and in age- and sex-matched non–HIV-infected subjects with normal renal function (eGFRCG ≥ 90 mL/min) following a single dose of TAF (Study GS-US-120-0108).

No clinically relevant differences in TAF or TFV PK were observed between healthy subjects and subjects with severe renal impairment. Plasma TFV exposure in subjects with mild to moderate renal impairment were within or below the range of TFV plasma exposure after administration of TDF 300 mg in both healthy, HIV-uninfected subjects and in HIV-infected patients with normal renal function. Additionally, population PK analyses of TAF and TFV from pooled Phase 1, 2, and 3 study populations showed that baseline estimated glomerular filtration rate (eGFR) was not a statistically or clinically relevant covariate influencing TAF PK.

RPV

In view of the negligible renal excretion of TMC278 (C119), a trial to investigate the exposure to TMC278 in subjects with renal impairment has not been conducted. In view of the negligible renal excretion of TMC278 (< 1%), no dose adjustment of RPV is required in patients with renal impairment.

FTC

Because renal excretion of the unchanged drug is the principal route of elimination for FTC, it is anticipated that the PK profiles of FTC in subjects with altered or deficient renal function may vary or deviate from those in subjects with normal renal function. Adult subjects with varying degrees of renal impairment (or insufficiency), as determined by estimated eGFRCG values, were evaluated in Study FTC-107. The results of this study are presented by the sponsor.

Study FTC-107 was an open-label, parallel group study with 6 subjects in each of the 5 groups with varying degrees of renal impairment as determined by estimated eGFRCG values (> 80 mL/min as normal function; 50-80 mL/min as mild impairment; 30-49 mL/min as moderate impairment; < 30 mL/min as severe impairment; or functional anephric requiring haemodialysis). The percentage of dose excreted as unchanged FTC in urine for the normal and mild renal impairment groups (eGFRCG 50-80 mL/min) was similar to that observed with healthy subjects (FTC-106) and HIV-infected subjects with normal renal function (FTC-101). However, in subjects with moderate and severe impairment (eGFRCG < 50 mL/min), the urinary recovery was lower (approximately 30%-50% of the dose) over a 72-hour collection period, primarily due to slower excretion of FTC by the impaired kidneys, which, in the absence of clinical experience of FTC in HIV-infected subjects with eGFRCG less than 60 mL/min, led to a dose interval adjustment recommendation (FTC-107 Dosing Interval Report).

A Phase 3 safety and efficacy study was conducted to evaluate the effect of the E/C/F/TAF on renal parameters in ART-naive and ART-experienced, HIV-infected adults with stable eGFRCG of 30 to 69 mL/min (Study GS-US-292-0112). This study included an intensive PK sub-study evaluating the PK of FTC following administration of E/C/F/TAF in subjects with eGFRCG of 30 to 69 mL/min (n = 30) and showed mean (%CV) FTC exposure AUC and C_{max} of 20,968.6 (25.5) ng•h/mL and 2645.3 (27.7) ng/mL, respectively, which were in the range of exposures where dose modification was not warranted in FTC-107. Importantly, the mean FTC AUC and C_{max} observed in GS-US-292-0112 subjects with eGFRCG of 30 to 69 mL/min is comparable with the AUC and Cmax of 19,900 (6.2)

ng•h/mL and 3800 (2.3) ng/mL, respectively, for subjects with eGFRCG of 50 to 80 mL/min who do not require dose adjustment {23270}, {30162}. Subjects with eGFRCG < 50 mL/min reported the same type and incidence of AEs as subjects with eGFRCG > 50 mL/min, and the observed laboratory abnormalities were consistent between the two groups.

The totality of these data only indirectly supports the recommendation that FTC/RPV/TAF may be safely administered once daily without dose adjustment in patients with mild to moderate renal impairment (eGFRCG 30 to 69 mL/min). As Odefsey has not been administered to subjects with renal impairment, it is not possible to directly conclude that the FDC has no impact on HIV-1 infected patients with renal impairment.

4.4.2. Pharmacokinetics according to age

Odefsey has only been administered to healthy adult subjects. It has not been administered to any patients with HIV-1 infection.

The effect of age of paediatric subjects on the PK of TAF and TFV was assessed based on data from Study GS-US-292-0106, where E/C/F/TAF was administered to HIV-infected, ART-naïve adolescents. TAF and TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration, indicating no relevant effects of paediatrics (age > 12 years) on the exposure of TAF. Additionally, in the pooled Phase 2 and Phase 3 study populations used for TAF population PK analyses, HIV-infected adolescent subjects had comparable TAF and TFV exposures versus HIV-infected adult subjects, respectively, again confirming that age was not a clinically relevant covariate, at least in adolescents above 12 years of age. Pharmacokinetics of FTC and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

> *Comment: Exposures of FTC and TAF achieved in 24 paediatric patients aged 12 to < 18 years were similar to exposures achieved in treatment-naïve adults. These studies were all conducted in subjects administered TAF and compared with Genvoya. There are no studies reported in adolescent subjects administered Odefsey. Therefore, the recommendation that Odefsey can be given to adolescents is not supported by the lack of clinical evidence.*

4.4.3. Pharmacokinetics related to genetic factors

Not applicable

4.4.4. Pharmacokinetics {in other special population / according to other population characteristic}

Odefsey has not been administered to any subjects in special populations.

4.5. Pharmacokinetic interactions

4.5.1. Pharmacokinetic interactions demonstrated in human studies

There has been a single study conducted with Odefsey submitted by the sponsor to determine pharmacokinetic interactions in humans. This is study GS-US-366-1689, which is detailed in this section.

4.5.2. Study GS-US-366-1689

- A Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between Emtricitabine/Rilpivirine/Tenofovir Alafenamide Fumarate (FTC/RPV/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablets

4.5.2.1. Study Period

This was a single centre Phase 1 study conducted during the period:

- 28 January 2015 (First Subject Screened)

- 22 March 2015 (Last Subject Observation for the Primary Endpoint).

4.5.2.2. Objectives

The primary objectives of this study were as follows:

- To evaluate the steady-state pharmacokinetics (PK) of FTC, RPV and TAF upon administration of FTC/RPV/TAF FDC with LDV/SOF FDC
- To evaluate the steady-state PK of SOF, its metabolites GS-566500 and GS-311007, and LDV upon administration of LDV/SOF FDC with FTC/RPV/TAF FDC

The secondary objectives of this study were as follows:

- To evaluate the steady-state PK of tenofovir (TFV) upon administration of FTC/RPV/TAF FDC with LDV/SOF FDC
- To evaluate the safety and tolerability of administration of LDV/SOF FDC or FTC/RPV/TAF FDC alone or in combination

4.5.2.3. Methodology

This randomized, open label, single-centre, multiple-dose, 3-way, 6-sequence, cross-over Phase 1 study evaluated the PK of SOF, its metabolites GS-566500 and GS-311007, and LDV upon administration of LDV/SOF with FTC/RPV/TAF, and the PK of FTC, RPV, and TAF upon administration of FTC/RPV/TAF with LDV/SOF in healthy volunteers. Subjects were randomized 1:1:1:1:1:1 to 1 of 6 treatment sequences and received the following 3 treatments:

- LDV/SOF (1 × 90/400 mg tablet once daily) administered orally under fed conditions in the morning (Treatment A)
- FTC/RPV/TAF (1 × 200/25/25 mg tablet once daily) administered orally under fed conditions in the morning (Treatment B)
- LDV/SOF (1 × 90/400 mg tablet once daily) plus FTC/RPV/TAF (1 × 200/25/25 mg tablet once daily) co-administered under fed conditions in the morning (Treatment C)
  The treatment sequences were ABC, ACB, BCA, BAC, CBA, and CAB. Each treatment in the sequence was taken for 11 days (i.e., first treatment on Days 1 to 11, second treatment on Days 12 to 22, and third treatment on Days 23 to 33).

4.5.2.4. Number of Subjects (Planned and Analysed)

Planned:

- A total of 42 subjects enrolled to obtain 36 evaluable subjects

Analysed:

- Randomized Analysis Set: 42 subjects
- PK Analysis Sets for LDV, SOF, GS-566500, GS-331007, RPV FTC, TAF, and TFV: 42 subjects
- Safety Analysis Set: 42 subjects

4.5.2.5. Diagnosis and Main Criteria for Inclusion

Eligible subjects were healthy male and non-pregnant, non-lactating female subjects from 18 to 45 years of age (inclusive) with a body mass index (BMI) of 19.0 to 30.0 kg/m2 (inclusive), normal 12-lead electrocardiogram (ECG), no significant medical history, and a normal renal function (estimated glomerular filtration rate [eGFR] ≥ 70 mL/min calculated using the Cockcroft-Gault method [eGFRCG]).

4.5.2.6. Duration of Treatment

The treatment duration was 33 days, with a follow-up phone call 7 (± 2) days after the last dose of study drug.

4.5.2.7. Test Product, Dose, Mode of Administration, and Lot No.

- LDV/SOF (1 × 90/400 mg tablet once daily) plus FTC/RPV/TAF (200/25/25 mg tablet once daily) co-administered orally under fed conditions in the morning (Treatment C)
- The lot numbers were DK1208B1R (LDV/SOF) and EF1401B1 (FTC/RPV/TAF).

4.5.2.8. Reference Therapy, Dose, Mode of Administration, and Lot No.

- LDV/SOF (1 × 90/400 mg tablet once daily) administered orally under fed conditions in the morning (Treatment A)
- FTC/RPV/TAF (1 × 200/25/25 mg tablet once daily) administered orally under fed conditions in the morning (Treatment B)
- The lot numbers were DK1208B1R (LDV/SOF) and EF1401B1 (FTC/RPV/TAF).

4.5.2.9. Criteria for Evaluation

Pharmacokinetics

Blood samples were collected on Days 11, 22, and 33 at the following time points relative to study drug administration: predose (≤5 min) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 8, 10, 12, 18, and 24 hours post-dose. As appropriate for each analyte, the following plasma PK parameters were calculated for FTC, RPV, TAF, TFV, SOF, GS-566500, GS-331007, and LDV: AUCtau, AUClast, Cmax, Tmax, Clast, Tlast, Ctau, λz, t1/2, CL/F, and Vz/F.

Safety

Safety was assessed by clinical laboratory tests, physical examinations, including vital sign measurements and ECGs at various time points during the study, and by documentation of adverse events (AEs).

4.5.2.10. Statistical Methods

Pharmacokinetics

Plasma concentrations and PK parameters for FTC, RPV, TAF, TFV, SOF, GS-566500, GS-331007, and LDV were listed and summarized using descriptive statistics sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, and median, minimum and maximum) by treatment, as applicable. In addition, an analysis of variance (ANOVA) using a mixed-effects model with treatment, period, and sequence as fixed effects and subject within sequence as a random effect was fit to the natural logarithmic transformation of PK parameters (eg, AUC_{tau} and C_{max}) for each analyte, as appropriate. Two-sided 90% confidence intervals (CIs) for the ratios of geometric least-squares means (GLSM) of test versus reference treatments were calculated for each of the primary PK parameters (C_{max}, AUC_{tau}, C_{tau}, AUC_{last} as applicable by analyte) and compared against lack of PK alteration bounds defined for each analyte. Lack of alteration in PK was concluded if the 90% CIs for the GLSM ratios were contained within the bounds for their respective test versus reference treatments:

- 70% to 143% for TAF, FTC, TFV, SOF, GS-566500, GS-311007, and LDV
- 80 to 125% for RPV

Safety

AE data were listed by subject. Treatment-emergent AEs, serious AEs (SAE), and AEs leading to permanent study drug discontinuation were summarized by treatment, system organ class, and preferred term using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

AEs were also summarized by relationship to study drug and severity. In addition, a listing of AEs leading to premature discontinuation of study drug or study was provided.

Listings of individual subject laboratory results were provided. Selected laboratory data were summarized by treatment at scheduled visits and for the corresponding change from predose. The incidence of treatment-emergent graded laboratory abnormalities was summarized by treatment.

Vital sign measurements were listed and summarized by treatment. Listings of concomitant medications and safety ECG data were provided.

4.5.2.11. Summary of results

Subject Disposition and Demographics

A total of 42 subjects (7 subjects in each treatment sequence) were enrolled and randomized in the study. All 42 randomized subjects received at least 1 dose of assigned study drug and were included in the Safety Analysis Set. Forty-one of 42 subjects completed dosing with study drugs and completed the study; 1 subject receiving LDV/SOF+FTC/RPV/TAF discontinued study drug dosing due to an AE of colitis.

The mean age was 34 years with a range of 18 to 45 years. Overall, there were more males than females (30 males [71.4%] and 12 females [28.6%]). The majority of subjects were white (61.9%) and Hispanic or Latino (52.4%). The mean BMI at baseline was 27.3 kg/m2 with a range of 22.8 to 29.9 kg/m2. The mean creatinine clearance (CLcr) at baseline was 122.3 mL/min with a range of 82.9 to 178.6 mL/min.

Pharmacokinetics Results

Co-administration of LDV/SOF with FTC/RPV/TAF did not notably affect the PK of FTC, RPV, or TAF. Compared to administration of FTC/RPV/TAF alone, LDV/SOF+FTC/RPV/TAF led to increases in TFV exposure (AUC_{tau}) of 75%, TFV C_{max} of 62%, and C_{tau} of 85%. However, these differences are not considered clinically relevant and no dose adjustment of FTC/RPV/TAF is necessary when co-administered with LDV/SOF. Co-administration of FTC/RPV/TAF with LDV/SOF did not notably affect the PK of LDV or SOF (including its metabolites GS-566500 or GS-331007). The mean and percentage coefficient of variation (%CV) of the primary PK parameters for FTC, RPV, TAF, TFV, SOF, GS-566500, GS-331007, and LDV following the administration FTC/RPV/TAF and LDV/SOF alone or in combination and the results of the statistical analysis are summarised below.

Table 4: Pharmacokinetics results.

PK Parameter	Mean (%CV) FTC/RPV/TAF (Treatment B) (N = 42)	Mean (%CV) LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	%GLSM Ratio (90% CI)
FTC			
AUC_{tau} (h*ng/mL)	10,764.1 (14.3)	10,805.1 (15.3)	100.29 (98.43,102.19)
C_{max} (ng/mL)	1707.6 (20.2)	1650.3 (17.6)	97.02 (92.72,101.53)
C_{tau} (ng/mL)	87.9 (28.2)	88.7 (25.1)	101.59 (98.47,104.81)
RPV			
AUC_{tau} (h*ng/mL)	3040.1 (27.3)	2857.6 (25.6)	94.59 (91.20,98.10)
C_{max} (ng/mL)	203.3 (25.4)	197.1 (28.3)	96.65 (91.73,101.84)
C_{tau} (ng/mL)	109.1 (31.6)	100.0 (26.0)	93.33 (89.38,97.45)
TAF			
AUC_{last} (h*ng/mL)	277.2 (37.5)	362.3 (34.4)	132.39 (124.99,140.22)
C_{max} (ng/mL)	200.0 (43.5)	204.5 (45.7)	103.12 (93.58,113.63)
TFV			
AUC_{tau} (h*ng/mL)	268.4 (22.6)	467.2 (21.0)	174.72 (168.78,180.86)
C_{max} (ng/mL)	15.8 (21.7)	25.4 (20.0)	161.50 (155.60,167.62)
C_{tau} (ng/mL)	9.0 (24.8)	16.7 (22.0)	184.86 (177.57,192.46)

PK Parameter	Mean (%CV) LDV/SOF (Treatment A) (N = 41)	Mean (%CV) LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	%GLSM Ratio (90% CI)
SOF			
AUC_{tau} (h*ng/mL)	2909.4 (32.8)	3068.9 (30.5)	104.69 (100.51,109.04)
C_{max} (ng/mL)	1469.5 (35.4)	1390.6 (32.3)	95.99 (88.80,103.76)
GS-566500			
AUC_{tau} (h*ng/mL)	2504.0 (16.4)	2575.4 (16.2)	102.05 (99.34,104.83)
C_{max} (ng/mL)	510.2 (20.1)	502.2 (18.2)	99.03 (95.24,102.97)
GS-331007			
AUC_{tau} (h*ng/mL)	11,766.4 (12.8)	12,883.3 (16.1)	107.98 (106.20,109.79)
C_{max} (ng/mL)	884.4 (13.7)	960.4 (14.8)	108.09 (105.05,111.20)
C_{tau} (ng/mL)	339.8 (16.4)	378.1 (18.9)	109.92 (107.46,112.44)
LDV			
AUC_{tau} (h*ng/mL)	11,590.4 (40.3)	11,944.8 (42.7)	101.53 (97.36, 105.88)
C_{max} (ng/mL)	647.4 (35.8)	658.4 (37.7)	100.62 (96.76, 104.63)
C_{tau} (ng/mL)	419.7 (45.9)	434.3 (47.4)	102.40 (98.02, 106.99)

Safety Results

Overall, FTC/RPV/TAF and LDV/SOF were generally well tolerated when administered alone or in combination. There were no Grade 3 or 4 AEs, deaths, SAEs, or pregnancies reported. One subject permanently discontinued any study drug due to an AE. By treatment group, the most commonly reported (i.e., in at least 2 subjects) AEs in the LDV/SOF group (Treatment A) were nausea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects); in the FTC/RPV/TAF group (Treatment B) was

constipation (9.5%, 4 subjects); and in the LDV/SOF+FTC/RPV/TAF group (Treatment C) were constipation (4.8%, 2 subjects) and headache (4.8%, 2 subjects).

Five subjects (11.9%) had AEs that were considered related to study drug by the investigator. Commonly reported (in at least 2 subjects) AEs considered related to study drug were only reported following treatment with LDV/SOF: nausea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects).

Overall, laboratory abnormalities were reported for 17 subjects (40.5%) following LDV/SOF (Treatment A), 20 subjects (47.6%) following FTC/RPV/TAF (Treatment B), and 20 subjects (47.6%) following LDV/SOF+FTC/RPV/TAF (Treatment C). The majority of the laboratory abnormalities were Grade 1 or 2 in severity. Three subjects had Grade 3 or 4 laboratory abnormalities, none of which resulted in an AE. The Grade 4 laboratory abnormality of increased creatine kinase was transient and consistent with physical exercise. No notable changes from baseline in vital signs were observed during the study.

4.5.2.12. Conclusions

The conclusions from Study GS-US-366-1689 are as follows:

- Co-administration of FTC/RPV/TAF and LDV/SOF does not lead to clinically relevant changes in any of the components of either FDC.
- LDV/SOF and FTC/RPV/TAF were well tolerated when administered alone or in combination.

> *Comment: This is the only drug-drug interaction study that directly investigates the pharmacokinetics of the FDC, Odefsey, with another agent that does not contain one of the components of Odefsey.*

Emtricitabine: In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low. FTC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of FTC with drugs that are eliminated by active tubular secretion may increase concentrations of FTC and/or the co-administered drug. Drugs that decrease renal function may increase concentrations of FTC. In drug interaction studies conducted with FTC, co-administration of FTC and famciclovir had no effect on the Cmax or AUC of either drug.

Rilpivirine: RPV is primarily metabolized by cytochrome CYP3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of RPV. Co-administration of ODEFSEY and drugs that induce CYP3A may result in decreased plasma concentrations of RPV and loss of virologic response and possible resistance. Co-administration of ODEFSEY and drugs that inhibit CYP3A may result in increased plasma concentrations of RPV. Co-administration of ODEFSEY with drugs that increase gastric pH may result in decreased plasma concentrations of RPV and loss of virologic response and possible resistance to RPV and to the class of NNRTIs.

Tenofovir Alafenamide: Tenofovir alafenamide is transported by P-glycoprotein (P-gp). Drugs that strongly affect P-gp activity may lead to changes in TAF absorption. TAF is a weak inhibitor of CYP3A4 in vitro.

Drug-drug interaction studies were conducted with ODEFSEY or the components of ODEFSEY (FTC, RPV, or TAF) as individual agents. The only Odefsey study was GS-US-366-1689 Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablets.

Most studies were conducted with rilpivirine dosage of 150mg, which is substantially higher than the recommended dose of 25mg per day.

Clinical implications of in vitro findings

The sponsor has presented three pharmacokinetic studies where the Odefsey has been used. The two studies that have clinical implications are GS-US-366-1689 and GS-US-366-1651. The first study showed that the Odefsey can be administered with the Hepatitis C therapy LDV/SOF, with no effect on the pharmacokinetics of either compound. The second study showed that Odefsey should be administered with a meal in order to improve the exposure to RPV. Although there is no recommendation regarding the type of meal, the exposure data would seem to indicate that a high-fat meal may improve exposure more than a medium-fat meal. The sponsor has not indicated the composition of the meal that would assist in determining if it is high or medium fat. However, as the difference in RPV exposure is not substantial and considering the challenges of adherence; it may be more practical to conclude that administering Odefsey with a meal is sufficient.

4.6. Evaluator's overall conclusions on pharmacokinetics

This dossier is an application for approval of Odefsey (F/RPV/TAF) as a treatment for HIV-1 infection in adults and adolescents. The pivotal data submitted by the sponsor is limited to three pharmacokinetic studies submitted. There are no other studies in this dossier to include any clinical efficacy or safety data as Odefsey has never been administered to the target population of HIV-1 infected adults or adolescents. The only data available to the assessor are two bioequivalence studies where Odefsey has been compared with Genvoya (E/F/C/TAF), for the TAF/FTC component, and compared with Edurant (RPV) for the RPV component. The assessor is unclear as to why the sponsor has chosen these comparators as Genvoya contains both a booster and an Integrase inhibitor, in addition to TAF/FTC and the dose of TAF is 10mg rather than 25mg as in Odefsey, while Edurant is a single agent compound, rather than an FDC and because there are comparator compounds that would have been more appropriate to utilise. As stated previously, Genvoya is currently under review and therefore the selection of this FDC in preference to Descovy (which is also under review) cannot be justified. Moreover, the selection of Edurant, in preference to Eviplera, considering that both are approved, remains to be justified.

The evaluator has the following concerns regarding the current submission:

- Inappropriate selection of comparator compounds; and
- The studies in the current dossier do not involve HIV infected patients, who are the targeted patient population for treatment with Odefsey.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration. Considering no pharmacodynamic studies have been done with Odefsey, it is not relevant to ascertain deficiencies.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

No Pharmacodynamic studies have been conducted with Odefsey in humans. Therefore the following section is not relevant. The studies submitted by the sponsor refer to the pharmacodynamics of Genvoya as a 'surrogate' for Odefsey and to various studies conducted with

RPV in combination with a range of anti-retroviral compounds, including FTC and TDF. No studies are presented with TAF/FTC/RPV in combination.

5.3. Evaluator's overall conclusions on pharmacodynamics

The sponsor has presented no pharmacodynamic studies utilising Odefsey, the FDC, for which this application has been made.[a] In addition, even in those studies for which the sponsor has included summary statements and made reference to an actual CSR and provided linked references, the sponsor has not included any of these reference CSRs and therefore the links are non-functional. While this is a valuable resource for noting the sponsor's summary of submitted studies, it expected that the original studies are included. This is not the case for this section.

6. Dosage selection for the pivotal studies

As there are no pivotal safety or efficacy studies submitted by the sponsor and as no patients with HIV-1 infection had been administered the FDC, Odefsey, the dosage described below was selected for the pharmacokinetic studies.

The selected dose of TAF single agent is 25 mg, based on the results from Study GS-US-120-0104 (not included in this dossier, although this was included in the Genvoya dossier, which was submitted as an unlinked, entirely separate dossier), in which various doses of TAF (8 mg, 25 mg, and 40 mg) were administered to HIV-1 infected subjects. In this study, TAF 25 mg resulted in near-maximal antiviral activity and plasma TFV exposure > 90% lower relative to TDF. TAF 25 mg is recommended with ARV agents that do not have a clinically relevant effect on TAF exposure. Study GS-US-120-1554 showed that RPV does not have a clinically relevant effect on TAF exposure. Therefore, the dose of TAF 25 mg is appropriate for the FTC/RPV/TAF FDC.

Rilpivirine 25 mg once daily is the approved dose for Edurant and Eviplera. Co-administration of TAF had no clinically relevant effect on the PK of RPV. Therefore, the dose of RPV 25 mg is appropriate for the FTC/RPV/TAF FDC. Emtricitabine 200 mg once daily is the approved dose for Emtriva.

7. Clinical efficacy

No clinical efficacy studies have been conducted with Odefsey.

8. Clinical safety

There have been no clinical safety studies conducted with Odefsey in the target population. The only clinical safety studies were conducted during the pharmacokinetic studies in healthy adult subjects. There have been no safety studies conducted with Odefsey in the target population of HIV-1 infected adolescent subjects. It should be noted that the submission contains only complete Study Reports of the three pharmacokinetic studies. While there are study summaries provided for a large number of other studies that have been conducted with Genvoya, Eviplera and Edurant; no CSRs are included. Moreover, the studies with RPV are clinical trial results where RPV is used in combination with multiple other agents.

[a] In this dossier, there is a lack of pharmacodynamics studies utilising Odefsey. The corresponding clinical data of those studies summarised were not observed in the clinical evaluation.

There are no pivotal safety studies. The safety assessments were included in the pharmacokinetic studies GS-US-366-1651; GS-US-366-1689 and study GS-US-366-1159. Safety observation are summarised below.

8.1. Studies providing evaluable safety data

8.1.1. Study GS-US-366-1159

All 96 subjects were included in the Safety Analysis Set.

8.1.2. Study GS-US-366-1651

All 60 subjects were included in the FTC, RPV, and TAF Analysis Sets.

8.1.3. Study GS-US-366-1689

All 42 randomized subjects (Randomized Analysis Set) received at least 1 dose of assigned study drug and were included in the Safety Analysis Set and PK Analysis Set.

8.1.4. Study GS-US-366-1159

Adverse events were reported in 6 subjects (6.3%) following FTC/RPV/TAF (Treatment A), 10 subjects (10.5%) following RPV (Treatment B), and 8 subjects (8.3%) following E/C/F/TAF (Treatment C). Adverse events that were considered related to study drug by the investigator were not reported in any subjects following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 4 subjects (4.2%) following E/C/F/TAF.

No deaths, SAEs, or AEs leading to premature study drug discontinuation were reported. All AEs were Grade 1 in severity. Overall, the most frequently reported AEs were constipation (9 subjects [9.4%]), nausea, and headache (6 subjects [6.3%] each). Constipation was reported for 2 subjects (2.1%) following FTC/RPV/TAF, 6 subjects (6.3%) following RPV, and 2 subjects (2.1%) following E/C/F/TAF. Nausea was reported for 1 subject (1.1%) following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 4 subjects (4.2%) following E/C/F/TAF. Headache was reported for 3 subjects (3.2%) following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 2 subjects (2.1%) following E/C/F/TAF.

8.1.5. Study GS-US-366-1651

Adverse events were reported in 8 of 60 subjects (13.3%) following FTC/RPV/TAF administered under fasted conditions, 1 of 30 subjects (3.3%) following FTC/RPV/TAF administered under fed conditions (moderate-fat food), and 4 of 30 subjects (13.3%) following FTC/RPV/TAF administered under fed conditions (high-calorie, high-fat food). One subject had AEs that were considered by the investigator as related to study drug (nausea, vomiting, and dizziness); these occurred after dosing on the day of administration of FTC/RPV/TAF under fed conditions (high-calorie, high-fat food), and resolved on the same day without treatment.

No deaths or SAEs were reported, and no subjects discontinued due to an AE. All AEs were Grade 1 (mild). None of the AEs were reported by more than 1 subject in any treatment group.

8.1.6. Study GS-US-366-1689

Overall, FTC/RPV/TAF and LDV/SOF were generally well tolerated when administered alone or in combination. There were no Grade 3 or 4 AEs, deaths, SAEs, or pregnancies reported and only 1 subject permanently discontinued any study drug due to an AE (non-serious, Grade 2 colitis). By treatment group, the most commonly reported (ie, for > 1 subject) AEs in the LDV/SOF group (Treatment A) were diarrhoea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects); in the FTC/RPV/TAF group (Treatment B) was constipation (9.5%, 4 subjects); and in the LDV/SOF+FTC/RPV/TAF group (Treatment C) were constipation (4.8%, 2 subjects) and headache (4.8%, 2 subjects).

Five subjects (11.9%) had AEs that were considered by the investigator to be treatment related.

AEs considered related to study drug were only reported for > 1 subject following treatment with LDV/SOF: nausea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects).

8.2. Post-marketing experience

The sponsor has included two reports of post-marketing adverse events related to Eviplera (FTC/RPV/TDF). These reports do not have study numbers and are not link referenced in the Module 2 safety summary. One report relates to severe skin reactions and allergies and the other report relates to weight gain in patients taking Eviplera/Complera.

8.3. Safety issues with the potential for major regulatory impact

8.3.1. Serious skin reactions

This cumulative review of severe skin and hypersensitivity reactions with Complera/Eviplera was prompted by receipt of a Food and Drug Administration (FDA) Safety Labelling Change Notification for Complera (dated 26 February 2015). The FDA has requested that the Complera United States Prescribing Information (US PI) be updated due to "post-marketing reports of skin and hypersensitivity reactions, including but not limited to angioedema, hypotension, Stevens-Johnson syndrome (SJS) and drug rash with eosinophilia and systemic symptoms (DRESS)". The FDA notes that "while some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions had additional organ dysfunctions, including elevations in hepatic serum biochemistries", and the FDA considers this information to be "new safety information" that should be included in labelling for Complera.

The current company core data sheet (CCDS) for Complera/Eviplera describes the undesirable effects of allergic reaction for the emtricitabine and tenofovir DF components and rash for the emtricitabine, rilpivirine and tenofovir DF components. A further description of rash events lists vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus and urticaria and skin discoloration as adverse drug reactions for emtricitabine.

The aim of this cumulative review is to assess all available data to determine whether there is a causal association between severe skin and hypersensitivity reactions and Complera/Eviplera. A comprehensive analysis of severe skin and hypersensitivity reactions for Complera/Eviplera was performed using the following sources of data.

A total of 106 cases were identified on the Gilead DSPH database for Complera/Eviplera with event terms potentially associated with severe skin reactions or hypersensitivity reactions and hypotension. These 106 cases described 136 events, of which 31 were considered serious. None of the events were fatal and one event of anaphylactic reaction was considered life-threatening (attributed to almond allergy and considered unrelated to Complera/Eviplera). Twenty-seven cases of interest were identified due to either the severity of the reactions or findings of skin or hypersensitivity events of relevance to the proposed US PI. The remaining 79 cases did not describe events of relevance to the US PI or had events that were consistent with current labelling. The 27 cases of interest are described below.

8.3.2. Stevens-Johnson syndrome

There were no cases of SJS identified from the database for Complera/Eviplera. One consumer (non-medically confirmed) case described an itchy rash with blisters, similar to 'being scalded by hot water, getting itchy and starting to peel off' that the patient believed 'could have led to SJS.' The patient continued treatment with Complera/Eviplera for several weeks prior to discontinuation, which is inconsistent with the clinical course of SJS. Therefore, it is unlikely that the case represents possible SJS.

8.3.3. DRESS syndrome

There were two cases of potential DRESS syndrome, prompting a cumulative review of DRESS syndrome that will be included in the Complera/Eviplera periodic benefit-risk evaluation report (PBRER) covering the period 11 August 2014 to 10 February 2015. All relevant data from the DRESS syndrome review have been included in this wider and more up to date review of severe skin and hypersensitivity reactions. While both cases had a temporal relationship, rash, eosinophil elevation and abnormal liver function tests (with the former case having a positive de-challenge), in neither case was the diagnosis unequivocal. Clinical details that were lacking in the cases to definitively confirm a diagnosis of DRESS syndrome included: clinical details of the patient's neutropenia, extent of hepatic involvement, the presence or absence of fever and lymphadenopathy, biopsy results and time to regression of the symptoms in case [information redacted]; and documented temperature meeting true fever criteria, lymphadenopathy and facial oedema in case [information redacted]. The symptoms in the second case could also occur with a possible viral illness, suggested by the presence of concurrent events of sore throat, congestion and cough. Following review of the cases, there is insufficient evidence for a causal association of DRESS syndrome with Complera/Eviplera.

8.3.4. Angioedema

Ten cases were identified as potentially associated with angioedema (lip swelling, n = 5; swelling face, n = 2; face oedema, angioedema, lip oedema and pharyngeal oedema, n = 1 each). Seven cases were suggestive of an allergic reaction with possible angioedema. However, one case was confounded by a concomitant medication, one case involved a prior medical history of lip swelling, and one contained limited information on the event. While the events in 5 of the 10 cases were classified as serious, none of the cases were life-threatening, none involved hospitalization or necessitated acute airway management, and none indicated impending shock. Instead, they were consistent with more typical and conventional allergic-mediated angioedema. Allergic reaction involving angioedema is an expected adverse drug reaction to the tenofovir DF component of Complera/Eviplera. These cases are consistent in terms of presentation and severity with current labelling for the event, although it is not possible to attribute causality to a particular component of Complera/Eviplera in these cases.

8.3.5. Hypotension or blood pressure decreased

Three cases were identified involving hypotension or blood pressure decreased. One case described hypotension in a pregnant patient (with no skin or hypersensitivity reactions). One case described mild hypotension (107/63) in a patient experiencing drug-induced allergic hepatitis (without any skin events). One case described a patient collapsing due to hypotension while experiencing an allergic reaction (severe, generalized papular rash with oedema on hands and face with a severe itch). There is currently no evidence to suggest that Complera/Eviplera causes isolated hypotension on its own, and insufficient evidence that skin or hypersensitivity reactions reported with Complera/Eviplera are associated with hypotension.

8.3.6. Other events of interest

Eleven cases involved other events of interest due to severity or the presence of additional symptoms of relevance to the US PI, including fever, blister, lymphadenopathy, hepatic events, skin exfoliation, conjunctivitis or eosinophilia. Given that some of these symptoms in the 11 cases were also reported in cases described in the categories above (such as SJS, DRESS syndrome and hypotension), the total number of cases out of the 27 cases of interest experiencing fever, hepatic events, blisters, skin exfoliation, conjunctivitis and eosinophilia are described below:

8.3.6.1. Fever

Fever was reported in 5 of the 27 cases of interest, including 1 case of possible DRESS syndrome and 1 case of hypotension with hepatic events and without skin events. Of the 3 remaining cases, fever occurred with rash and lymphadenopathy in one case, in the second case the length of time (9

months) to onset of symptoms suggests alternative aetiology, and the available information in the third case (from a consumer) was limited.

8.3.6.2. Hepatic events

Hepatic events were reported in 5 of the 27 cases of interest, including 2 cases of possible DRESS syndrome and 1 case of hypotension with hepatic events and without skin events. In the remaining 2 cases, transient transaminase elevations occurred around the same time as the rash events, both resolving with Complera/Eviplera discontinuation. Both rash and hepatic events are expected adverse drug reactions to Complera/Eviplera treatment.

8.3.6.3. Blisters, skin exfoliation and conjunctivitis

Blisters, skin exfoliation and conjunctivitis were reported in 7 of the 27 cases of interest, including 1 case where the consumer reported possible SJS (blister, skin exfoliation, not medically confirmed) and 1 case of possible DRESS syndrome (conjunctivitis and blistering). In the remaining 5 cases, rash events occurred in conjunction with blisters (2 cases), skin exfoliation (2 cases) or conjunctivitis (1 case).

8.3.6.4. Eosinophilia

Eosinophilia was reported in 3 of the 27 cases of interest, including 2 cases of possible DRESS syndrome. In the remaining case, eosinophil levels increased in a patient experiencing rash.

8.3.6.5. Conclusions

Upon review of all available data, the following conclusions are made:

- There is insufficient evidence of a causal association between life-threatening hypersensitivity reactions (such as SJS and DRESS syndrome), hypotension and oral lesions with Complera/Eviplera. The current data do not support inclusion of these terms in Complera/Eviplera labelling.
- There have been reports of possible angioedema in patients receiving Complera/Eviplera, and these reports are consistent in terms of nature and severity with current labelling, where angioedema is considered an adverse reaction or undesirable effect to the tenofovir DF component of Complera/Eviplera. However, it is not possible to attribute angioedema to a particular component of Complera/Eviplera from the cases received. Given that none of the cases were life-threatening, necessitated acute airway management or hospitalization, and none involved impending shock, current evidence does not support highlighting angioedema as a potential severe hypersensitivity reaction in the Warnings and Precautions of Complera/Eviplera labelling.
- Cases of serious or severe skin or allergic reactions with systemic symptoms, including fever, blisters, conjunctivitis, elevated liver function tests and eosinophilia have been reported for Complera/Eviplera. Additional wording in Complera/Eviplera labelling is recommended to indicate the severe skin reactions with systemic symptoms that have been reported so far.

8.3.7. Weight gain in patients taking Complera/Eviplera

This cumulative review of weight gain for Complera/Eviplera was prompted following receipt of a literature article describing 4 cases of weight gain in patients switching to Complera/Eviplera and due to the growing number of post-marketing cases of weight gain on the Gilead DSPH database.

Weight gain with Complera/Eviplera has been previously reviewed by Gilead during the analysis of Week 48 and Week 96 data from Study GS-US-264-0110 (A Phase IIIb, Randomised, Open label Study to Evaluate the Safety and Efficacy of a Single Tablet Regimen of FTC/RPV/TDF Compared with a Single Tablet Regimen of EFV/FTC/TDF in HIV-1 Infected, Antiretroviral Treatment Naïve Adults), prompted by a CHMP question upon submission of Week 48 and Week 96 GS-US-264-0110 data on how the weight gain of more than 1 kg in 24 weeks observed in the Complera/Eviplera arm could be reconciled with the known RPV adverse reaction of loss of appetite. At each analysis

(Week 48 and Week 96), weight gain was not considered a validated signal due to insufficient evidence for a causal association. A response to specifically address the CHMP's question regarding weight gain and appetite was submitted in June 2014 (response to a RSI dated 17 June 2014). In this response, Gilead concluded that the relationship between weight gain and appetite is complex and the minimal mean and median increases in weight observed in subjects receiving RPV in the clinical studies is clinically insignificant. The CHMP endorsed Gilead's conclusions on the GS-US-264-0110 Week 96 weight gain analyses in correspondence dated 24 July 2014.

In this review, an analysis of weight gain was performed using the following sources of data.

8.3.7.1. Cases on the Gilead DSPH database

A search of Complera/Eviplera cases on the Gilead DSPH database revealed 51 cases involving events potentially associated with weight gain, of which 45 cases described actual weight gain and 6 cases did not report weight gain. The 45 cases describing weight gain are summarised below:

- Of these 45 cases, 5 cases were considered cases of interest due to being fairly well documented, having a temporal association to Complera/Eviplera and absence of alternative aetiologies for the weight gain; 3 of these cases also reported a positive de-challenge. In these 5 cases, weight gain ranged from 1.8 kg to 13.2 kg over a time period of 1 to 5 months; in the 3 positive de-challenge cases, time for weight to return to baseline following discontinuation was 1 month in 1 case, 6 months in another, and not specified in the third case. Of the remaining 40 cases, 6 cases had potential alternative explanations for the weight gain, 2 cases reported the weight gain occurring prior to initiation of Complera/Eviplera, 1 case reported the weight gain resolving with Complera/Eviplera continued, and 31 cases were considered poorly documented.
- The magnitude of weight gain was specified in 27 of the 45 cases: weight gained was ≤ 5 kg in 7 cases, between > 5 to ≤ 10 kg in 14 cases, > 10 to ≤ 20 kg in 5 cases and > 20 to ≤ 30 kg in 1 case. The mean weight gain in the 27 cases was 8.1 kg (median 7.0 kg, range 1.8 kg to 25 kg). The time period of the weight gain was reported in 22 of the 45 cases, with weight gain occurring over a mean time period of 4.9 months (median 4.5 months, range 10 days to 27 months).
- Thirteen of the 45 cases specified the type of weight gain. Eleven cases involved central fat accumulation or chest/mammary fat accumulation (3 had central fat accumulation alone, 2 had central fat accumulation and chest/mammary fat accumulation, 1 had gynaecomastia, 1 had breast enlargement, and 4 had central fat accumulation and acquiredlipodystrophy). One case reported gain of weight in muscle, not fat. One further case of acquired lipodystrophy was reported, but the event started prior to initiation of Complera/Eviplera therapy. While lipodystrophy has been associated with combination antiretroviral therapy, it is unclear whether the 4 cases of central fat accumulation and lipodystrophy acquired in patients receiving Complera/Eviplera represent true fat redistribution (lipodystrophy) or simply weight gain and fat deposition in the abdominal area.

8.3.7.2. Disproportionality analysis

Five events potentially associated with weight gain cumulative to Q1 2014 were identified on the FDA SRS/AERS database for FTC + RPV +tenofovir/tenofovir disoproxil (increased appetite, eating disorder, hunger, hyperphagia, weight increased). There was no evidence of any disproportional reporting (EB05 > 2.0).

8.3.7.3. Information from clinical trials

A trend towards greater mean increase in weight from baseline was observed in the RPV arm versus EFV arm in ECHO/THRIVE studies (2.9 kg versus 1.8 kg at Week 96) and in the Complera/Eviplera arm versus Atripla arm in Study GS-US-264-0110 (2.6 kg versus 1.3 kg at Week 96). TEAEs potentially associated with weight gain were reported at a low frequency in the Week 96 analyses of both ECHO/THRIVE and GS-US-264-0110 studies and no consistent or significant differences were observed between the arms in the studies. There were consistent trends towards

higher proportions of subjects experiencing > 15 kg increases in weight from baseline in the RPV versus EFV arms in ECHO/THRIVE (3.64% versus 2.01%, or 2.73% versus 0.73% when considering only subjects who had > 15 kg weight gain on 2 consecutive visits [p = 0.0182]) and in the Complera/Eviplera versus Atripla arms in GS-US-264-0110 (5.08% versus 2.81%, or 3.55% versus 2.04% on 2 consecutive visits). Similar trends were observed for subjects experiencing > 20 kg increase in weight from baseline in subjects receiving a RPV- versus EFV-containing regimen in ECHO/THRIVE (1.45% versus 0.73%, or 0.73% versus 0.37% on 2 consecutive visits) and in GS-US-264-0110 (1.78% versus 1.02%, or 0.76% versus 0.26% on 2 consecutive visits).

8.3.7.4. Information from epidemiological studies

Two sources of epidemiological data were assessed:

- In limited data in the latest report from the Janssen-sponsored Drug Utilization Study of RPV versus EFV, no adverse events describing weight gain were reported.
- In a separate epidemiological study utilizing administrative healthcare claims data, there was no evidence of an association of weight gain with Complera/Eviplera. This non-concurrent, prospective cohort study was based on a large set (n = 35,167) of patients in the US receiving an antiretroviral regimen in the IMS Pharmetrics Plus claims database. After adjusting for prior medical conditions and other potential confounding factors, these analyses did not demonstrate any elevated risk of weight gain (obesity/overweight, polyphagia, abnormal weight gain) associated with RPV-containing regimens (Complera/Eviplera and Edurant [RPV]) when compared to other antiretroviral regimens.
- *Information from the published literature:* Five individual case safety reports that were identified from the literature have been included in the review of cases on the Gilead DSPH safety database (including the 4 cases reported by Gantner et al which prompted this cumulative review). No additional literature articles were identified in the published literature describing a possible association between RPV or Complera/Eviplera and weight gain.
- *Information from nonclinical studies:* Findings from nonclinical studies are inconsistent with respect to weight gain. One 3-month repeat-dose study in mice (Study TMC278-NC119 [TOX6739]) showed weight gain in both males and females throughout the dosing period for the highest RPV dose tested (320 mg/kg/day), in line with increased food consumption throughout the dosing period (mice could feed ad libitum in this study). Other animal studies instead showed no effects on body weight or showed reduced body weight gain.

The reason for reported weight gain in some patients receiving Complera/Eviplera is unclear, but the following factors could potentially play a role:

8.3.7.5. Improvement of general health status

Minimal weight gain following initiation of Complera/Eviplera could potentially reflect the effectiveness of the anti HIV-1 medication and represent improvement of general health status. One of the 45 cases of weight gain noted that she considered the reported weight gain as a positive change. Such effects have been observed with other antiretroviral medications in other studies of HIV infected subjects receiving combination antiretroviral therapy.

8.3.7.6. Awareness of the caloric requirement of RPV dosing

Patient awareness of the caloric requirement of 500 kcal for RPV dosing may have potentially led to increased total food consumption, or consumption of foods with a higher fat content, which in turn would have led to weight gain. Four of the 45 weight gain cases attributed the weight gain to the calorie requirement or fat requirement of RPV dosing.

8.3.7.7. Increased appetite/hunger

Five of the 45 cases reporting weight gain noted that the patient experienced increased appetite (n = 3) or hunger (n = 2) after initiation of Complera/Eviplera. In addition, 3 of the 6 cases in which no

weight gain was reported described increased appetite (n = 2) or hunger (n = 1) following initiation of Complera/Eviplera. Increased appetite and hunger are unlisted events for Complera/Eviplera; to the contrary, decreased appetite is a listed event for the RPV component of Complera/Eviplera. The increased appetite reported in a small number of patients receiving Complera/Eviplera could potentially be linked to improvement of general health status upon initiation of an effective antiretroviral regimen.

8.3.7.8. Accentuated weight gain with Complera/Eviplera when using Atripla as a comparator

A trend towards higher mean weight gain was observed with RPV versus EFV and Complera/Eviplera versus Atripla in the ECHO/THRIVE and GS-US-264-0110 clinical studies, respectively. Differences in weight gain may be accentuated when using Atripla as the comparator, given that EFV is dosed on an empty stomach and decreased appetite due to gastrointestinal events is common when starting a new antiretroviral regimen, particularly Atripla.

Following review of the cumulative data, in particular the post-marketing data (with supporting data from clinical trials), it is considered that there is sufficient evidence to add weight gain (preferred term 'weight increased') to the CCDS as an adverse drug reaction for Complera/Eviplera identified through post-marketing experience.

8.4. Evaluator's overall conclusions on clinical safety

Considering the total absence of any clinical safety data on Odefsey in the target population, the only conclusion that can be drawn is that it is not possible to determine the safety profile of Odefsey in patients who have HIV-1 infection. As such, it is not possible to recommend Odefsey as meeting the minimum safety requirements for approval. The sponsor has used data on adverse events from the Genvoya versus Stribild clinical studies to extrapolate the potential renal and bone mineral density problems from Stribild to Odefsey, and then concluding that by replacing TDF as in Eviplera with TAF in Odefsey these adverse events will be ameliorated. However, the sponsor has not mentioned if the same renal and BMD adverse events noted in the Genvoya/Stribild studies have been observed in patients who are being administered Complera/Eviplera, given there are around 200,000 patient years of experience with Eviplera. The evaluator has concerns regarding lack of treatment-related safety data for Odefsey in the targeted patient population with HIV infection.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Odefsey in the proposed usage are:

- There may be a hypothetical benefit of Odefsey, compared with Eviplera, in relation to the substitution of TDF (in Eviplera) for TAF (in Odefsey) in the potential reduction of renal and bone mineral density adverse events. However, this submission does not provide evidence to support this possibility and the extrapolations of clinical study results from the Genvoya dossier do not appear to be relevant.

9.2. First round assessment of risks

The risks of Odefsey in the proposed usage are:

- The sponsor proposes to extend the indication of Odefsey to adolescents 12 to 18 years of age. Currently, Eviplera is approved for adults > 18 years old. There is insufficient evidence to

support sponsor's proposal to extended indication to adolescents. The rationale for extrapolation of evidence from Genvoya dossier does not seem to be acceptable.

- As Odefsey has not been administered, in any context, to the target population, it is not possible to determine the clinical or safety potential risks.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Odefsey is neither favourable nor unfavourable given the proposed usage, but could become favourable if the changes recommended are adopted.

10. First round recommendation regarding authorisation

The recommendation is that this application should be rejected.

11. Clinical questions

11.1. Pharmacokinetics

1. It is unclear why the sponsor chose the bioequivalent comparators of Genvoya and Edurant and, while in the summary, the sponsor has focussed on using Eviplera as the main clinical comparator to Odefsey. It is suggested the sponsor consider conducting bioequivalent studies with Descovy and Eviplera, which would then provide some evidential basis for using Eviplera as a clinical comparator.
2. It is unclear why the sponsor has decided that while the exposure to RPV increases more with a high-fat meal compared with a moderate fat meal there is no specific instruction as to the composition of the meal and how Odefsey should be taken e.g. before, with or just after the meal.
3. As in the Descovy application, administration of TAF 10mg with a meal results in almost the same bioequivalence exposure as administering TAF 25mg, why the sponsor dismisses the possibility of having a 10mg dose of TAF in Odefsey is not explained in the dossier, other than to dismiss the increased exposure to TAF when administered with food as 'not clinically relevant'.
4. It is unclear why the sponsor chose to conduct the single bioequivalence study on a drug-drug interaction with Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) tablets. No rational is given for this choice as it does not necessarily fit with the context of the application or with the recommended clinical indications.

11.2. Pharmacodynamics

5. There are no pharmacodynamic data on Odefsey FDC. The pharmacokinetic data are derived from Genvoya and Eviplera studies and may not be applicable to the Odefsey FDC. It is unclear why the sponsor chose not to conduct a single pharmacodynamic study using Odefsey in the target population.

11.3. Efficacy

6. As stated previously, Odefsey has never been administered to the target population and therefore the sponsor has extrapolated efficacy results from Genvoya (currently not approved and not relevant as a comparator) for the FTC/TAF component of Odefsey and results from

Eviplera studies for the RPV component of Odefsey. While the Genvoya dossier is attached to the submission, there are no clinical study reports related to Eviplera or Edurant, even though these studies are referenced and linked to the clinical summaries. It is strongly recommended that the sponsor consider conducting a clinical equivalence study comparing Eviplera and Odefsey. There are a number of study designs that would meet this recommendation.

From a regulatory perspective, the clinical and scientific rationale for extrapolating data from unrelated compounds does not seem to be acceptable.

11.4. Safety

7. Specifically, the sponsor should be conducting a safety study on adolescents in the target group to determine safety aspects of Odefsey prior to making application for approval of Odefsey for this age group. The pivotal safety study currently underway where Odefsey equivalent constituents are being trialled was briefly described in the Descovy submission as GS-US-311-1089, which is an ongoing Phase 3, randomised, double-blind, switch study to evaluate the efficacy of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF as determined by the proportion of subjects with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48. In this trial there will be patients who remain on Eviplera and those who switch to FTC/RPV/TAF and these subjects in the target population may provide data to support both the safety and efficacy aspects of this submission. The preliminary PBMC data on TFV-DP concentration in the three (3) subjects reported indicated a range of intracellular concentration of 0.1-2271.4 pg per 10^6 cells with a geometric mean of 16.1 TFV-DP concentration in pg per 10^6 cells. These data need further clarification and consideration by the sponsor in light of availability of clinical safety and efficacy results. Clinical data from this ongoing safety study was not included in the dossier. The evaluator considers that the preliminary efficacy and safety results from this study would also contribute to the overall benefit-risk assessment of Odefsey.

12. Second round evaluation of clinical data

The sponsor has submitted responses to the detailed questions from the Evaluator. The responses address only a few issues raised by the Evaluator in terms of providing new data as the Sponsor generally refers to data originally presented in the Round one submission. The rationale given for not addressing the issues raised by the Evaluator is that overseas jurisdictions did not require the Sponsor to provide data as requested by this Evaluator. However, there does not appear any evidence the Sponsor consulted with the TGA in the same way they consulted with parallel authorities in the US and EU. The following are the specific questions and responses:

12.1. Question 1

It is unclear why the sponsor chose the bioequivalent comparators of Genvoya and Edurant and, while in the summary, the sponsor has focussed on using Eviplera as the main clinical comparator to Odefsey. It is suggested the sponsor consider conducting bioequivalent studies with Descovy and Eviplera, which would then provide some evidential basis for using Eviplera as a clinical comparator.

12.1.1. Sponsor response

This Category 1 Application seeking registration of ODEFSEY FDC tablets is based on a pivotal bioequivalence study (GS-US-366-1159) that demonstrates the following:

- Bioequivalence of TAF and FTC exposures between the ODEFSEY FDC (200/25/25 mg) and Gilead's FDC tablet containing the HIV-1 integrase strand transfer inhibitor (INSTI) elvitegravir (EVG, E), the pharmacoenhancer cobicistat (COBI, C), FTC, and TAF, GENVOYA (E/C/F/TAF

150/150/200/10 mg), thereby supporting extrapolation of the demonstrated safety and efficacy of TAF and FTC exposures in the ODEFSEY FDC to those from GENVOYA.

- Bioequivalence of RPV exposure between the ODEFSEY FDC tablet and the marketed product Edurant (RPV 25 mg tablet), thereby supporting extrapolation of the demonstrated safety and efficacy of RPV exposures in the ODEFSEY FDC to those from Edurant.

ODEFSEY FDC tablets are similar to the TGA approved FDC tablet, EVIPLERA (RPV/FTC/TDF 25/200/300, AUST R 176537) which is the treatment most likely to be replaced in practice following the availability of ODEFSEY. Due to the similarities in their co-formulated components, the drug interaction profiles of ODEFSEY and EVIPLERA overlap to a large extent. The key difference between ODEFSEY and EVIPLERA is the different form of TFV, i.e. TAF vs. TDF, which results in differences in the recommended precautions regarding renal function and renal adverse events.

Since exposures to the FTC and TAF components of the ODEFSEY FDC have been shown to be bioequivalent to the exposures to those components obtained from GENVOYA, the safety and efficacy data for GENVOYA can be reliably extrapolated to ODEFSEY. Likewise, since exposure to the RPV component of ODEFSEY has been shown to be bioequivalent to the RPV exposure obtained from Edurant, the safety and efficacy data for Edurant (and therefore EVIPLERA) can be reliably extrapolated to ODEFSEY.

Gilead's original proposal was to compare FTC/RPV/TAF to FTC/RPV/TDF for the RPV component and to FTC/TAF for the FTC and TAF components. The US FDA disagreed and recommended that BE be demonstrated by comparing FTC/RPV/TAF 200/25/25 mg to EVG/COBI/FTC/TAF 150/150/200/10mg and to RPV (Edurant, 25 mg) as the reference products for which clinical efficacy data would be available. For the US NDA, the FDA confirmed that the fed BE Study GS-US-366-1159 (Study 1159) with RPV and E/C/F/TAF used as references, and the food effect Study GS-US-366-1651 (Study 1651) using the FTC/RPV/TAF proposed commercial formulation, support the registration of FTC/RPV/TAF with no additional biopharmaceutical studies required. This BE strategy is further supported by Study GS-US-311-1089 (Study 1089) a Phase 3, randomised, double-blind, multicentre, active-controlled study to evaluate F/TAF in virologically suppressed patients with HIV on regimens containing TRUVADA® plus a third agent, including but not limited to RPV. In order to accurately reflect the intended population, the data presented within Study 1089 includes analyses for the subgroups of patients who received RPV or any NNRTI (nevirapine [NVP], efavirenz [EFV] or RPV) as a third agent in addition to analyses for the total trial population. While the patient numbers in the RPV subgroup were small (F/TAF + RPV, n=3 [0.9%]; TRUVADA® + RPV, n=6 [1.8%]), results for the total cohort are applicable to the RPV subgroup. The RPV subgroup represents the intended population for ODEFSEY FDC tablets and therefore these results are considered relevant to this submission.

Results from Study 1089 were provided to the TGA in response to the Milestone 3 Consolidated S31 Request for Information during evaluation of DESCOVY (F/TAF) tablets.

Subsequently, the relative bioavailability of the RPV component between ODEFSEY and EVIPLERA was evaluated in the Phase 1 Study GS-US-366-1881 (Study 1881). The primary PK parameters and statistical comparisons of the RPV are presented below. The GLSM ratios and corresponding 90% CIs of AUClast, AUCinf, and Cmax for RPV were contained within the pre-specified, protocol defined boundary criteria of 80% to 125%, indicating bioequivalent RPV exposure between ODEFSEY and EVIPLERA.

Table 5: GS-US-366-1881: Primary PK parameters and statistical comparisons for RPV.

RPV PK Parameter	N	Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs FTC/RPV/TDF (200/25/300 mg) (Reference)						
AUC_{last} (ng•h/mL)	28	3540.5 (30.5)	27	3266.0 (31.9)	108.99	101.81, 116.68
AUC_{inf} (ng•h/mL)	28	3870.9 (35.3)	27	3577.4 (34.7)	108.52	101.69, 115.80
C_{max} (ng/mL)	28	105.5 (29.2)	27	95.4 (27.3)	109.76	101.82, 118.32

Therefore, in addition to Studies 1089, 1159 and 1881, evidence to support the clinical safety and efficacy of ODEFSEY is also provided by the comprehensive clinical development program for GENVOYA, EVIPLERA and Edurant.

In its entirety, the clinical evidence supports the conclusion that the administration of ODEFSEY is non-inferior to EVIPLERA in terms of comparative safety and efficacy, with a favourable profile in terms of renal and bone safety.

12.1.2. Evaluation of response

The Sponsor has presented summary additional data as the BE table of results of GS-US-366-1881 to answer the Evaluator's questions. The Sponsor has not provided the report of this BE clinical study, so the only information is referred to in the above table. The Sponsor is requested to submit all relevant clinical information on this study to support the conclusions apparently drawn from the results of GS-US-366-1881. It would be necessary for the Sponsor to submit the Clinical Study Report of GS-US-366-1881 to the TGA to assess the validity of the data presented in the summary table. The Sponsor refers to apparent pre-submission discussions with the U.S. FDA. These discussions were not conveyed to the Evaluator in documents provided by the Sponsor (unless they were overlooked, but there is no specific reference to them in the Sponsor's response).

12.2. Question 2

It is unclear why the sponsor has decided that while the exposure to RPV increases more with a high-fat meal compared with a moderate fat meal there is no specific instruction as to the composition of the meal and how Odefsey should be taken e.g. before, with or just after the meal.

12.2.1. Sponsor response

Edurant, the reference comparator for RPV in the pivotal bioequivalence study, is a marketed product with clinical efficacy and safety established when administered under fed conditions. Accordingly, bioequivalence of RPV has been demonstrated between ODEFSEY and Edurant under fed conditions. Additionally, the effect of food on the absorption/bioavailability of ODEFSEY tablets was evaluated in Study GS-US-366-1651 (Study 1651).

In Study 1651, ODEFSEY was administered under fed conditions compared with fasted conditions, RPV AUCinf increased by 13% and 73% after moderate-fat and high-calorie, high-fat food, respectively. Importantly, administration of ODEFSEY under fed conditions irrespective of meal types results in RPV exposures that are associated with efficacy following administration of Edurant or EVIPLERA.

As such, the proposed PI recommends that ODEFSEY tablets are to be taken with food. Additionally, these dosing instructions are also consistent with the general labelling language that is conventionally used to communicate dosing recommendations with regard to food in antiretrovirals for treatment of HIV-1 infection, including the current approved Australian PI for EVIPLERA.

12.2.2. Evaluation of response

The Evaluator accepts this response.

12.3. Question 3

Evaluator's question: As in the Descovy application, administration of TAF 10mg with a meal results in almost the same bioequivalence exposure as administering TAF 25mg, why the sponsor dismisses the possibility of having a 10mg dose of TAF in Odefsey is not explained in the dossier, other than to dismiss the increased exposure to TAF when administered with food as 'not clinically relevant'.

12.3.1. Sponsor response

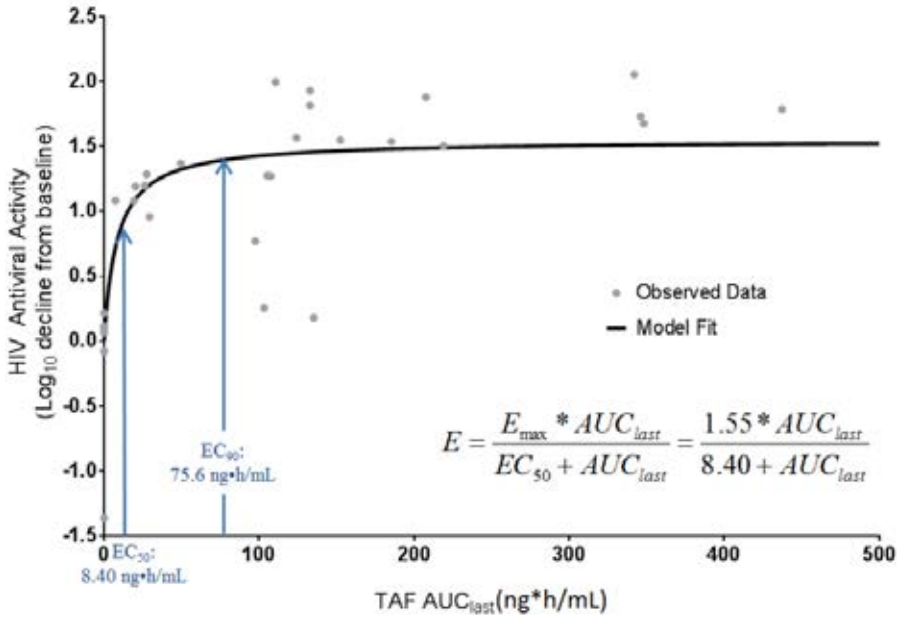
Based upon results of the Proof-of-Concept Study GS-US-120-0104, in which various doses of TAF (8 mg, 25 mg, and 40 mg) were administered to HIV-infected patients as monotherapy, the range of exposure achieved with TAF 25 mg was chosen as the reference exposure. In this study, while TAF 8 mg was equipotent to TDF 300 mg, TAF 25 mg resulted in near-maximal antiviral activity and plasma TFV exposure > 90% lower relative to TDF 300 mg.

TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine Co-adminstration of TAF with pharmacokinetic enhancer that inhibits P-gp (e.g, COBI or RTV) reduces TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed approximately 2.5-fold, whereas the increase in TAF in the presence of food (high-fat meal) was approximately 54%. Cumulative results from Studies GS-US-311-1473, GS-US-292-0103, and GS-US-292-0101, indicated that TAF exposure following a 10 mg dose (either as a single agent coadministered with COBI 150 mg or as a component of GENVOYA) was comparable with the exposure achieved following administration of TAF 25 mg either as a single agent or as a component of F/TAF.

Based on the totality of the data, including data from Phase 3 clinical studies, TAF 25 mg is recommended with third agents when administered without a pharmacokinetic enhancer.

Study GS-US-120-1554 showed that RPV does not have a clinically relevant effect on TAF exposure and the bioequivalence of TAF exposures between ODEFSEY and GENVOYA was demonstrated in the pivotal bioequivalence Study GS-US-366-1159. Moreover, based on the plasma TAF exposure-response model for HIV antiviral activity, administration of TAF 25 mg in ODEFSEY or TAF 10 mg as a component of GENVOYA (which contains the pharmacokinetic enhancer, COBI) result in TAF exposures that exceed > 90% of Emax and are associated with maximal antiviral activity. As such, the dose of TAF 25 mg is appropriate for the ODEFSEY FDC.

Figure 5: GS-US-120-0104: TAF Exposure-Response Model for AUClast and HIV Antiviral Activity.



12.3.2. Evaluation of response

The Sponsor refers to clinical study GS-US-120-1554, by cross reference to TGA. The Sponsor is requested to provide the complete report of this study. The evaluator accepts the response by the Sponsor on the basis that study GS-US-120-1554 reports data that confirms the statement by the Sponsor that RPV has no clinically relevant effect on TAF exposure. It is interesting to note that the US FDA had approved the 25mg dose of TAF, irrespective of administration with or without a boosting agent.

12.4. Question 4

It is unclear why the sponsor chose to conduct the single bioequivalence study on a drug-drug interaction with Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) tablets. No rational is given for this choice as it does not necessarily fit with the context of the application or with the recommended clinical indications.

12.4.1. Sponsor response

Gilead has noted that in the clinical evaluation report, the evaluator is referring to the pharmacokinetic drug-drug interaction with ODEFSEY and LDV/SOF Study GS-US-366-1689, and not the pivotal bioequivalence study as suggested within the question.

ODEFSEY is a complete regimen for the treatment of HIV-1 infection. The drug-drug interaction studies described in the dossier, or in the proposed PI, provide helpful information to guide the potential coadministration of concomitant medication(s) for comorbidities. Liver related complications associated with viral hepatitis are a leading cause of death in the HIV-infected population, with HCV accounting for the majority of co-infection, particularly in the US and EU. It is estimated that there are over 4 million HIV/HCV co-infected individuals globally. In Australia the prevalence of HCV antibody in people with HIV coinfection was found to be 13.1% by the Australia HIV Observation Database (AHOD). Thus, there is a critical need for an oral antiviral regimen in the HIV/HCV co-infected population that demonstrates improved efficacy safety as well as a shortened duration of therapy.

Study GS-US-366-1689 evaluated the drug-drug interaction potential between ODEFSEY and ledipasvir/sofosbuvir (HARVONI), supporting the coadministration of ODEFSEY and HARVONI without dose modification. These results are important, and fit within the context of the application with regard to the proposed patient population which is likely to include a number of HIV/HCV co-infected patients.

12.4.2. Evaluation of response

It was considered that the issue did not require further follow up.

12.5. Question 5

There are no pharmacodynamic data on Odefsey FDC. The pharmacokinetic data are derived from Genvoya and Eviplera studies and may not be applicable to the Odefsey FDC. It is unclear why the sponsor chose not to conduct a single pharmacodynamic study using Odefsey in the target population.

12.5.1. Sponsor response

As discussed in response to Question 2 the registration strategy for ODEFSEY tablets is based on the pivotal bioequivalence study (GS-US-366-1159) that demonstrated bioequivalence of TAF and FTC exposures between ODEFSEY (FTC/RPV/TAF 200/25/25 mg) and GENVOYA (EVG/COBI/FTC/TAF 150/150/200/10 mg), thereby supporting extrapolation of the demonstrated clinical safety and efficacy of TAF and FTC exposures in ODEFSEY to those from GENVOYA, and bioequivalence of RPV exposure between ODEFSEY and Edurant (RPV 25 mg), thereby supporting extrapolation of the demonstrated clinical safety and efficacy of RPV exposures

in ODEFSEY to those from Edurant. Overall, a comprehensive program of 64 clinical studies characterises the PK of ODEFSEY and its components. This includes data from studies conducted with ODEFSEY, GENVOYA, TAF, F/TAF, RPV, EVIPLERA, FTC, or FTC/TDF. In accordance with the TGA adopted industry guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) conducting a single pharmacodynamic study using ODEFSEY in the target population is not a requirement.

12.5.2. Evaluation of response

As noted previously, the Sponsor has presented additional data contained in a single table in the response to question 2 which was unaccompanied by the clinical study report to support the conclusions of BE between Odefsey and Eviplera but again referring to previous studies that the Evaluator regarded as only tangentially relevant to the current submission. However, it is concluded that requiring new pharmacodynamic data are not crucial to proceeding with this Section 31 assessment and therefore the Evaluator accepts the Sponsor's response.

12.6. Question 6

As stated previously, Odefsey has never been administered to the target population and therefore the sponsor has extrapolated efficacy results from Genvoya (currently not approved and not relevant as a comparator) for the FTC/TAF component of Odefsey and results from Eviplera studies for the RPV component of Odefsey. While the Genvoya dossier is attached to the submission there are not clinical study reports related to Eviplera or Edurant, even though these studies are referenced and linked to the clinical summaries. It is strongly recommended that the sponsor consider conducting a clinical equivalence study comparing Eviplera and Odefsey. There are a number of study designs that would meet this recommendation.

From a regulatory perspective, the clinical and scientific rationale for extrapolating data from unrelated compounds does not seem to be acceptable.

12.6.1. Sponsor response

Gilead has addressed each of the evaluator's comments below.

- *The concept of extracting efficacy data from different compounds and then applying these results to a composite third compound, with no clinical data at all, is not acceptable from a biological or clinical perspective. It is unclear why the sponsor expected this illogical approach to be considered reasonable.*

Scientific advice on the development of ODEFSEY tablets, and consequently the approach to the registration strategy of ODEFSEY tablets was sought from the Medicinal Products Agency (MPA), Medicines and Healthcare products Regulatory Agency (MHRA), National Agency of Medicine and Health Products Safety (ANSM), and Medicines Evaluation Board (MEB), as well as in consultation with the US FDA. Based on these discussions, ODEFSEY was registered based on a bioequivalent strategy. This registration approach is consistent with the TGA adopted industry guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

The pivotal bioequivalence study (GS-US-366-1159) demonstrated the following:

- Bioequivalence of TAF and FTC exposures between the ODEFSEY FDC (200/25/25 mg) and GENVOYA FDC, thereby supporting extrapolation of the demonstrated safety and efficacy of TAF and FTC exposures in the ODEFSEY FDC to those from GENVOYA.
- Bioequivalence of RPV exposure between the ODEFSEY FDC tablet and Edurant, thereby supporting extrapolation of the demonstrated safety and efficacy of RPV exposures in the ODEFSEY FDC to those from Edurant.

In accordance with the bioequivalence approach outlined above, the safety and efficacy of ODEFSEY in various patient populations is extrapolated as follows:

- Antiretroviral treatment (ART)-naive adult patients:
  - Two pivotal Phase 3 studies conducted with GENVOYA (Studies GS-US-292-0104 and GS-US-292-0111)
  - Two pivotal Phase 3 studies conducted with RPV in combination with a nucleos(t)ide reverse transcriptase inhibitor (N[t]RTI) backbone, which included FTC and tenofovir disoproxil fumarate (TDF; VIREAD®) (Studies TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215]). The FTC/TDF subset analysis provides clinical data for RPV and FTC when administered with a tenofovir (TFV) prodrug and, therefore, contains the most relevant data for ODEFSEY.
- Virologically suppressed adult patients:
  - One Phase 3 GENVOYA study (GS-US-292-0109)
  - Two Phase 2b and 3 EVIPLERA studies (GS-US-264-0111 and GS-US-264-0106)
- Adult patients with mild to moderate renal impairment:
  - One Phase 3 E/C/F/TAF study (GS-US-292-0112)
  - RPV is approved without dose adjustment for patients with mild to moderate renal impairment
- Adolescent patients:
  - One Phase 2/3 E/C/F/TAF study (GS-US-292-0106)
  - One Phase 2 RPV study (TMC278 TiDP38-C213 [C213])

Acceptability of the BE strategy as outlined above has been validated by the recent approval of ODEFSEY by the US FDA. Extrapolation to ODEFSEY is further supported by the bioequivalence of RPV exposures between EVIPLERA and Edurant (Study GS-US-264-0103). Similarly, EVIPLERA was approved by the TGA based on a BE strategy supported by data demonstrating that EVIPLERA was bioequivalent to the individual dosage forms administered concurrently, and by cross-reference to the clinical efficacy and safety data previously provided to TGA for the products VIREAD, EMTRIVA, TRUVADA and ATRIPLA.

- *Genvoya (currently not approved and not relevant as a comparator)*

At the time of this Category 1 Application, the studies conducted with GENVOYA were under review in multiple countries, including Australia, the US and EU. GENVOYA was approved by the US FDA and EU in November 2015 and by the TGA on 12 January 2016. The studies conducted with Edurant or EVIPLERA have previously been approved by the TGA.

- *There are not clinical study reports related to Eviplera or Edurant, even though these studies are referenced and linked to the clinical summaries*

As outlined within the cover letter of the Category 1 Application, registration of ODEFSEY tablets is also supported by cross-reference to the clinical data previously evaluated and approved by the TGA for the individual components. This approach is in line with TGA guidance which states that supporting data can consist of the dossier lodged in the first instance, and any dossiers provided to the TGA previously that are referenced by the application. Only studies which have not been previously submitted, evaluated, and approved by the TGA were provided within this application and details of the applications which are being cross-referenced were provided.

- *It is strongly recommended that the sponsor consider conducting a clinical equivalence study comparing Eviplera and Odefsey*

As discussed on response to Question 2, ODEFSEY FDC tablets are similar to the TGA approved FDC tablet, EVIPLERA (RPV/FTC/TDF 20/200/300) and it is anticipated that ODEFSEY, will have similar indication for use in treatment-naive and virologically suppressed patients to EVIPLERA.

The key difference between ODEFSEY and EVIPLERA is the different form of TFV, i.e. TAF vs. TDF, which results in differences in the recommended precautions regarding renal function and renal adverse events.

Whilst conducting a clinical equivalence study comparing EVIPLERA and ODEFSEY may simplify the evaluation, in accordance with the TGA adopted industry guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) as mentioned above, it is not a requirement for the purpose of registration.

12.6.2. Evaluation of response

The Sponsor has presented additional data as a single table contained in the response to question 2, but unaccompanied by the clinical study report in order to support response to the Evaluator's questions. In referring to pre-submission discussions with regulatory agencies in Europe and the U.S.A., the Sponsor is assuming the discussions had been verified, although no information is provided to support these conclusions. The Evaluator requests that the Sponsor submit any data it has related to clinical study C213, which does not appear in the Odefsey dossier. These data should be submitted to the TGA.

12.7. Question 7

Specifically, the sponsor should be conducting a safety study on adolescents in the target group to determine safety aspects of Odefsey prior to making application for approval of Odefsey for this age group.

12.7.1. Sponsor response

Data in the use of TAF and RPV in adolescents are available from Studies GS-US-292-0106 (Study 0106) and C213. As discussed in response to Questions 2 and 7, the registration strategy for ODEFSEY tablets is based on the pivotal bioequivalence study (GS-US-366-1159) that demonstrated bioequivalence of TAF and FTC exposures between the ODEFSEY and, GENVOYA, thereby supporting extrapolation of the demonstrated safety and efficacy of TAF and FTC exposures in the ODEFSEY FDC to those from GENVOYA. Bioequivalence of RPV exposure between ODEFSEY and the marketed product Edurant (RPV 25 mg tablet), supports extrapolation of the demonstrated safety and efficacy of RPV exposures in ODEFSEY to those from Edurant.

GENVOYA was approved by the TGA on 12 Jan 2016 for use in adults and adolescents aged 12 years of age and older with body weight at least 35 kg.

Study 0106, is a Phase 2/3, multi-centre, open-label study to characterise pharmacokinetics (PK) and confirm the dose of GENVOYA in antiretroviral therapy (ART) naive paediatric patients with HIV-1 infection, as well as to evaluate safety, tolerability, and antiviral activity of GENVOYA in this population. Study 0106 demonstrated potent antiviral efficacy in adolescents and that the safety profile in adolescents is similar to that in adults, and the PK data shows equivalent exposures between adults and adolescents.

Edurant is approved in the US, EU, and UK for use in adult and adolescents aged 12 years or older as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL.

Study C213 is a Phase 2, open-label, single-arm study evaluating the PK, safety, tolerability, and antiviral activity of RPV plus an investigator-selected regimen containing 2 NRTIs (67% of which were FTC+TDF, referred to as the FTC/TDF subset) in ART-naive adolescent patients with HIV-1 infection. The PK of RPV in Study C213 supports the efficacy of the RPV component of FTC/RPV/TAF in adolescent patients. The 48-week efficacy and safety results demonstrate that RPV 25 mg qd, in combination with 2 NRTIs, is efficacious, safe and well tolerated in adolescents.

Since the exposures to the FTC, TAF and RPV components of the ODEFSEY FDC have been shown to be bioequivalent to the exposures to those components obtained from GENVOYA and Edurant, the

safety and efficacy data for GENVOYA and Edurant can be reliably extrapolated to ODEFSEY. As such Gilead maintains that the safety aspects of ODEFSEY for use in the adolescent patient population have been established for the ODEFSEY FDC tablet.

Conducting clinical research on children is a difficult and challenging expectation; it would be unreasonable to expect clinical research in children in different sub-populations when the safety and efficacy of ODEFSEY in adolescents can be extrapolated from the clinical studies in Edurant and GENVOYA.

12.7.2. Evaluation of response

The Sponsor has presented minimal additional data which is accessible to the Evaluator to support response to this question. The Sponsor is requested to submit the CSR for C213. The Sponsor refers to submissions that at the time of this submission had not been approved and therefore the data were not applicable. However, the Genvoya submission has now been approved, which, according to the Sponsor, makes the Genvoya data, admissible. There is agreement that additional studies on adolescents should be minimised, if at all possible. Moreover, the statement that Eviplera is approved for adolescents in the US, EU and UK is noted by the evaluator to this application as it is not approved for this indication in Australia. The Sponsor has referred to clinical study C213 to support the efficacy of Odefsey in adolescents. It appears this study is available to authorities in the US, UK and EU for the purpose of supporting an adolescent indication for COMPLERA/EVIPLERA which is not being sought in Australia. The Sponsor is requested to provide the full CSR to TGA.

12.8. Question 8

The pivotal safety study currently underway where Odefsey equivalent constituents are being trialled was briefly described in the Descovy submission as GS-US-311-1089, which is an ongoing Phase 3, randomised, double-blind, switch study to evaluate the efficacy of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF as determined by the proportion of subjects with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48. In this trial there will be patients who remain on Eviplera and those who switch to FTC/RPV/TAF and these subjects in the target population may provide data to support both the safety and efficacy aspects of this submission.

12.8.1. Sponsor response

In Study GS-US-311-1089 (Study 1089) Week 48 analysis, 9 of 663 (0.5%) randomized and treated patients received RPV with their study medication; 3 patients received F/TAF+RPV and 6 patients received FTC/TDF+RPV. None of the patients receiving F/TAF+RPV experienced virologic failure by FDA snapshot algorithm (HIV-1RNA ≥ 50 copies/mL) at Week 48. One patients receiving FTC/TDF+RPV experienced virologic failure but did not meet the criteria for resistance analysis and subsequently resuppressed without a change in regimen.

Study 1089 was provided in response to a question from the clinical evaluator at milestone 3 of the DESCOVY (F/TAF) evaluation. Gilead considers that the safety of ODEFSEY has been established via the comprehensive program of clinical studies with GENVOYA, and Edurant, the individual components and subsequent bioequivalence studies.

Whilst conducting clinical trials in every possible population, would simplify the evaluation, it would also unnecessarily delay registration, when in accordance with the TGA adopted industry guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), such studies are not required for the purposes of registration.

As a Sponsor of therapeutic goods, Gilead continues to conduct clinical trials throughout the lifecycle of a product in order to provide physicians with additional data regarding efficacy and safety of a product. Studies GS-US-366-1160 and GS-US-366-1216 are randomized, double-blinded, ongoing phase 3b switch studies investigating ODEFSEY.

- Study GS-US-366-1160 is a randomized, double-blind study designed to evaluate maintenance of virologic suppression (HIV-1 RNA < 50 copies/mL at Week 48) in virologically suppressed, HIV-1 infected patients when switching from a regimen consisting of EFV/FTC/TDF FDC to FTC/RPV/TAF FDC.
- Study GS-US-366-1216 is a randomized, double-blind study designed to evaluate maintenance of virologic suppression (HIV-1 RNA < 50 copies/mL at Week 48) in virologically suppressed, HIV-1 infected patients when switching from FTC/RPV/TDF FDC to FTC/RPV/TAF FDC.

Gilead will provide the data to TGA for review in a post approval application when available.

12.8.2. Evaluation of response

The Sponsor has now identified relevant data that appears to have been available at the time of submission, but not included until now. At the very least the Sponsor was aware of the existence and design and timeframe for these studies The Evaluator is requesting the clinical study report for GS-US-366-1160 and GS-US-366-1216 either as a preliminary report and the final report when it is available. The Sponsor is requested to provide a timeframe for availability of these reports. It is agreed that the number of relevant cases in GS-US-366-1089 is relatively few. However, these data should have been included in the original Odefsey submission.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of Odefsey are unchanged from those identified in the first round assessment.

13.2. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Odefsey are unchanged from those identified in the first round assessment.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Odefsey, given the proposed usage, is favourable because the sponsor has provided additional information in the response.

14. Second round recommendation regarding authorisation

It is recommended that Odefsey should be granted authorisation. This is a shift from the recommendation of the first round. The reason for this change is based on the provision of additional data by the sponsor with respect of the summary table from clinical Study GS-US-366-1881. This table provides bioequivalence data for Eviplera versus Odefsey and demonstrates no difference. In addition, Odefsey has now been approved in the US and EU. The evaluator concludes that on-balance the dossier supports patients with HIV-1 infection to have TDF replaced by TAF in Odefsey as this will reduce the risk of renal and bone mineral density adverse effects for patients. Study C231, has data to extend approval for adolescents

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