Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for emtricitabine / rilpivirine / tenofovir alafenamide fumarate

Proprietary Product Name: Odefsey

Sponsor: Gilead Sciences Pty Ltd

October 2017

TGA Health Safety Regulation

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Contents

Common abbreviations

Abbreviation	Meaning
3TC	lamivudine
ABC	abacavir
ACPM	Advisory Committee on Prescription Medicines
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

Abbreviation	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
FDC	fixed-dose combination
FEPO4	fractional excretion of phosphate
FEUA	fractional excretion of uric acid
FTC, F	emtricitabine (Emtriva)

Abbreviation	Meaning
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
NNRTI	nonnucleoside reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
NVP	nevirapine
OLE	open label extension

Abbreviation	Meaning
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PEP	postexposure prophylaxis
P-gp	P-glycoprotein
PI	Product Information
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
RT	reverse transcriptase
RNA	ribonucleic acid
ROW	Rest of World
RPV, R	rilpivirine

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

I. Introduction to product submission

Submission details

Type of submission:	New fixed dose combination
Decision:	Approved
Date of decision:	16 August 2016
Date of entry onto ARTG	30 August 2016
Active ingredients:	Emtricitabine / rilpivirine / tenofovir alafenamide fumarate
Product name:	Odefsey
Sponsor's name and address:	Gilead Sciences Pty Ltd Level 6, 417 St Kilda Road Melbourne VIC 3004
Dose form:	Fixed dose combination tablet
Strengths:	200 mg emtricitabine / 25 mg rilpivirine / 25 mg tenofovir alafenamide fumarate
Container:	HDPE bottles with a child resistant closure
Pack size:	30 tablets
Approved therapeutic use:	Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤100,000 copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.
Route of administration:	Oral
Dosage:	One tablet per day
ARTG number:	260634

Product background

This AusPAR describes the application by Gilead Sciences Pty Ltd to register Odefsey as a new fixed dose combination (FDC) oral tablet containing 200 mg emtricitabine (FTC, F), 25 mg rilpivirine (RPV, R) and 25 mg tenofovir alafenamide (as fumarate) (TAF) for the following proposed indication in Australia:

> *Odefsey is 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.*

FTC/RPV/TAF has been developed for the treatment of HIV-1 infection for once-daily oral administration. The FDC is a combination of a nucleoside reverse transcriptase inhibitor (FTC), a nonnucleoside reverse transcriptase inhibitor (RPV), and a nucleotide reverse transcriptase inhibitor (TAF). There is no currently approved indication for this FDC.

The proposed dose is one tablet taken daily with food. The proposed tradename is Odefsey (FTC/RPV/TAF 200/25/25 mg).

The currently approved equivalent product containing tenofovir disoproxil fumarate (TDF) is Eviplera (FTC/RPV/TDF 200/25/300 mg) approved for the following indication in Australia:

> *Eviplera is indicated for the treatment of HIV infection in treatment-naïve adult patients with plasma HIV-1 RNA ≤ 100,000 copies/mL at the start of therapy.*
>
> *Eviplera is also indicated in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of resistance to any of the components of Eviplera (tenofovir DF, emtricitabine or rilpivirine).*

The restriction to 'adult' patients for Eviplera relates to its RPV component which, in its registration as single agent Edurant, has restriction of use in children ("Treatment with Edurant is not recommended in paediatric patients (<18 years) due to insufficient data in this patient population"). Overseas approved prescribing information documents in the USA and EU indicate that paediatric data (Study 213 identified by the sponsor in second round) were used to update recommendations in those jurisdictions but not in Australia.

TAF has been approved in Australia as FDC Genvoya (EVG/COB/FTC/TAF 150/150/200/10 mg) for:

> *the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older with body weight at least 35 kg who are either treatment-naïve; or virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya.*

TAF has now been approved as FDC in Descovy (FTC/TAF 200/25 and 200/10 mg) after consideration at the June 2016 meeting of ACPM and is indicated:

> *in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Descovy (see PHARMACOLOGY). Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).*

Regulatory status

The current international regulatory status is listed in Table 1.

Table 1: International regulatory status for Odefsey at time of submission to TGA.

Country	Submission date	Approval date	Indication (if applicable)
US	1 Jul 2015	1 Mar 2016	ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and 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; or to replace a stable antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of ODEFSEY.
EU	29 Jul 2015	21 Jun 2016	Odefsey is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus- 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.
Canada	19 Feb 2016	10 Feb 2017	ODEFSEY (200 mg emtricitabine [FTC]/25 mg rilpivirine [RPV]/25 mg tenofovir alafenamide [TAF]) is indicated as a complete regimen for the treatment of adults infected with HIV-1 with no known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or FTC, and with a viral load ≤ 100,000 copies/mL.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

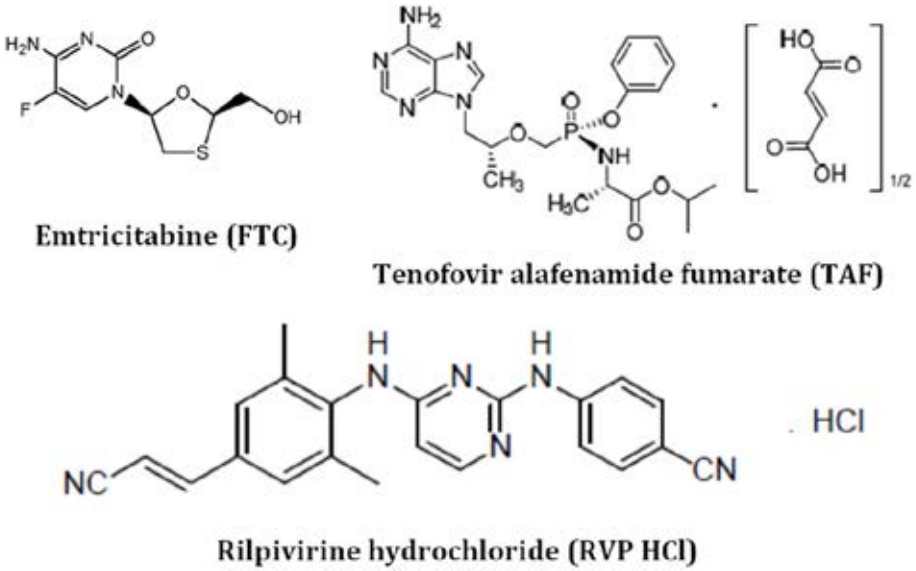
II. Quality findings

Introduction

Drug substance (active ingredient)

The components are shown in Figure 1.

Figure 1: Chemical structures.



Emtricitabine (FTC)

The chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for Emtriva FTC 200 mg capsules.

Tenofovir alafenamide (as fumarate) (TAF)

The chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for Genvoya Elvitegravir (150 mg), Cobicistat (150 mg), FTC (200 mg) and TAF (10 mg) tablets.

Rilpivirine hydrochloride (RPV HCl)

The chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for Edurant RPV 25 mg (as hydrochloride) tablets.

Drug product

The proposed FDC tablet is an immediate release, film-coated tablet. The formulation of the tablet is conventional and the tablets are composed of lactose, microcrystalline cellulose, povidone, Polysorbate 20, croscarmellose sodium, and magnesium stearate in the core and Opadry II complete film coating system 85F17636 grey in the film coat. The proposed tablets are packed in HDPE bottles with a child resistant closure containing 30 tablets.

The proposed tablet appearance is below:

60 mg tablet: grey, capsule shaped, film coated tablets debossed with "GSI" on one side and "255" on the other side. The tablet dimensions are 15 mm in length by 7 mm in width.

FTC/RPV/TAF tablets are manufactured in a series of manufacturing steps. RPV HCl is fluid bed granulated with intra granular excipients to produce RPV granules, which are subsequently dried, milled, and blended with extra granular excipients to produce RPV final powder blend. FTC and TAF fumarate are co-dry granulated with intra granular excipients and lubricated with extra granular magnesium stearate to produce FTC/TAF final powder blend. The RPV final powder blend and the FTC/TAF final powder blend are compressed into bilayer tablet cores that are then film coated for appearance using Opadry II Gray 85F17636.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity, water content, assay, degradation products, uniformity of dosage units, dissolution and microbiological content. Specified degradation products at levels above the ICH qualification threshold have been qualified based on toxicological data

A shelf life of 24 months when stored below 30°C is recommended for the proposed drug product.

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

- Study GS-US-366-1159: A Phase I, Randomised, 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)

This study assessed the bioequivalence of a single dose of FTC, RPV and TAF in the proposed tablets to that of 25 mg Edurant tablets (RPV) and 150/150/200/10 mg E/C/F/TAF FDC tablets. The results show that the FTC, RPV and TAF components of the proposed Odefsey FTC/RPV/TAF 200/25/25 mg fixed-dose combination tablet are bioequivalent to the Genvoya E/C/F/TAF 150/150/200/10mg fixed-dose combination tablet and the Edurant (25 mg RPV) tablet.

Table 2: Cmax and AUC_t values for FTV, RPV and TAF.

	FTC		RPV		TAF	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
C_{max}	100.81%	97.52 - 104.21%	113.52%	108.40 - 118.89%	100.78	91.63 - 110.85%
AUC_t	92.24%	90.84 - 93.67%	111.70%	106.31 - 117.38%	102.85	98.18 - 107.75%

Quality summary and conclusions

Registration of the product is recommended from a chemistry and quality control perspective.

III. Nonclinical findings

Assessment

In support of the proposed registration, the sponsor submitted data regarding the in vitro anti HIV activity of TAF in combination with FTC and RPV, in a two drug combination assay. Details of this study are included. The submitted in vitro study in acutely infected MT-2 cells clearly demonstrated a synergistic anti HIV activity, with absence of antagonism, when tested in different combinations. Data from a three drug combination were not provided, however since every possible proposed drug combination in the two drug study provided were tested and synergistic anti HIV activity was clearly observed in every combination, further studies were not required.

No nonclinical safety studies with FTC/RPV/TAF combination were provided however, as FDC combinations of these drugs have been previously approved in a number of combination therapies, it is not considered a requirement for approval. FTC (200 mg) and RPV (25 mg) have been approved in combination with 300 mg of TDF in Eviplera. Like TAF, TDF is the first generation prodrug of tenofovir but has higher risks associated with nephrotoxicity and reduction in bone mineral density. TAF (10 mg) has recently been approved in combination with elvitegravir (150 mg), cobicistat (150 mg) and FTC (200 mg) in Genvoya, and TAF (25 mg) in combination with FTC (200 mg) in Descovy. Adequate justification was provided by the sponsor for the lack of nonclinical toxicity studies with the fixed triple combination, which was consistent with EMA guideline on the nonclinical developmental of fixed combination of medicinal products[1] and the ICH M3(R2) guidelines[2] that state toxicity studies are generally not warranted for drug combinations for HIV.

Nonclinical summary and conclusions

In vitro studies demonstrated synergistic anti HIV activity of the triple drug combination.

The sponsor has provided adequate justification for the lack of nonclinical toxicity studies with the triple combination.

There are no nonclinical objections to registration of the FDC of FTC/RPV/TAF, 200/25/25 mg provided that the clinical evaluator is satisfied that bioequivalence has been demonstrated between TAF 25 mg in Odefsey and TAF 10 mg in Descovy, and between RPV 25 mg in Odefsey and RPV 25 mg in Edurant.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

[1] European Medicines Agency, Guidelines on the non-clinical development of fixed combinations in medicinal products, EMEA/CHMP/SWP/258498/2005, 24 January 2008.
[2] ICH M3 (R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. March 2011.

Introduction

Clinical rationale

Standard of care for the treatment of HIV-1 infection uses combination 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 two 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 FTC/RPV/TAF (Odefsey) tablet, may provide the potential for the longevity of treatment that optimizes tolerability, long term safety, and durable efficacy. For HIV infected patients, Odefsey, with its substitution of TDF for TAF, may have advantages over the existing marketed product containing TDF/FTC and RPV (Eviplera); specifically, less proteinuria, less need for renal monitoring, and less impact on bone mineralisation relative to FTC/TDF/RPV treatment. The relatively low dose of TAF (25 mg versus 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.*

Guidance

During the pre-submission assessment, TGA noted the proposed indication is:

> *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 FTC/RPV/TAF combination.*

TGA further noted:

> *The proposed F/R/TAF 200/25/25 FDC is supported in principle, given the currently registered F/R/TDF 200/25/300 FDC. It is noted that TAF is currently not on the ARTG as a mono-agent or as a component of any FDC.*

Please note that this advice is without prejudice and does not imply adequacy of the BE study to support the registration or the adequacy and relevance of the clinical data for the E/C/F/TAF 150/150/200/10 (Feb 2015 batch) or F/TAF 200/10 and 200/25 (no submission yet) or the data supporting use of TDF. These are evaluation matters and will be dependent on the outcome of the full evaluation process.

At present, the registered products Eviplera (FTC/RPV/TDF), Truvada (FTC/TDF), Edurant (RPV) or Stribild (EVG/COB/FTC/TDF) are approved for use in adults (> 18 years of age). Genvoya and Descovy were not registered at the time of Odefsey submission

This apparent discrepancy has been addressed in the clinical evaluation report. As noted, one of the major comparator substances, Genvoya, remained under review by TGA at the time of the clinical assessment; therefore, the validity of the use of this comparator remained questionable.

TGA has adopted the following EU guidelines relevant to this submission:

- Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection EMEA/CPMP/EWP/633/02 Revision 2,[3] which came into effect in June 2009 and as adopted by TGA in July 2009;
- Points to Consider on Switching Between Superiority and Non inferiority CPMP/EWP/482/99,[4] which came into effect in July 2000 and was adopted by TGA in June 2000;
- Guideline on Reporting the Results of Population Pharmacokinetic Analyses. CHMP/EWP/185990/06,[5] which came into effect in January 2008 and was adopted by TGA in February 2009.

Contents 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 25 mg, whereas the dose in Genvoya is 10 mg, albeit boosted with 150 mg 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 I 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 I two way crossover study comparing the bioequivalence of FTC/TAF administered as Genvoya (E/C/F/TAF) with FTC/TAF administered as Odefsey (F/RPV/TAF), and RPV administered as a single tablet, compared with RPV administered as Odefsey. The second PK study is a Phase I study,

[3] European Medicines Agency, Guideline on the clinical development of medicinal products for the treatment of HIV infection, EMEA/CPMP/EWP/633/02 Revision 2, 20 November 2008.
[4] European Medicines Agency, Points to consider on switching between superiority and non-inferiority, CPMP/EWP/482/99, 27 July 2000.
[5] European Medicines Agency, Guideline on reporting the results of population pharmacokinetic analyses, CHMP/EWP/185990/06, 21 June 2007.

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.

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 200 mg/25 mg/25 mg as there are no bioequivalence studies presented in the dossier to enable determination of the relationship of the 10mg TAF boosted with 150 mg Cobicistat dosage as used in the Genvoya Study GS-US-292-0106.

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 US 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.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic.

Table 3: 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.

Evaluator's 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 in this section. 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 10 mg rather than 25 mg 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.

Pharmacodynamics

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.

Evaluator's conclusions on pharmacodynamics

The sponsor has presented no pharmacodynamic studies utilising Odefsey, the FDC, for which this application has been made.[6] In addition, even in those studies for which the sponsor has included summary statements and made reference to an actual CSR and

[6] 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.

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.

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 sincluded in the Genvoya 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.

RPV 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. FTC 200 mg once daily is the approved dose for Emtriva.

Efficacy

No clinical efficacy studies have been conducted with Odefsey.

Safety

Studies providing safety data

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 only complete Study Reports are included 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.

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.

Study GS-US-366-1159

All 96 subjects were included in the Safety Analysis Set.

Study GS-US-366-1651

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

Study GS-US-366-1689

All 42 randomised subjects (Randomised Analysis Set) received at least one dose of assigned study drug and were included in the Safety Analysis Set and PK Analysis Set.

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.

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 one subject in any treatment group.

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 (that is, 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).

Safety issues with the potential for major regulatory impact

Serious skin reactions

This cumulative review of severe skin and hypersensitivity reactions with Complera/Eviplera was prompted by receipt of a FDA Safety Labelling Change Notification

for Complera (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 FTC and tenofovir DF components and rash for the FTC, RPV 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 FTC.

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). A total of 27 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:

- 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.
- 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; and documented temperature meeting true fever criteria, lymphadenopathy and facial oedema. 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.

- 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 hospitalisation 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.
- 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, generalised 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.
- 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:
  - 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.
  - 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.
  - 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).

– 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.

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 hospitalisation, 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.

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:

· 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 (of which 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 acquired lipodystrophy). One case reported gain of muscle mass and not fat mass. 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.
- 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).
- 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).

- Information from epidemiological studies: Two sources of epidemiological data were assessed:
  - In limited data in the latest report from the Janssen-sponsored Drug Utilisation 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 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:

- 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.
- 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.
- 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.

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.

Post marketing data

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

Evaluator's conclusions on 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.

First round benefit-risk assessment

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.

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.

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.

First round recommendation regarding authorisation

The recommendation is that this application should be rejected.

Clinical questions

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, for example, before, with or just after the meal.
3. As in the Descovy application, administration of TAF 10 mg with a meal results in almost the same bioequivalence exposure as administering TAF 25 mg, why the sponsor dismisses the possibility of having a 10 mg 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) 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.

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.

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 is 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.

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.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

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.

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.

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.

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.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 0.1 [dated 14 July 2015, Data Lock Point 28 April 2015]) and Australian Specific Annex (ASA) Version 0.1 (dated September 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4: Ongoing safety concerns.

Safety Concerns		FDC component
Important identified risks	Post-treatment hepatic flares in HIV/HBV co-infected patients	FTC, TAF
	Development of drug resistance	RPV
	Depression	
	Severe skin reactions	
Important potential risks	Overdose (including overdose through accidental concurrent use of FTC/RPV/TAF with RPV-containing products)	FTC/RPV/TAF^, RPV
	Off-label use in patients with a baseline viral load >100,000 HIV-1 RNA copies/mL	
	QT interval prolongation	RPV
	Hepatotoxicity	RPV
	Blood cortisol decreased	RPV
Missing information	Long-term safety information in adults and adolescents	FTC/RPV/TAF^, TAF (adolescents)
	Safety in children aged 4 weeks to < 12 years	RPV, TAF
	Safety in elderly patients	RPV
	Safety in pregnancy	FTC, RPV, TAF
	Safety in lactation	
	Safety in patients with severe hepatic impairment (CPT score C)	RPV, TAF

Safety Concerns		FDC component
	Safety in patients with HBV or HCV coinfection	TAF
	Safety in patients with renal impairment ($eGFR_{creat}$ <50 L/min/1.73 m^2)	RPV

FTC = Emtricitabine; RPV = Rilpivirine; TAF = Tenofovir Alafenamide; ^ = as single tablet

RMP reviewer comment

The listed safety concerns are generally consistent with those for Descovy and Genvoya, and for the RPV component of Eviplera. However, "drug-drug interactions" is listed as missing information for the RPV component of Eviplera. Therefore, the Sponsor should provide a justification for this difference, or add the concern as missing information for Odefsey.

The missing information safety concern of "Safety in children aged 4 weeks to <12 years" should be modified to include paediatric patients aged 12 years or over but weighing <35 kg.

The clinical evaluator's concerns regarding renal and bone toxicity are noted. However, the approach taken is consistent with other FDC involving TAF.

The omission of lactic acidosis and lipodystrophy as important identified risks is supported by a PRAC review which recommended the removal of these warnings for this class of medicines.

Pharmacovigilance plan

Routine pharmacovigilance[7] is proposed for all safety concerns except "missing information – long-term safety information in adults and adolescents". Additional pharmacovigilance activities for specified safety concerns are summarised in Table 5.

Table 5: Additional pharmacovigilance activities for missing information.

Assigned safety concern	Additional activity	Actions/outcome proposed	Est. planned submission of final data
Safety in pregnancy (RPV, TAF, FTC)	***Antiretroviral pregnancy registry***	Collection of information on the risk of birth defects in patients exposed to antiretrovirals, including ODEFSEY during pregnancy.	Interim reports to be included in ODEFSEY PSURs
	Clinical trial Study TMC114HIV3015	Pharmacokinetic study of RPV in HIV-1 infected pregnant women	Q4 2016 (EU)
Safety in children aged 4 weeks to <12 years (RPV, TAF)	***Clinical trials***		
	GENVOYA in HIV-1 infected patients aged 6 to <18 years – GS-US-292-0106 (ASA)	Pharmacokinetics, safety, and antiviral activity of the GENVOYA STR in HIV-1 infected antiretroviral	48 wk report Q1 2016 (EU); final report Q2

[7] Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

Assigned safety concern	Additional activity	Actions/outcome proposed	Est. planned submission of final data
	GS-US-292-0113 (EU-RMP)	treatment naive adolescents	2022
	GS-US-292-1515	In ASA only; no study details given	Not indicated
	RPV – clinical study in HIV-1 infected adolescents from 6 to <12 years of age – C220 (ASA) and/or C213 (EU-RMP).	*Note – indicated as Study C213 in ASA* efficacy, pharmacokinetics, safety, and tolerability, of RPV in antiretroviral treatment-naïve HIV-1 infected children (<12 Years).	Q2 2019 (EU)
Long-term safety information in adults and adolescents (F/R/TAF as STR) (TAF for adolescents)	***Phase 3 clinical trials***		
	• HIV-1 infected adults:		
	GS-US-292-0104^ & GS-US-292-0111	Comparison of safety and efficacy of STRIBILD and GENVOYA (TDF *cf.* TAF)	96 wk report Q3 2016 (EU)
	GS-US-292-0109^	Evaluate switching from TDF and TAF containing single tablet regimens	96 wk report Q1 2017 (EU)
	• HIV-1 infected adolescent patients:		
	GS-US-292-0106	See above	See above
	GS-US-292-1515	In ASA only; no study details given	Not indicated
	• RPV clinical study in HIV-1 infected adolescents (C213).	pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine in antiretroviral naïve HIV-1 infected adolescents aged 12 to < 18 Years.	Final report (incl. long-term extension <240 wks): Q4 2018 (EU)
	• ODEFSEY clinical studies in HIV-infected adult patients: GS-US-366-1160	Switching from a Regimen Consisting of ATRIPLA to ODEFSEY in Virologically-Suppressed, HIV-1 Infected Subjects	Final report Q4 2017 (EU)
	GS-US-366-1216	Safety and Efficacy of ODEFSEY in HIV-1 Positive Subjects who are Virologically Suppressed on EVIPLERA	Final report Q3 2017 (EU)
Safety in patients with HBV or HCV coinfection (TAF)	***Clinical trial*** GS-US-292-1249	Efficacy and Safety of GENVOYA in HIV 1/Hepatitis B Coinfected Adults	Q3 2016 (EU)

FTC = emtricitabine; RPV = rilpivirine; STR = single tablet regimen; TAF = tenofovir alafenamide fumarate;
ATRIPLA = efavirenz/emtricitabine/ tenofovir disoproxil fumarate;
STRIBILD = Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate
^ = study includes Australian patients

RMP reviewer comment

The pharmacovigilance activities reported in the ASA is incomplete as it does not report all studies referenced in the EU-RMP. Similarly, the summary of pharmacovigilance activities in the ASA is inconsistent with those listed in the EU-RMP. The sponsor should also clarify any Australian involvement in the studies that are added to the revised ASA. The following safety concerns have additional pharmacovigilance activities reported in the EU-RMP, which should also be included in the ASA:

- Development of drug resistance
- Depression
- QT prolongation
- Hepatotoxicity
- Safety in children aged 4 weeks to <12 years (studies reported in ASA inconsistent with those in EU-RMP)
- Safety in pregnancy (additional pharmacovigilance study in EU-RMP)

Study GS-US-292-0112 is reported as being underway, and should be included in Table 6 as addressing the missing information for safety in patients with mild to moderate renal impairment. It should also be added to the EU-RMP.

Details of Study GS-US-292-1515 should be provided, and the sponsor should incorporate the anticipated dates for the submission of pharmacovigilance study reports in Australia into the ASA.

Risk minimisation activities

The sponsor concludes that routine risk minimisation activities[8] for all the specified safety concerns and missing information are sufficient, except for the important potential risk: 'blood cortisol decreased', and the missing information: 'Long-term safety information in adults and adolescents' for which no risk minimisation is proposed.

RMP reviewer comment

As indicated above, the ASA states that no routine risk minimisation activities are planned for effects on blood cortisol levels. However, statements regarding effects on cortisol levels in the context of adrenal function in the Australian PI are comparable to those in the SmPC, and therefore PI statements should be included as routine risk minimisation for this important potential risk.

The potential for overdose is addressed as an important potential risk. The sponsor concluded there is a low risk for Odefsey to transmit infectious disease, or to be misused for illegal purposes. This conclusion is supported by the tablet formulation and mechanism of action which does not involve the CNS.

The potential for off-label use included use in patients with a baseline viral load of >100,000 HIV-1 RNA copies/mL, which is identified as an important potential risk. In addition, the potential for paediatric off-label use in children aged <12 years of age was considered. The sponsor claims that minimal use of other single tablet regimens have been reported in children aged <12 years of age in PSURs/PBRERs for these products. The sponsor has committed to investigating the extent of adult and paediatric off-label uses in PSURs/PBRERs for Odefsey.

[8] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

One patient population that may be at risk of off-label use is children aged ≥12 years of age but weighing <35 kg. It is recommended that the proposed indication be modified to address this concern by including the minimum weight in the indication, as has been done in the EU.

Summary of recommendations

Issues in relation to the RMP

The sponsor should revise the ASA to:

- Align its contents with that of the EU-RMP with respect to the summary of pharmacovigilance activities described in ASA;
- Indicate Australian involvement in the pharmacovigilance activities, and indicate their anticipated date of submission to TGA;
- Clarify the proposed additional risk minimisation activities for QT prolongation in Australia (none or n/a; clarify the meaning of n/a if required);
- Include the exact wording of statements in the EU SmPC and proposed Australian PI in the ASA;
- If retained, the proposed removal of advice to not use Odefsey in patients with severe hepatic impairment from the PI should be reflected in the ASA.

Recommendation to the Delegate

The suggested wording for the conditions of registration is:

> *The European RMP (dated 14 July 2015, DLP 28 April 2015), with ASA (Version 0.1, dated September 2015), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no outstanding issues. Approval is recommended. The submission was not sent to the PSC.

Nonclinical

There are no toxicology objections to the approval. Recommendations for PI have been provided.

Clinical

The clinical dossier is based on 2 Bioequivalence studies, 1 food study, and 1 drug-drug interaction study.

Bioequivalence (BE)

The dossier supporting Odefsey consists of 2 relative bioequivalence studies, Study 1159 & Study 1881 as follows.

BE Study 1159

This was 2 separate, single dose, randomised, crossover trials in healthy volunteers under fed state, to ascertain pharmacokinetic bioequivalence of:

- FTC & TAF in ODEFSEY (FTC/RPV/TAF 200/25/25 mg)

  versus

  FTC & TAF in GENVOYA (EVG/COB/FTC/TAF 150/150/200/10 mg)

- RPV in ODEFSEY (FTC/RPV/TAF 200/25/25 mg)

  versus

  RPV in EDURANT (RPV 25mg)

The results were as follows.

Table 6: BE Study 1159 PK parameters.

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

Thus, bioequivalence was satisfactorily demonstrated, based on conventional criterion of 90% confidence interval for the ratio of means for AUC and Cmax to be within 80-125% equivalence margin, for all 3 components, including TAF 25mg unboosted in Odefsey versus TAF 10mg boosted with cobicistat in Genvoya.

BE Study 1881

This study was initially not included in the dossier and was identified only in the Section 31 response. The report was supplied at the conclusion of evaluation process. The sponsor explained that the US FDA declared a preference for comparison of Odefsey with Genvoya and Edurant rather than with Eviplera. The reasons are not clear, but may have to do with the need to prioritise the equivalence of TAF and link it to the clinical efficacy of Genvoya in the absence of clinical studies of Odefsey.

This was a single dose, randomised, crossover trial in healthy volunteers under fed state, to ascertain relative bioequivalence of RPV in Odefsey (FTC/RPV/TAF 200/25/25 mg) versus Eviplera (FTC/RPV/TDF 200/25/300 mg). The results were as follows.

Table 7: GS-US-366-1881: statistical comparisons of PK parameter estimates between test and reference treatments (RPV PK analysis set).

RPV PK Parameter	GLSM		GLSM Ratio (%) (90% CI)
	Test (N = 28)	Reference (N = 27)	
ODE (Test) vs CPA (Reference)			
AUC_{last} (ng•h/mL)	3379.45	3100.75	108.99 (101.81,116.68)
AUC_{inf} (ng•h/mL)	3658.85	3371.68	108.52 (101.69,115.80)
C_{max} (ng/mL)	100.66	91.71	109.76 (101.82,118.32)

Thus, the bioequivalence was satisfactorily demonstrated with respect to RPV component in Odefsey and Eviplera.

Clinical Efficacy/Safety

No clinical efficacy/safety data are available for Odefsey at present.

Risk management plan

The EU-RMP (dated 14 July 2015, DLP 28 April 2015), with ASA (Version 0.1, dated September 2015) applies to this submission.

Risk-benefit analysis

Delegate's considerations

The FTC, RPV and TAF components in Odefsey were found to be bioequivalent to the respective components in Genvoya, Edurant and Eviplera.

The selected 25mg dose of TAF in Odefsey (FTC/RPV/TAF 200/25/25 mg) is based on results of Study GS-US-120-0104 in the previously evaluated GENVOYA dossier in which 3 dose levels of TAF (8, 25 and 40 mg) were examined in HIV patients as monotherapy. TAF 8 mg was found to be equipotent to TDF 300 mg, whereas TAF 25 mg resulted in near maximal antiviral activity with plasma TFV exposure lower by more than 90% relative to TDF 300 mg.

TAF 25 mg is also a component in Descovy (FTC/TAF 200/25), which will also be made available in 200/10 mg strength in Australia for use in the presence of a boosting agent.

Genvoya contains 10mg TAF due to inclusion of cobicistat as boosting agent in this product. Unboosted TAF 25 mg and boosted TAF 10 mg are considered bioequivalent based on data seen previously, as well as data in this submission (Study 1159).

In terms of suitability of the Odefsey as a fixed dose formulation, a single dose study (GS-US-120-0117) of RPV (25 mg) and TAF (25 mg) in healthy volunteers in Genvoya dossier did not show clinically relevant changes in TAF, TFV and RPV exposure levels on co-administration compared to administration alone. Furthermore, multiple dose study (GS-US-120-1554) of RPV (25 mg) and TAF (25 mg) in Descovy dossier also did not show clinically relevant changes in TAF, TFV and RPV exposure levels on co-administration. The amount of FTC (200 mg) and RPV (25 mg) in Odefsey are same as in the currently approved Eviplera.

This submission also included a food study (GS-US-366-1651) of Odefsey and a drug-drug interaction study (GS-US-366-1689) of Odefsey with ledipasvir/sofosbuvir (90/400 mg). A clinically significant food effect (AUC of 87%, 172% and 153% for FTC, RPV & TAF respectively with high fat diet compared to fasting) or a pharmacokinetic interaction with ledipasvir or sofosbuvir (all 5 components) was not demonstrated.

The bioequivalence strategy supporting Odefsey is based on implied extrapolation of clinical efficacy and safety of Genvoya, Edurant and Eviplera to Odefsey. The known drug interactions also apply to Odefsey by extrapolation.

A very small amount of relevant clinical exposure data was identified in Study GS-US-311-1089 which was evaluated in the Descovy submission. This was a Phase III, randomised, double-blind study to examine switching to Descovy (FTC/TAF) in virologically-suppressed HIV patients stable on regimens containing Truvada (FTC/TDF) plus a third agent. At Week 48, it is noted that 9/663 (0.5%) patients received RPV as the 3rd agent (3 patients in FTC/TAF and 6 patients in FTC/TDF group) in this study.

An additional issue is that Edurant and Eviplera are not approved for use in children <18 years of age in Australia. These are approved for use in adults and adolescents aged 12 years or older in EU and USA. The approved prescribing information from these jurisdictions indicates that a single arm, Phase II, Study C213 in 36 treatment naïve adolescent (≥12 to <18 years age) HIV patients was used to expand the use to adolescent population. This update was not done in Australia. The clinical study report for this trial has now been provided and a description of it is also proposed for inclusion in the Odefsey PI. This study involved the use of RPV (25mg daily) in combination with a regimen containing 2 NRTIs (67% of which were FTC+TDF). The PK results were as follows and were demonstrative of PK bioequivalence with respect to RPV exposure (AUC) in treatment-naïve adolescents and treatment naïve adult HIV patients (reference group).

Table 8: Summary of statistical analysis of the steady-state PK parameters of RPV after multiple dose administration of RPV 25 mg qd in adolescents (this study Part 1) and in adults (pooled data of TMC278-C209/C215 PK sub studies).

Parameter	LS means[a]		LS means ratio, %	90% CI,% [b]
	TMC278-C209 + TMC278-C215 (reference)	TMC278-C213 (Part 1a + 1b) (test)		
C_{trough}, ng/mL	58.3	70.6	121.07	95.45 – 153.58
C_{max}, ng/mL	47.5	51.3	108.09	87.44 – 133.61
C_{max}, ng/mL	116	102	88.24	71.09 – 109.54
AUC_{24h}, ng.h/mL	1782	1750	98.19	80.53 - 119.73

[a] N=44 for reference and N=23 for test
[b] 90% confidence intervals
LS: least squares

The Week 48 efficacy data in Study 213 were also reported as follows.

Table 9: Virologic outcome at Week 24 and 48 (<50 copies/ml, TLOVR); ITT.

n (%)	RPV 25 mg qd (N=36)	
	Week 24	**Week 48**
Responder	27 (75.0%)	26 (72.2%)
Virologic failure	7 (19.4%)	8 (22.2%)
never suppressed	6 (16.7%)	4 (11.1%)
initial lack of response*	1 (2.8%)	1 (2.8%)
rebounder	1 (2.8%)	4 (11.1%)
Discontinued due to AE**	1 (2.8%)	1 (2.8%)
Discontinued due to reason other than AE	1 (2.8%)	1 (2.8%)

N=number of subjects with data, n=number of subjects with that observation
* Confirmed decrease in plasma viral load of <1.0 log10 at Week 12 from the baseline plasma viral load (ie, 2 consecutive measurements at least 2 weeks apart)
** One subject (213-0026) discontinued due to an AE of pulmonary tuberculosis (mandatory withdrawal criterion).

In addition, data from study GS-US-292-0106 in Genvoya dossier have also been previously evaluated which formed the basis of approval of Genvoya of use in adolescent patients above 12 years of age and subsequent approval of Descovy in this age group. Hence, the proposed use of Odefsey in adolescents >12 years of age is supported.

Proposed action

Pending advice from the ACPM, approval is supported for the following indication:

> *ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older and with body weight at least 35 kg) with plasma HIV-1 RNA ≤100,000 copies/mL at the start of therapy. The patients* ***must not have history of treatment failure*** *or known mutations associated with resistance to the individual components of ODEFSEY.*

Note restriction to patients with baseline viral RNA ≤100,000 copies/mL is based on Edurant/Eviplera dossiers.

The following clinical efficacy studies of Odefsey are currently underway and provision of results and clinical study reports to TGA as soon as available will be included as a condition of approval:

- Study GS-US-366-1160 is a randomised, double blind study to evaluate maintenance of virologic suppression in virologically suppressed, HIV-1 patients on switching from EFV/FTC/TDF (Atripla) to FTC/RPV/TAF (Odefsey).
- Study GS-US-366-1216 is a randomised, double blind study to evaluate maintenance of virologic suppression in virologically suppressed, HIV-1 patients on switching from FTC/RPV/TDF (Eviplera) to FTC/RPV/TAF (Odefsey).

The Delegate has no reason to say, at this time, that the application for Odefsey should not be approved for registration.

This report is submitted to the ACPM for advice.

Request for ACPM advice

The ACPM is requested to provide advice on the following specific issues:

1. Does the ACPM support approval based on bioequivalence data only, with extrapolation of clinical efficacy/safety from related but not equivalent products?
2. Could the ACPM please provide advice on appropriate the therapeutic indication to capture the relevant patient population?

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Summary

Gilead agrees with the Delegates recommendation that the application for Odefsey should be approved for registration with the indication statement as follows:

> *ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤100,000 copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of ODEFSEY.*

Discussion of Delegate's comments

ACPM advice being sought by the TGA Delegate

- *1. Does the ACPM support approval based on bioequivalence data only, with extrapolation of clinical efficacy/safety from related but not equivalent products?*

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.[9] Acceptability of the BE strategy as outlined above has been validated by the recent approval of Odefsey by the US FDA on 1 March 2016, and EMA on 21 June 2016.

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 Edurant.

In its entirety, the clinical evidence provided 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:

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

- Bioequivalence of TAF and FTC exposures between the Odefsey FDC 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 derived from clinical studies previously evaluated by TGA in registration applications for Genvoya and Eviplera as follows:

- ART naive adult patients
  - Two pivotal Phase III studies conducted with Genvoya (Studies GS-US-292-0104 and GS-US- 292-0111)
  - Two pivotal Phase III studies conducted with RPV in combination with a N[t]RTI backbone, which included FTC and TDF (Studies TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215]).
- Virologically suppressed adult patients
  - One Phase III Genvoya study (GS-US-292-0109)
  - Two Phase IIb and Phase III Eviplera studies (GS-US-264-0111 and GS-US-264-0106)
- Adult patients with mild to moderate renal impairment
  - One Phase III Genvoya study (GS-US-292-0112)

[9] European Medicines Agency, Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 20 January 2010.

- § RPV is approved without dose adjustment for patients with mild to moderate renal impairment

– Adolescent patients

- § One Phase II/III Genvoya study (GS-US-292-0106)
- § One Phase II RPV study (TMC278 TiDP38-C213 [C213]) (provided to TGA during current evaluation).

Extrapolation to Odefsey is further supported by the bioequivalence of RPV exposures between Eviplera and Edurant (Study GS-US-264-0103).

While conducting clinical trials in every possible population, would simplify evaluation, it would also unnecessarily delay registration, when in accordance with the TGA adopted industry guideline on the investigation of bioequivalence,[10] such studies are not required for the purposes of registration.

In addition to clinical evidence provided, 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 IIIb switch studies investigating Odefsey:

– Study GS-US-366-1160 is a randomised, 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 Atripla (FTC/TDF/EFV 200/300/600) FDC to Odefsey FDC.

– Study GS-US-366-1216 is a randomised, 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 Eviplera FDC to Odefsey FDC.

Gilead has noted the Delegate's comments that provision of these studies will be included as a condition of approval and commit to provide the data to TGA for review in a post approval application when available.

· *2. Could the ACPM please provide advice on the therapeutic indication to capture the relevant patient population?*

Gilead agrees with the Delegate's recommendation that the application for Odefsey should be approved for registration with the indication statement as follows:

> *Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤100,000 copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.*

As outlined in response to question 1, 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, therefore 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.

[10] European Medicines Agency, Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 20 January 2010.

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, Descovy, TAF, RPV, Eviplera, Emtriva, and Truvada. The data provided in support of this application includes treatment naïve adults and adolescents, virologically suppressed adults who switched from protease inhibitor based regimens, NNRTI based regimens, or integrase strand transfer inhibitor based regimens, and virologically suppressed adults with mild-to-moderate renal impairment. As such, Gilead believes the totality of data supports the therapeutic indication in capturing the relevant patient population.

It is noted by the Delegate that Edurant and Eviplera are not approved for use in children <18 years of age in Australia. Genvoya is similar to the TGA approved Stribild, and Descovy is similar to the TGA approved Truvada, which are both likely to be replaced in clinical practice following the availability of Genvoya and Descovy. Neither Stribild nor Truvada are approved for the treatment of HIV-1 infection in children <18 years of age in Australia.

Genvoya was approved by TGA on 12 January 2016, and Descovy on 28 June 2016 for use in adults and adolescents aged 12 years of age and older with body weight at least 35 kg. These indications were supported by results from the Genvoya study GS-US-292-0106 (Study 0106).

In addition to Study 0106, Study C213 supports the proposed indication of Odefsey FDC tablets in adolescents. Study C213 is a Phase II, 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 Odefsey as well as Eviplera in adolescent patients. The 48 week efficacy and safety results demonstrate that RPV 25 mg once daily, in combination with 2 NRTIs, is efficacious, safe and well tolerated in adolescents. A summary of the results from Study C213 are included in the proposed PI.

Indication

Gilead agrees with the Delegate's recommendation that the application for ODEFSEY should be approved for registration with the indication statement as follows:

> *Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤100,000 copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.*

Advisory Committee considerations

The ACPM resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of bioequivalence, efficacy, safety and quality, agreed with the delegate and considered Odefsey tablet containing FTC 200 mg/RPV 25 mg/TAF 25 mg to have an overall positive benefit-risk profile for the amended indication:

> *Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤100,000 copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.*

In making this recommendation, the ACPM:

- Noted that the comparable efficacy of Truvada and Descovy and Stribild and Genvoya and the bioequivalence of each of TAF, FTC and RPV in the pharmacokinetic studies

provided sufficient evidence to allow extrapolation of clinical efficacy and safety for Odefsey.

- Was of the view that dose combination delivers sufficient TAF to achieve reasonable efficacy for the proposed indication with no major safety issues.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration

Proposed PI/ CMI amendments

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does the ACPM support approval based on bioequivalence data only, with extrapolation of clinical efficacy/safety from related but not equivalent products?

The ACPM supported approval of new combination of active ingredients based on the comparable efficacy of Truvada and Descovy and Stribild and Genvoya and the bioequivalence of each of TAF, FTC and RPV in the pharmacokinetic studies provided.

2. Could the ACPM please provide advice on the appropriate therapeutic indication to capture the relevant patient population?

The ACPM advised on the following indication to appropriately capture the relevant patient population:

> *Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in treatment-naïve adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤100,000 copies/mL at the start of therapy. ODEFSEY is also indicated in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) adult patients and adolescents ≥ 12 years with body weight ≥ 35 Kg on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen. Patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.*

3. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Prescribers of this formulation should be aware that FTC and tenofovir alafenamide have activity against HBV. This could be better addressed in the PI.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Odefsey (200 mg emtricitabine/25 mg rilpivirine/25 mg tenofovir alafenamide fumarate) FDC tablets, indicated for:

> *Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA ≤ 100,000 copies/mL at the start of therapy. The patients must*

not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.

Specific conditions of registration applying to these goods

- The Odefsey fixed dose combination of (200 mg emtricitabine/25 mg rilpivirine/25 mg tenofovir alafenamide fumarate) RMP: EU-RMP Version 0.1 (dated 14 July 2015, DLP 28 April 2015) and ASA Version 0.1 (dated September 2015), and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Odefsey at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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