28 April 2016
EMA/335723/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Odefsey

International non-proprietary name: emtricitabine / rilpivirine / tenofovir alafenamide

Procedure No. EMEA/H/C/004156/0000

Note

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

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List of abbreviations

3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
aGFR	actual glomerular filtration rate
AN(C)OVA	analysis of (co) variance
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
BMD	bone mineral density
BMI	body mass index
COBI, C	cobicistat (Tybost®)
C-telopeptide	type I collagen C-telopeptide
ddI	didanosine
dNTP	2' deoxynucleoside triphosphate
DRV, D	darunavir
DTG	dolutegravir
DXA	dual-energy x-ray absorptiometry
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
ESRD	end-stage renal disease
EVG, E	elvitegravir (Vitekta®)
FAS	Full Analysis Set
FTC, F	emtricitabine (Emtriva®)
FTC-DP	emtricitabine diphosphate
HDL	high-density lipoprotein
INSTI	integrase strand-transfer inhibitor
LDL	low-density lipoprotein

LOCF	last observation carried forward
LSM	least-squares mean
M = F	missing = failure
mtDNA	mitochondrial DNA
N or n	number of subjects in a population (N) or subset (n)
NCEP	National Cholesterol Education Program
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OATP	organic anion transporting polypeptide
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PI	protease inhibitor
PRT	proximal renal tubulopathy
PSP	Pediatric Study Plan
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
RBP	retinol binding protein
rNTP	ribonucleoside triphosphate
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SI	selectivity index (ratio of CC_{50} to IC_{50})
STB	elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (coformulated; Stribild®)
TAF	tenofovir alafenamide
TAF fumarate	tenofovir alafenamide fumarate
TAM	thymidine analog mutation
TDF	tenofovir disoproxil fumarate (Viread®)

TFV	tenofovir
TFV-DP	tenofovir diphosphate
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
UACR	urine albumin to creatinine ratio
UGT	uridine diphosphate glucuronosyltransferase
UPCR	urine protein to creatinine ratio

List of abbreviations related to quality

AS	Active substance
AR	Assessment Report
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CPP	Critical process parameter
CQA	Critical Quality Attribute
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EP	European Pharmacopoeia
EU	European Union
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
LT	Less than

MA	Marketing Authorisation
MS	Mass Spectrometry
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range
PAR	Proven Acceptable Range
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
QbD	Quality by design
QWP	Quality Working Party
RH	Relative Humidity
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd submitted on 29 July 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Odefsey, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 January 2015.

The applicant applied for the following indication: treatment of adults and adolescents aged 12 years and older weighing 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 (see sections 4.2, 4.4 and 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tenofovir alafenamide was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0107/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0107/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

New active Substance status

The applicant requested the active substance tenofovir alafenamide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18/10/2012 and 25/04/2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 29 July 2015.
- The procedure started on 20 August 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 October 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 6 November 2015.
- The PRAC Rapporteur's RMP Assessment Report was circulated to all CHMP and PRAC members on 20 November 2015.
- During the meeting on 17 December 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 December 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 January 2016.
- During a meeting of a SAG Working Party on 15 February 2016, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 March 2016.
- The PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 17 March 2016.
- During the CHMP meeting on 1 April 2016, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 05 April 2016.
- The Rapporteurs circulated the Updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 April 2016.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 April 2016.
- The Rapporteurs circulated the Updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 April 2016.
- During the meeting on 28 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Odefsey.

2. Scientific discussion

2.1. Introduction

The application concerns a fixed dose combination (FDC) tablet containing 200 mg emtricitabine (FTC), 25 mg rilpivirine (RPV) corresponding to 27.5 mg of RPV hydrochloride and 25 mg tenofovir alafenamide (TAF), corresponding to 28 mg TAF fumarate. This new FDC (F/R/TAF) results in systemic exposure to the same three active substances as provided by the marketed FDC Eviplera. The difference is replacement of TDF with TAF, giving lower tenofovir (TFV) plasma levels vs. TDF, but the resulting active substance (TFV diphosphate; TFV-DP) is the same.

TAF was a new active substance in the EU at the time of filing the application dossier for F/R/TAF. Both FTC (Emtriva) and RPV (Edurant) are well established licensed agents in the EU and both are already available in other FDC presentations that include TDF. The applicant provided a full application dossier. Fundamentally, the application is based on a pivotal clinical bioequivalence study (GS-US-366-1159) that compares F/R/TAF to each of the marketed RPV 25 mg tablet (Edurant) and to Genvoya (E/C/F/TAF; recently reviewed and given a positive opinion by the CHMP). This bioequivalence (BE) study is intended to bridge the safety and efficacy documented for each of Edurant and Genvoya to F/R/TAF.

Some relevant studies that are specific to the intended FDC are:

- The pivotal BE study (GS-US-366-1159)
- The FDC food effect study (GS-US-366-1651)
- A DDI study with the FDC and ledipasvir/sofosbuvir (GS-US-366-1689)

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (as 27.5 mg of the hydrochloride - RPV) and 25 mg of tenofovir alafenamide (as 28.0 mg of the fumarate – TAF) as active substances.

Other ingredients are:

Tablet core: croscarmellose sodium, lactose (as monohydrate), magnesium stearate, microcrystalline cellulose, polysorbate 20 and povidone.

Film-coating: macrogol, polyvinyl alcohol, talc, titanium dioxide (E171) and iron oxide black (E172).

The product is packaged in high density polyethylene (HDPE) bottle with a polypropylene (PP) continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner. Each bottle contains silica gel desiccant and a polyester coil as described in section 6.5 of the SmPC.

2.2.2. Active substance

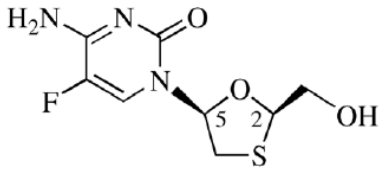
Emtricitabine (FTC)

The information on chemistry, manufacturing and control of emtricitabine active substance has been previously assessed through centralised procedure and approved in the EU as part of the marketing authorisation applications for Emtriva, Truvada, Atripla, Eviplera and Stribild.

The Module 3.2.S sections of the dossier for emtricitabine provided by the applicant are identical to the 3.2.S sections submitted and approved with the aforementioned marketing authorisations.

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one and has the following structure:



The structure of the active substance was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry and single crystal x-ray determination.

Emtricitabine appears as a white to off-white non-hygroscopic crystalline powder, freely soluble in methanol and water. Its pKa is 2.65 and the partition coefficient Log P is -0.43. It has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. Two enantiomeric pairs of diastereomers can exist: *cis*-(-)-FTC and *cis*-(+)-FTC, *trans*-(-)-FTC and *trans*-(+)-FTC. The synthetic route has been chosen to be stereoselective for the formation of the desired *cis*-(-) enantiomer, emtricitabine. Three polymorphs of emtricitabine have been observed. However, the most stable thermodynamically form at room temperature, is consistently produced.

Manufacture, characterisation and process controls

Emtricitabine is manufactured by two possible synthetic routes sharing a common first step and followed by two options comprising either one or two extra steps. The synthesis was described in sufficient detail.

The synthetic process results in the stereoselective formation of an intermediate and thus the formation of the desired emtricitabine enantiomer. Five manufacturing sites are involved. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The process has been shown to consistently produce emtricitabine that meets the required quality standards.

The active substance packaging is in compliance with EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

Emtricitabine specification includes tests and limits for appearance (visual), identification (IR, HPLC), clarity of solution (visual), water content (Ph. Eur.), enantiomeric purity (chiral HPLC), assay (HPLC), impurities (HPLC), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.), residual solvents (GC), and particle size (Laser Light Scattering). Analytical methods have been validated in accordance with ICH guidelines. The testing and the proposed limits applied, conform to current ICH guidelines and are acceptable from a toxicological and clinical perspective.

Extended testing during development has demonstrated that only a single polymorphic form results from the synthetic process of emtricitabine. Therefore as per ICH Q6A, testing for polymorphic form at release is not necessary. Development data demonstrate the absence of indicator organisms and therefore, as per ICH Q6, microbial testing of the active substance is not required. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data on 22 commercial scale batches of the active substance from all proposed manufacturers were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Thirteen commercial scale and additional pilot scale batches of emtricitabine manufactured using both synthetic routes and packaged in the proposed container were put on stability testing in accordance with the ICH Q1A (R2) Guideline under long-term conditions (25 ºC/60% RH) for up to 36 months. Of the above batches, eight commercial scale and five pilot batches were stored under accelerated conditions (40 ºC/75% RH) for up to 6 months. In addition another three batches were stored under intermediate conditions (30 ºC/65% RH) for up to 12 months. Samples were tested for appearance, impurities, assay, water content and for enantiomeric purity by validated stability indicating methods. Stability data for emtricitabine manufactured by both synthetic routes were comparable. The majority of tested parameters remained within the specification limits throughout the study period for all three stability conditions. In one isolated batch, one degradation product exceeded the specification limit at the last time point (36 months). The same degradation product is observed in emtricitabine stored under accelerated conditions. Four batches stored under accelerated conditions exceeded the specification limit at 6 months. These data indicate that emtricitabine should not be exposed to elevated temperatures for extended periods of time.

A photostability study was conducted on one batch of emtricitabine. The results showed no significant changes in appearance, purity, and impurity content and indicate that emtricitabine is not sensitive to light.

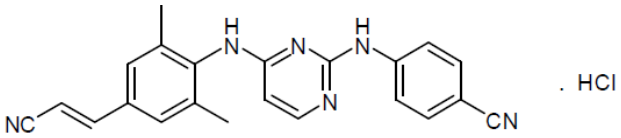
Based on the long-term stability data, the proposed re-test period and storage conditions when the active substance is packed in the proposed packaging materials is considered acceptable.

Rilpivirine (RPV)

Rilpivirine is currently approved in Eviplera tablets and in other mono-component and combination products. The manufacturing methods, specifications and analytical procedures applied to this active substance are in accordance with those currently authorised. An ASMF procedure was used.

General information

The chemical name of rilpivirine hydrochloride is 4-[[4-[[4-[(*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride corresponding to the molecular formula $C_{22}H_{18}N_6 \cdot HCl$ and it has the following structure:



The chemical structure of rilpivirine was adequately demonstrated by elemental analysis, UV absorption spectroscopy, FT-IR, ^{1}H and ^{13}C NMR and MS.

Rilpivirine hydrochloride is a non-hygroscopic white to almost white powder, practically insoluble in water at neutral, basic and acidic pH and in apolar organic solvents. Its pKa is 5.6 and the partition coefficient log P is 4.86. The active substance does not contain chiral centres.

Three polymorphic forms (Form A, Form B and Form C) of rilpivirine were identified and a number of solvates can also be formed with a variety of organic solvents. A hydrated form (form D) was also identified. Form A was determined to be the thermodynamically most stable polymorphic form and is routinely produced by the synthetic process described in the dossier. The solid state properties of the polymorphic forms were fully characterised by IR, XRD, DSC, TGA and dynamic vapour sorption.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance was provided in the restricted part of the ASMF, already approved in the frame of the authorised medicine Eviplera, and it was considered satisfactory. Rilpivirine is obtained from two manufacturing sites.

The active substance is synthesized in five steps using well defined starting materials with acceptable specifications.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents were presented. The *E*-olefin is formed selectively during the process and the minor *Z*-isomer is limited in the active substance specification.

The active substance packaging is in compliance with the current European guideline on plastic immediate packaging materials CPMP/QWP/4359/03.

Specification

The active substance specification includes tests for appearance (visual examination), identification (IR, identification of chloride (Ph. Eur.), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), particle size (laser diffraction), sulphated ash (Ph. Eur.) and heavy metals (USP).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological studies and appropriate specifications have been set. One genotoxic impurity was found in the drug substance and is controlled by suitable tests and limits in an intermediate and the drug substance specification in line with ICH M7.

Skip testing for residual solvents, water content, sulphated ash and heavy metals was justified.

Omission of testing for polymorphism and palladium was justified. Regarding polymorphism, it was demonstrated that Form A was consistently produced in the process and the IR identification method was able to discriminate between Forms A, B, C and D. No changes in polymorphic form were observed in the primary stability batches stored at different ICH conditions. Palladium testing was omitted based on the batch data submitted and the fact that Pd was controlled in-process.

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

Batch analysis data on 10 production scale batches of rilpivirine hydrochloride were provided. The results were within the specifications and consistent from batch to batch. Batch analysis data on development batches used in toxicological and clinical studies and manufactured by slightly different synthesis methods and tested against the specifications applied at the time of manufacture were also provided.

Stability

Stability data on three production scale batches of rilpivirine hydrochloride from one of the proposed manufacturers stored in the intended commercial package for up to 36 months under long term (25 °C / 60% RH) and intermediate conditions (30°C / 65% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) in line with the ICH guidelines was provided. Stability studies were also conducted for 36 months at 5°C and 30°C / 75% RH. Photostability testing following the ICH Q1B was performed on one batch. Results under stressed conditions (oxidative conditions, unbuffered aqueous suspensions and DMF or DMF + 0.1 N HCl or DMF + H_2O_2) were also provided on one batch.

Active substance specifications are the same at both manufacturing sites and batch results presented demonstrated equivalency of the sites with regard to the quality characteristics of the active substance. Because of this equivalency, stability data from only one of the manufacturing sites is provided and considered acceptable. Nevertheless, the three validation batches manufactured at the second manufacturing site were placed on stability and the study protocol was provided, along with a commitment to undertake the study up to the end of shelf life.

The following parameters were tested: appearance, assay, chromatographic purity, water content, particle size, microbiological purity and identification of polymorph. Some of the analytical methods used were the same as for release and were stability indicating. The additional analytical methods (microbiological purity, polymorphism and chromatographic purity) and changes in the analytical methods implemented during the

course of the stability studies were adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

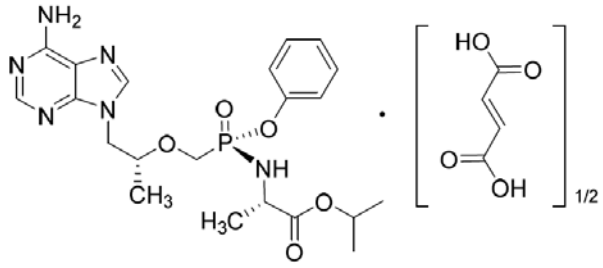
The active substance remained unchanged at all time points and under all conditions tested. No significant trends were observed for any test parameter under any conditions with the exception of the photostability study. A slight increase in particle size at 40° C/ 75% RH was also observed. All tested parameters were within the specifications. In solution (0.03% H_2O_2), the active substance was shown to be prone to oxidation and some degradation was observed in 0.1N aqueous NaOH suspensions as well as in DMF or DMF + 0.1 N HCl or DMF + H_2O_2.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period at the proposed storage conditions in the proposed container and protected from light.

Tenofovir alafenamide fumarate (TAF fumarate)

General information

The chemical name of tenofovir alafenamide fumarate is propan-2-yl *N*-[(*S*)-({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2*E*)-but-2-enedioate (2:1) and has the following structure:



The chemical structure of tenofovir alafenamide fumarate has been adequately demonstrated by infrared spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H, ^{13}C, and ^{31}P), mass spectrometry, elemental analysis, ultraviolet absorption spectroscopy, and X-ray crystallography.

The active substance is a white to off-white or tan, slightly hygroscopic powder. Tenofovir alafenamide fumarate is a BCS Class III compound, with pH-dependent aqueous solubility decreasing with increasing basicity. It is soluble at low pH (pH 2.0), sparingly soluble at pH 3.8, and slightly soluble at pH values up to 8.0. Tenofovir alafenamide fumarate is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol and slightly soluble in acetone.

Tenofovir alafenamide exhibits stereoisomerism due to the presence of three chiral centres. The chiral centre at the propyloxy- side chain is in the *R*-configuration. The absolute stereoconfiguration of the carbonylethylamino- substituent has the *S*-configuration at the alpha-carbon. The remaining stereocentre is located at the phosphorus atom and is in the *S*- configuration. Enantiomeric purity is monitored routinely by chiral HPLC.

Polymorphism has been observed for tenofovir alafenamide fumarate. A single polymorphic form is consistently generated through the manufacturing process and this form has been adequately characterized.

The applicant has provided justification for TAF to be considered as a new active substance (NAS) on the basis of its unique chemical structure. However, both TAF and tenofovir disoproxil fumarate (TDF), which is a known active substance, are prodrugs being metabolised to the same major active metabolite tenofovir (TFV) *in vivo*. Therefore, both active substances share the same therapeutic moiety and as such, TAF is not considered a NAS on quality grounds.

Manufacture, characterisation and process controls

Tenofovir alafenamide fumarate is obtained from two manufacturers using the same synthetic route.

The active substance is synthesized in multiple steps. During the evaluation procedure, the active substance starting materials were re-defined to ensure enough of the process is documented in the dossier in line with ICH Q11. Commercially available well-defined starting materials with acceptable specifications are used.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Potential and actual impurities were well discussed with regards to their origin and characterised.

Critical process parameters were identified using a risk assessment approach.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance packaging is in compliance with the EC directive 2002/72/EC and EC 10/2011 as amended.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Specification

The active substance specification includes tests for appearance (visual examination), identity (IR, HPLC), identity of fumaric acid (HPLC), clarity of solution (visual examination), water content (Ph. Eur.), assay (HPLC), impurities (HPLC, HPLC-MS, GC), residual solvents (GC), elemental impurities (ICP MS), and melting point (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

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

Batch analysis data (n=16 using the proposed commercial process; 13 of which were commercial scale and 3 pilot scale) of the active substance, manufactured at both proposed manufacturing sites are provided. Additional batch analysis data for development batches used in pre-clinical pharmacokinetics and toxicological studies are provided. The results are within the specifications and consistent from batch to batch.

The active substance specifications are based on the active substance critical quality attributes (CQA).

Stability

Stability data on 6 commercial scale batches of active substance from the both proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions at 5 ºC and for up to 24 months under accelerated conditions at 25 ºC / 60% RH according to the ICH guidelines were provided. Results under stress conditions for up to 6 months at 40 ºC / 75% RH on 5 batches were provided. Additionally, results for 4 days at 60 ºC / ambient RH; for 4 days at 50 ºC / ambient RH; and for 4 days at -20 ºC were also provided on one batch.

Samples were tested for appearance, impurities, assay, water content, and solid state characteristics (XRD and melting point). The analytical methods used were the same as for release and were stability indicating.

Degradation products increased under accelerated conditions but remained within the specification.

Photostability testing following the ICH guideline Q1B was performed on one batch, indicating that the active substance is not photosensitive.

The stability results indicate that the active substance manufactured by the both proposed suppliers is sufficiently stable. The stability results justify the proposed re-test period at the recommended long-term storage condition the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Emtricitabine/rilpivirine/tenofovir alafenamide fumarate (FTC/RPV/TAF) fixed dose combination tablets are an immediate-release dosage form containing 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV) and 25 mg of tenofovir alafenamide (TAF). RPV is incorporated into the finished product as the RPV hydrochloride (RPV HCl) salt and TAF as the hemifumarate form (TAF fumarate). FTC/RPV/TAF tablets are grey, capsule-shaped, film coated tablets, of dimensions 15 mm x 7mm, debossed with “GSI” on one side of the tablet and “255” on the other side of the tablet.

The overall goal of FTC/RPV/TAF tablet development was to create a tablet containing the same established doses and physical, chemical, and biopharmaceutical performance of FTC and RPV as currently combined in Eviplera and to replace tenofovir disoproxil fumarate with an efficacious dose of TAF, a second-generation prodrug of tenofovir, ensuring TAF chemical stability. Formulation and process selection were based on the biopharmaceutical properties of FTC, RPV HCl, and TAF fumarate, the chemical stability of TAF fumarate, and the physical and chemical compatibility of FTC, RPV HCl and TAF fumarate. This formulation approach was based on prior knowledge gained during development of Eviplera tablet. Moreover, this approach enabled the use of a RPV final powder blend composition equivalent to that of the RPV layer in Eviplera and an FTC/TAF final powder blend composition equivalent to that in Descovy.

FTC is a BCS Class I compound with high aqueous solubility and high permeability. RPV HCl is a BCS Class II compound with low aqueous solubility and high permeability. The RPV HCl particle size was controlled to the

same specification as used for the authorised Eviplera formulation. TAF fumarate is a BCS Class III compound with high aqueous solubility and low permeability and it is susceptible to hydrolysis.

The physical and chemical compatibility of FTC and TAF fumarate were previously established during development of Genvoya and Descovy. Formulations containing FTC and TAF fumarate in combination have exhibited excellent physical, chemical, and biopharmaceutical properties, including suitable FTC and TAF chemical stability, content uniformity, dissolution, and pharmacokinetic performance.

The choice of manufacturing process was based on the properties of the active substances.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or other relevant standards except for the film coating material, which is commercially available and tested according to an in-house standard. All the components of the coating material comply with the standards in EU Regulation 231/2012 or compendial monographs. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The physical and chemical compatibility between TAF fumarate, FTC and excipients was evaluated by studying the chemical stability of the prototype FTC/TAF formulation matrices under accelerated conditions (40 ºC/75% RH) and no incompatibilities were found after 3 months of storage.

A detailed account of the evolution of the formulation and manufacturing process throughout clinical development was presented. The clinical bioequivalence batches were representative of the commercial product and were manufactured at the commercial manufacturing site. Comparative dissolution data was provided. Results of bioequivalence studies demonstrated that the FTC/RPV/TAF tablet is bioequivalent to Genvoya as the FTC and TAF comparator, and to Edurant, the single agent RPV comparator.

Two separate dissolution methods were used to control the final finished product given the chemical instability of TAF at low pH and the incomplete dissolution of RPV at high pH. The development of the dissolution methods has been discussed and the methods are considered to be acceptable. The discriminatory power of the dissolution methods was demonstrated.

Pharmaceutical development of the finished product contains QbD elements. The manufacturing development has been evaluated through the use of risk assessment and design of experiments (DoE) to identify the critical product quality attributes and critical process parameters. The critical quality attributes (CQAs) were identified. A risk analysis was performed in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The results of this initial risk assessment supported the evaluation of certain unit operations and process parameters in development studies to define the control strategy for the commercial manufacturing process. The critical process parameters have been adequately identified.

The manufacturing process development history and key outcomes of each development step that influenced the designated commercial manufacturing process were presented including details of the establishment of proven acceptable ranges (PARs), normal operating ranges (NORs), and operating parameter targets for all key units operations.

Although multi-variate experiments (DoE) were carried out for a number of the process development studies, no design spaces are claimed. It is intended to operate within the NORs defined for all process parameters and unit operations. PARs have been accepted for several parameters but only one parameter at a time may be varied from its set-point.

The primary packaging is a high density polyethylene (HDPE) bottle with a propylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner. Each bottle contains silica gel desiccant and polyester coil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of multiple steps: blending of the active substance with intragranular/extragranular excipients, fluid-bed granulation/dry granulation and milling, compression, tablet film-coating, and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies carried out at representative commercial-scale. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Full validation will be carried out on commercial scale for at least 3 consecutive batches prior to release the market and a suitable scheme has been provided. The in-process controls are adequate for this pharmaceutical form.

Adequate justification for holding times of bulk intermediates (powder blends, tablet cores, and film-coated tablets prior to packaging), has been provided and is discussed in the stability section.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance, identification (UPLC, UV), water content (KF), strength (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.) and microbial examination (Ph. Eur.).

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

Batch analysis results from both proposed production sites are provided for seven full or representative commercial-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released to the market based on the above release specifications, through final product release testing.

Stability of the product

Stability data on six pilot scale batches of finished product stored for up to 12 months under long term (25 ºC/60 % RH) and intermediate (30 ºC/75 % RH) conditions, and for up to 6 months under accelerated conditions (40 ºC/75 % RH), in line with ICH guidelines, was provided. The batches tested were manufactured at both commercial manufacturing sites, were representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, one batch from one manufacturing site was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Stressed studies were carried out to evaluate conditions which may be experienced during shipping and handling. Studies were conducted on one batch from one manufacturing site at -20 ºC for 14 days and at 50 ºC / ambient humidity or 60 ºC / ambient humidity for 4 days. Additionally, studies

were carried out on FTC/RPV/TAF tablets stored at 25 °C / 60% RH and 30 °C / 75% RH without primary packaging for 4 weeks.

Samples were tested for appearance, strength, degradation products, water content, dissolution and microbiological examination. The analytical procedures used are stability indicating.

Stability data for all batches of FTC/RPV/TAF finished product tested met the acceptance criteria for all stability test attributes at all studied time points. No trends were observed for any of the measured parameters except for TAF strength and TAF-related degradation products. A slight decrease in TAF strength and a slight increase of TAF-degradation products was observed at accelerated conditions. No RPV- and FTC-related degradation products were observed. Also, the water content of the tablets showed a slight decrease upon storage as an effect of desiccant present in primary packaging at long, intermediate and accelerated conditions.

Regarding photostability studies, no significant difference between the dark control and the sample exposed to light was observed for any of the measured parameters, except for a slight increase in water content. This was attributed to atmospheric moisture as the study was carried out on un-packaged tablets. The data confirm that FTC/RPV/TAF tablets are not photosensitive.

The quality attributes monitored during stability remained within the acceptance limits when tablets were stored at -20 °C, 50 °C and 60 °C for short durations representative of excursions, and when the tablets were stored without primary packaging at 25 °C / 60% RH and 30 °C / 75% RH. No changes to any of the measured parameters were observed other than a slight decrease in TAF strength and a slight increase in TAF degradation products at 60 ºC / ambient humidity and 30 °C / 75% RH without protection from primary packaging conditions. No RPV- and FTC-related degradation products were observed. A slight increase in water content was observed at 25 °C/60% RH and 30 °C/75% RH without protection from primary packaging. However, all measured parameters remained within their specification limits.

Studies on bulk storage of intermediate products were also carried out. The bulk holding times are supported by stability data. Satisfactory information was provided on containers and bulk transport conditions and supported by stability data.

The comparative stability analysis demonstrates that the stability of the three active substances in FTC/RPV/TAF tablets is comparable to the stability in already authorized medicinal products containing these active substances.

Based on available stability data for FTC/RPV/TAF tablets and comparative stability data, the proposed shelf-life of 24 months without specific storage conditions when stored in the commercial container closure system, as stated in the SmPC (section 6.3), is acceptable.

Appropriate post-approval stability protocol and stability commitments have been provided.

Adventitious agents

It is confirmed that the lactose monohydrate is sourced from bovine milk from healthy animals in the same conditions as milk collected for human consumption. No other ruminant or animal materials are used during the process. Lactose monohydrate is therefore excluded from the scope of the note for guidance on minimising the risk of transmitting TSE.

The magnesium stearate is of vegetable origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The medicinal product is a fixed-dose combination containing three active substances already approved in marketed products. The applicant has successfully developed a tablet which separates incompatible components whilst ensuring adequate bioavailability of the active ingredients.

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The development strategy was to use the knowledge obtained for other products containing the same active substances. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD elements in the development of the finished product and the manufacturing process. PARs are justified for some manufacturing steps although no design space was claimed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacology programmes have been completed for each of the components of FTC, RPV and TAF, comprising of primary pharmacology, secondary pharmacology and safety pharmacology studies.

2.3.2. Pharmacology

Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor (NRTI), and intracellularly it is phosphorylated to the active metabolite, emtricitabine triphosphate which has activity against HIV and hepatitis B virus.

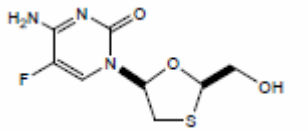
Rilpivirine (RPV) is a non-nucleotide reverse transcriptase inhibitor (NNRTI) that does not require modification for anti-viral activity. RPV binds to HIV-1 reverse transcriptase (RT), and shows at least nanomolar EC_{50} values against wild-type HIV-1 isolates.

Tenofovir alafenamide (TAF) is a prodrug of tenofovir (TFV), and after absorption TAF is converted to TFV intracellularly, which is phosphorylated to the active metabolite, tenofovir diphosphate (TFV-DP), that competes with natural 2'-deoxyadenosine triphosphate (dATP) for incorporation by the HIV-1 or HBV reverse transcriptase (RT) and, once incorporated, results in chain-termination. TAF differs from tenofovir disoproxil fumarate (TDF) as it is more stable in human plasma than TDF despite rapidly undergoing intracellular conversion to TFV. Treatment with TAF results in higher levels of TFV-DP in PBMCs and 90% lower circulating levels of TFV relative to TDF.

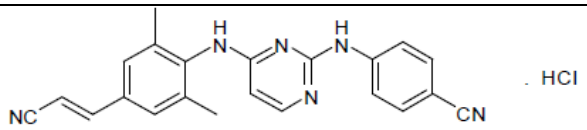
In the main, the proposed FDC is based on the complimentary pharmacological mechanisms of action of FTC, RPV and TAF along with clinical evidence.

Physical chemistry

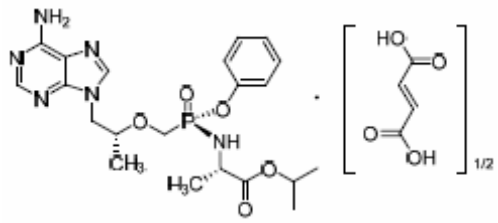
Emtricitabine (FTC, F)

Structure of the active substance Site of labelling (see structure).	 $C_8H_{10}FN_3O_3S$
Molecular weight.	247.24
Solubility in water.	112 mg/mL
pka.	2.65
Distribution coefficient.	-0.43
Solubility in other solvents.	4 mg/mL in acetonitrile, 113 mg/mL in methanol 170 mg/mL in 0.1 N HCl 115 mg/mL in 0.1 N NaOH 0.3 mg/mL in isopropyl acetate
Possible chirality and its consequences.	The cis-(-)-enantiomer has a specific rotation of –137.9º when a 1% (w/v) solution in methanol is measured at 25 ºC.

Rilpivirine (RPV, R)

Structure of the active substance Site of labelling (see structure).	 $C_{22}H_{18}N_6$. HCl
Molecular weight.	402.88
Solubility in water.	<0.01 mg/mL
pka.	5.6
Partition coefficient.	4.86
Solubility in other solvents.	0.19 mg/mL in acetonitrile, 5.8 mg/mL in methanol 0.67 mg/mL in ethanol 0.11 mg/mL in isopropanol 7.0 mg/mL in propylene glycol 14 mg/mL in sulfinylbismethane
Possible chirality and its consequences.	None

Tenofovir alafenamide (TAF) fumarate

Structure of the active substance Site of labelling (see structure).	 $C_{23}H_{31}O_7N_6P$ ($C_{21}H_{29}O_5N_6P$ as free base)
Molecular weight.	534.6 (476.5 free base)
Solubility in water.	4.70 mg/mL (pH 6.8) 4.86 mg/mL (pH 8.0 85.4 mg/mL (pH 2.0 in HCl)
pka.	3.96
Partition coefficient.	1.6
Solubility in other solvents.	2.30 mg/mL in acetonitrile, 189 mg/mL in methanol 69.6 mg/mL in ethanol 27.7 in isopropanol 9.16 in acetone 0.14 mg/mL in toluene
Possible chirality and its consequences.	Three chiral centres. Stereo isomer - GS-7339

Primary pharmacodynamic studies

FTC:

Emtricitabine (FTC) is a synthetic analogue of the naturally occurring pyrimidine nucleoside, 2′-deoxycytidine. Intracellularly, FTC is converted through 3 phosphorylation reactions to its active tri-phosphorylated anabolite FTC-TP.

Emtricitabine triphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxycytidine triphosphate; dCTP), and after incorporation into DNA, by DNA chain termination. Published literature describes that the EC_{50} of FTC against laboratory adapted strains of HIV-1 ranged from 0.001 to 0.62 µM depending on cell type and virus strain used in the assay. With clinical isolates of HIV-1, EC_{50} values ranged from 0.002 to 0.028 µM.

In vivo animal studies have been completed with FTC or FTC in combination to demonstrate its activity against immune deficiency in the macaque monkey. Macaques were infected with the simian immunodeficiency virus (SIV) and 50 days post-inoculation animals were treated subcutaneously with either TFV (20 mg/kg) and FTC (50 mg/kg) or were not given any drugs. The treated macaques achieved SIV levels that were below the limit of detection (ie, < 100 copies/mL of viral RNA), whereas only 1 of the non-treated macaques showed a decrease in SIV RNA. SIV levels remained low in all treated animals for up to 6 months.

In another study, monkeys were exposed to 14 weekly doses of SHIV (SIV/HIV chimeric virus). Rhesus macaques were injected subcutaneously with TFV/FTC daily, at 2 hours before and 24 hours after the first virus exposure or at 2 hours before first virus exposure only. Twenty of the 21 control animals became infected. However, all 6 of animals treated with TFV/FTC daily or before and 24 hours after the first challenge were fully protected after 14 challenges. In the single-dose group, 1 of 6 animals was infected, confirming that multiple dose therapy was highly effective at protecting these animals against rectal transmission of HIV.

RPV:

Rilpivirine (RPV, TMC278) is a non-nucleoside reverse transcriptase (RT) inhibitor that does not require modification for antiviral activity. Crystal structures of the binding site between RPV and the HIV-1 RT complex revealed that RPV, similarly to other members of the diarylpyrimidine family of inhibitors, binds to HIV-1 RT and adapts to the conformational changes in the NNRTI-binding pocket, which may explain the increased genetic barrier to the development of *in vitro* resistance. RPV shows sub-nanomolar EC_{50} values against wild-type HIV-1 group M isolates A, B, C, D, E, F, and G (0.07 to 1.01 nM), HIV-1IIIB (0.73 nM), and nanomolar EC_{50} values against HIV-1 group O isolates (2.88 to 8.45 nM). RPV retained antiviral activity against 63.0% (136 of 216) of the HIV-1/HXB2 site-directed mutant (SDMs) carrying single, double, triple and quadruple RT mutations. No *in vivo* pharmacodynamic studies have been conducted with RPV.

TAF:

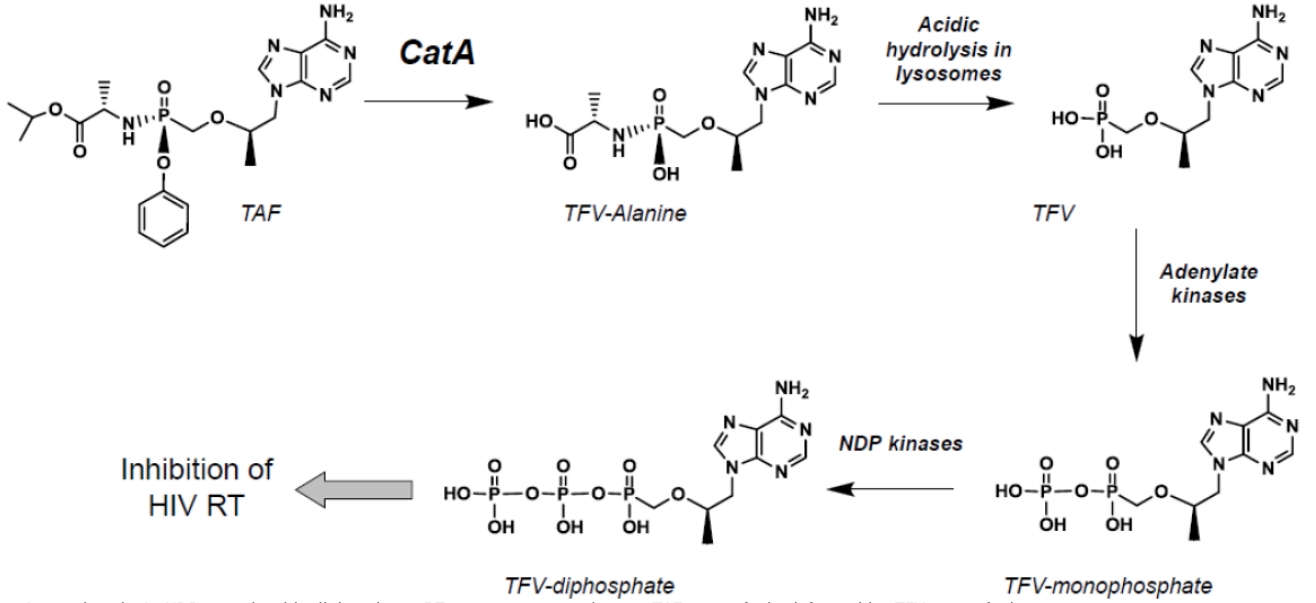
Tenofovir alafenamide is hydrolysed to tenofovir (TFV) by the lysosomal carboxypeptidase, Cathepsin A (CatA). To investigate the intracellular activity of TAF in lymphoid cells and tissues, $CD4^+$ T lymphocytes and monocyte-derived macrophage (MDMs) were isolated from PBMCs from viable donors and extent of CatA activity determined by measuring the rate of conversion of TAF to TFV-alanine (Figure 2.1.1). Level of active CatA was similar across all donors, as was the rate of conversion from TAF to TFV-alanine in $CD4^+$ cells. Cathepsin A activity was approximately 2-fold greater in MDMs compared with $CD4^+$ T cells. There was conversion of TAF to TFV-DP across both cell types in all donor extracts (Figure 2).

As shown in Figure 1, TAF is hydrolysed to TFV, and is then metabolised to the active metabolite, TFV-DP, which is an inhibitor of HIV-1, HIV-2 and HBV polymerases, and is an inhibitor of HIV-1 RT that competes with deoxyadenosine triphosphate (dATP) for incorporation into nascent DNA and terminates the elongation of the viral DNA chain during the process of retroviral reverse transcription, thereby effectively blocking the replication and spread of infectious HIV.

In vitro studies have shown that TAF has effective anti-HIV activity in lymphoid T-cells, primary human PBMCs, and macrophages with EC_{50} values ranging from 3 to 14 nM. The *in vitro* activity of TAF against HIV-1 is 100- to 600-fold greater than TFV and 4- to 6-fold greater than TDF (Robbins *et al.* 1998).

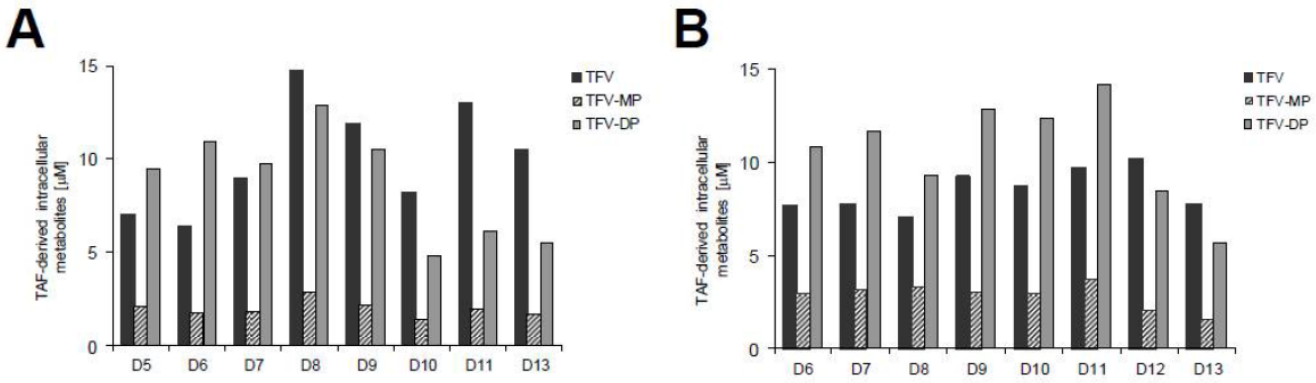
In MT-2 cells, TAF shows low cytotoxicity with a selectivity index (SI) of > 10,000). Based on data generated with the parent nucleotide TFV, TAF is expected to be active against a wide range of HIV-1 subtypes and also against HIV-2. In addition, TAF is a potent inhibitor of HBV replication, exhibiting *in vitro* activity comparable to that of TDF with an EC_{50} value of 18 nM.

Figure 1. Intracellular Activation of TAF in Lymphoid Cells and Tissues



Cat A = cathepsin A; NDP = nucleoside diphosphate; RT = reverse transcriptase; TAF = tenofovir alafenamide; TFV = tenofovir

Figure 2. Intracellular TAF Metabolites in CD4+ T cells and Monocyte-derived Macrophages from Different Donors



D= Donor; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-MP = tenofovir monophosphate; TFV-DP = tenofovir diphosphate

Following incubation for 4 hours with 1µM TAF, the formation and quantity of intracellular TAF metabolites in CD4+ T cells (A) and MDMs (B) were determined by HPLC combined with mass spectrometry.

The interaction potential of TAF with other CatA inhibitors such as HIV protease inhibitors (PIs) (Study No. PC-120-2001) has been evaluated. The HIV PIs DRV, ATV, lopinavir (LPV), and RTV, as well as the pharmaco-enhancing agent COBI, did not inhibit CatA-mediated hydrolysis of TAF up to a concentration of 50 µM, well above the clinical Cmax of each drug. In a similar manner, the potential for interaction with HCV PIs - TMC-435, BI-201355, MK-5172, GS-9256, and GS-9451 showed little-to-no inhibition of CatA, with IC_{50} values ranging from 25 to >50 µM. Two irreversible inhibitors of the HCV protease, telaprevir and boceprevir, were identified as potent inhibitors of CatA-mediated hydrolysis of TAF, with IC_{50} values of 0.3 and 0.2 µM, respectively. When adjusted for plasma binding, these IC_{50} values are 6 to 8-fold below the clinical maximum concentration (Cmax) levels observed in patients.

No *in vivo* work with TAF was conducted. However, this has been completed with the active component of TAF, TFV. Monkeys received a single dose of 30 mg/kg radiolabelled TFV subcutaneously, and the extent of TFV in plasma and levels of intracellular TFV and TFV metabolite concentrations were determined. The TFV concentration in plasma reached a maximum of approximately 50 µM and declined with a t1/2 of 5 to 7 hours. As was seen in the *in vitro* studies, TFV is efficiently taken up by PBMCs and is metabolised to TFV-DP, with the intracellular concentrations of the active metabolite TFV-DP reaching 0.9 µM.

FTV / RPV / TAF:

No additional studies for the FTC/RPV/TAF FDC have been conducted in animal models in view of the extensive clinical experience with the use of FTC, RPV, and TDF, FTC/TDF containing regimens, and the EVG (elvitegravir, Vitekta®)/COBI (Tybost®)/FTC/TAF FDC for the treatment of HIV-1 infection. FTC, RPV, and TAF/TFV are potent and selective inhibitors of HIV-1, which all show potent antiretroviral activity against diverse subtypes of HIV-1 *in vitro*. Emtricitabine and TAF/TFV are phosphorylated intracellularly through non-overlapping pathways, and in combination show no antagonism for the formation of their active metabolites.

Secondary pharmacodynamic studies

The ability FTC, RPV or TAF (TFV) to affect anti-viral activity of other anti-retrovirals has been explored in detail, reviewing in vitro cytotoxicity, mitochondrial toxicity, off target activity and potential metabolic toxicities.

FTC:

For FTC, no cytotoxicity was observed *in vitro* in human PBMC, MT-2, HepG2, CEM, MOLT-4, and Vero cells at concentrations up to 100 µM. FTC was also found to be nontoxic to human bone marrow progenitor cells *in vitro*.

The potential for mitochondrial toxicity with FTC was evaluated. FTC was incubated with HepG2 cells at concentrations ranging between 0.1 and 10 µM for 2 weeks, and MT-2 cells were incubated with FTC at concentrations up to 100 µM for up to 8 weeks (Study No. TPI 11963, non-GLP). FTC had no adverse effects on cell growth, mitochondrial DNA synthesis, or lactic acid production. Further studies confirmed this finding.

The inhibition of mitochondrial DNA synthesis was also assessed in an *in vitro* cell culture assay using Molt-4 cells (a T-lymphoblast cell line) (Study No. TGZZ/93/0016 and TGZZ/93/0023, non-GLP). FTC did not reduce the ratio of mitochondrial to cellular DNA when tested at concentrations of up to 100 µM after 7 days of continuous cell exposure.

FTC had no significant binding affinity at 19 different receptors (Study No. TPZZ/93/0002, non-GLP), has shown little or no direct effect on various isolated muscle preparations (cholinergic, adrenergic, histaminergic, and serotonergic), and had no major inhibitory effects on the contractile responses to acetylcholine, norepinephrine, serotonin, isoproterenol, arachidonic acid, histamine, bradykinin, and angiotensin II (Study No. TPZZ/92/0055, non-GLP).

RPV:

RPV has no effect on DNA synthesis by human polymerase α, β or γ when tested at concentrations up to 1000 µM (Study No. TMC278-1646_0005343, non-GLP). In addition, RPV caused no significant inhibition of binding to α- or β-adrenergic, dopaminergic, serotonergic, opioid, interleukin or chemokine receptors at concentrations up to 10 µM (Study No. TMC278-870219, non-GLP).

RPV (9.1 mg/kg) showed a 20% increase in gastric acidity in the pentagastrin-stimulated gastric acidity assay in rats compared to vehicle (Study No. TMC278-NC204[1]). The significance of the small increase in gastric acidity is unknown.

In vitro cytotoxicity of RPV was investigated in a range of cell lines, including HeLa, HepG2, Hep-2, MRC-5 and A549 (Study No. TMC278-IV2-AVMR, non-GLP). Inhibition of cell proliferation by 50% (expressed as CC_{50}) ranged from 16.9-35.6 µM on Day 3 and 5. Inhibition of cell viability was indicated by a reduction in growth by 50% (expressed as TC_{50}), and ranged from 31.9->40µM on Day 3 and 5.

TAF / TFV:

A range of studies have been completed to examine the potential secondary effects of TAF, utilising studies already completed for TFV.

The effect of the major metabolite of TAF, TFV, and the other prodrug of TFV, TDF, on the inhibition or stimulation of binding was investigated against a series of protein targets including neuroreceptors, ion channels, transporters, and nuclear receptors, Study No. V2000020). There was no significant inhibition or stimulation of ligand by either TFV or TDF, confirming that neither TFV nor TDF significantly interacts with any of the 111 protein targets tested.

The cytotoxicity profiles (CC_{50} values) of TAF, its stereoisomer GS-7339, TDF, and TFV were investigated in resting and dividing human PBMCs following 5 days of continuous drug incubation (Study No. PC-120-2009, non-GLP). The maximum concentrations of drugs used were 100, 100, 50, and 2000 µM, for TAF, GS-7339, TDF, and TFV, respectively. TAF doses used in this *in vitro* study were supra-therapeutic in concentration and duration. CC_{50} values for TAF ranged from 6.8 µM in dividing PBMCs to 25.1 µM in resting PBMCs. TAF showed low cytotoxicity in resting and in dividing PBMCs.

The cytotoxicity profiles (CC_{50} values) of TAF, TDF, TFV, and a panel of clinically relevant antiretroviral inhibitors were also evaluated in 2 T-lymphoblastoid cell lines (MT-2 and MT-4) following 5 days of exposure (Study No. PC-120-2007, non-GLP), TAF showed low cytotoxicity in T-lymphoblastoid cells providing ≥1997-fold increased selectivity relative to antiviral activity in T-lymphoblastoid cell lines. Similarly TAF demonstrated low cytotoxicity to hepatic cells (Study No. PC-120-2007, non-GLP).

Tenofovir alafenamide also showed little to no effect on erythroid and myeloid progenitor proliferation *in vitro* (Study No. PC-120-2016, non-GLP).

TFV exhibited low levels of cytotoxicity in resting and activated human PBMCs, and in an established T-lymphocyte cell line, with CC_{50} values >1 mM. Similar findings for TFV were observed in HepG2 cells, skeletal muscle cells of human origin, and in human renal proximal tubule epithelial cells (RPTECs). Similarly, TFV has shown no effect on haematopoietic progenitor cells *in vitro* (Study No. PC-120-2016, non-GLP). Overall, TFV has a low order of cytotoxicity *in vitro*.

The cytotoxicity of TAF and TFV was assessed in human HEK293T cells transiently expressing OAT1 and OAT3 (Study No. PC-120-2018, non-GLP). Cells were incubated with serial dilutions of TFV or TAF for 4 days. TAF did not interact with the renal organic anion transporters 1 or 3 (OAT1 or OAT3), and TAF exhibited no OAT-dependent cytotoxicity in human epithelial kidney cells transiently expressing these transporters. In addition, the selectivity index (considering CC_{50} in renal HEK293 cells expressing OAT1 or OAT3 relative to EC_{50} in primary $CD4^+$ T lymphocytes) for TAF (29,000 and 4270, respectively) was much higher than for TFV (14 and 82, respectively). As a result TAF is unlikely to accumulate in renal proximal tubules in an OAT-dependent manner, supporting the hypothesis that it has the potential for an improved renal safety profile. TFV has been investigated in a number of *in vitro* models for renal proximal tubular toxicity, where it was shown to

have negligible effects on cell growth and viability (Study No. P4331-00037). In addition, TFV had no effect on the integrity of the differentiated proximal tubule epithelium after 10 day incubation *in vitro* (Cihlar *et al*, 2001).

When primary osteoblasts and PBMCs were treated with TAF doses consistent with human therapeutic exposure, comparable TFV-DP levels were achieved (Study No. PC-120-2008). At these therapeutically relevant doses of TAF, there were no *in vitro* effects on cell viability with primary osteoblasts or PBMCs.

The impact of TAF on mitochondrial toxicity was assessed. Previous studies have demonstrated a minimal effect of TFV on the mitochondrial DNA synthesis *in vitro*. The potential for TAF to induce mitochondrial DNA depletion was evaluated in HepG2 cells (Study No. PC-120-2006, non-GLP). HepG2 cells treated with TAF (0.1, 0.3, or 1.0 µM) for 10 days exhibited no significant reduction in mitochondrial DNA compared with untreated cells.

No effect of TFV was seen on the synthesis of mitochondrial DNA or lactic acid production (a mitochondrial marker) in HepG2 human liver cells or in normal human skeletal muscle cells (SkMCs) (Study No. P1278-00042, non-GLP). The results confirm the low potential for TFV to interfere with mitochondrial functions.

Combinations

The combination of TFV and FTC was studied for cytotoxicity observed at the highest concentrations tested, up to 50 µM TFV and 5 µM FTC (Study No. PC-164-2002, non-GLP). Cytotoxicity studies were also conducted on the combination of TFV and FTC in HepG2 cells to evaluate their potential combined mitochondrial toxicity; no cytotoxicity was observed (Study No. TX-104-2001, non-GLP). Similarly, in human renal proximal tubule epithelial cells (RPTECs), TFV alone or in combination with FTC was not cytotoxic after 5 days incubation *in vitro* (Study No. PC-164-2002). Mitochondrial toxicity studies conducted in HepG2 cells with FTC and TFV alone or in combination indicated that the potential for interference with mitochondrial functions was low (Study No. TOX-104-2001).

Given the lack of effects in the *in vitro* studies with the individual agents or with other combinations, no additional secondary pharmacodynamic studies have been conducted for the FTC/RPV/TAF combination.

Safety pharmacology programme

FTC:

Cardiovascular System:

In vitro the effects of FTC on cardiac preparations was evaluated using isolated cardiac muscle from rat, guinea pigs and cats (Study No. TPZZ/92/0056, non-GLP). Results from these *in vitro* studies suggested that FTC was free of negative cardiac effects at 1 µM.

No effects on the cardiovascular system were reported in anesthetised dogs administered a cumulative dose of 38.5 mg/kg of FTC intravenously over a 1-hour period (Study No. TPZZ/92/0076, non-GLP). Rats given oral doses of up to 250 mg/kg FTC showed no effect on heart rate or blood pressure (Study No. TPZZ/92/0057, non-GLP). In addition, there were no abnormalities reported on the ECG data obtained from the repeated-dose toxicity studies in monkeys, where AUC exposures were up to 26-fold higher than in humans at 200 mg.

Central Nervous System:

A range of central nervous system effects were examined in a single study conducted with male ICR rats (Study No. 477, non-GLP). Mice (10/dose) were given FTC orally at 0 (distilled water), 10, 30, or 100 mg/kg as a single dose. FTC did not affect reflex, spontaneous locomotion, motor coordination, anticonvulsant activity, pro-convulsant activity or analgesic activity at any dose tested.

A further two studies in rats examined the effects of FTC on reflexes, analgesic activity and conditioned avoidance (Study Nos. TPZZ/93/0001 and TPZZ/93/0119, non-GLP). FTC had no effect on these parameters.

Respiratory System:

Effects of FTC on the respiratory system have been examined in mice, rats and dogs. In mice (Study No. TPZZ/93/0001, GLP) and rats (Study No. TPZZ/93/0001, GLP), animals were exposed to up to 1000 mg/kg of oral FTC with no effect on respiratory rate at any dose. In dogs (Study No. TPZZ/92/0076, GLP), male beagle dogs were intravenously administered FTC at 1, 2.5, 5, 10, and 20 mg/kg (cumulative dose = 38.5 mg/kg) over an hour. No changes were observed on respiratory function at any dose.

Gastrointestinal System:

Male ICR mice (10/dose) were given FTC orally at 0 (distilled water), 10, 30, or 100 mg/kg, then given a charcoal suspension orally at 1 hour post-dose. Emtricitabine did not affect GI motility at any dose (Study No. 477, non-GLP).

Renal System:

Male Long Evans-derived rats were given FTC orally at 0 (distilled water), 10, 30, or 100 mg/kg and urine was collected for 6 hours post-dose. FTC did not affect urine output, pH, or electrolyte excretion at any dose (Study No. 477, non-GLP).

RPV:

Cardiovascular System:

In Chinese hamster ovary (CHO) cells transfected with hERG encoding the I_{Kr} channel, RPV caused a concentration-dependent inhibition of I_{Kr} ranging from 10% at 0.1µM (0.037 µg/mL) to 80% at 3 µM (1.1 µg/mL, Study No. TCM278-CPF730, non-GLP).

In *ex vivo* isolated guinea pig right atrium (Study No. TMC278-N168576, non-GLP), RPV caused a concentration-dependent decrease of the rate of spontaneous contractions to 86%, 72%, and 44% of baseline at 1, 3, and 10 µM (0.369, 1.11, and 3.69 µg/mL), respectively. No effects of the force of spontaneous contractions and effective refractory period were noted. In anaesthetised guinea pigs (Study No. TCM278-CPF643, non-GLP), RPV (up to 5 mg/kg IV) had no effect on heart rate and mean arterial blood pressure. While a trend to an increase in QT interval (+18% compared to +10% in vehicle group) was observed after administration of 5 mg/kg, after correction for heart rate using Bazett's formula, no RPV-induced effects on QT interval were evident.

Anaesthetised beagle dogs receiving an intravenous infusion of RPV (5 mg/kg), showed no effects on ECG parameters (Study No. TMC278-CPF648, non-GLP). However, effects were noted on systemic vascular resistance, pulmonary vascular resistance and cardiac output at the end of the infusion. The interpretation of these findings may have been confounded by cardio-haemodynamic effects observed with the vehicle used in the study, which contained PEG400. In instrumented, conscious dogs, a single oral dose of RPV had no effects on heart rate, blood pressure, systolic pressure rate product, LV dp/dt max, LV dp/dt min, LV dp/dt

max/pd, cardiac output, stroke volume, systemic vascular resistance, and ECG intervals (Study No. TMC278-CPF654, non-GLP). In addition, telemetered conscious dogs receiving single oral doses of RPV (up to 160 mg/kg), showed no effects on cardio-haemodynamic or ECG parameters (Study No. TMC278-5555, GLP).

To investigate the mechanism of the QTc prolongation and of the delayed onset observed clinically after 11 days of dosing with doses of 75 mg and above, additional non-clinical studies were conducted. The potential of RPV to induce pro-arrhythmic effects, in particular Torsade de Pointes (TdP), was also evaluated.

RPV caused a concentration-dependent block in CHO cells *in vitro* of I_{Ks} from 1 µM (0.37 µg/mL) and above, with an IC_{50} of 3.1 µM (1.15 µg/mL, Study No. TMC278-NC342, non-GLP). In addition, in HEK293 cells, RPV at nominal concentrations of 0.1, 0.3, and 1 µM (0.037, 0.11, and 0.37 µg/mL) caused 19.1% inhibition of I_{Ks} at 1 µM (0.37 µg/mL), and 13.6% and 35.5% inhibition of I_{to} at 0.3 and 1µM (0.1 and 0.37 µg/mL), respectively. RPV had no biologically relevant effects on I_{K1}, I_{Na}, or $I_{Ca,L}$ at 1 µM (Study No. TMC278-NC331, non-GLP).

One mechanism possibly considered responsible for the delayed-onset QTc-prolongation observed in the clinical TQT study was inhibition by RPV of the synthesis, assembly in the endoplasmic reticulum, and/or transport of the hERG channel to the cell membrane. This was investigated in HEK293 cells transfected with either wild-type hERG (hERG-WT) or a single mutant channel (hERG-SM, Study No. TCM278-NC330, non-GLP). RPV caused reduced expression of the hERG-WT on the cell membrane (29% and 36% of control expression at 10 and 30 µM, respectively), and therefore appears to have the potential to reduce trafficking of the hERG channel. Overexpression of hERG-SM on the cell membrane was observed (146%-213% of control values at RPV concentrations between 1-30 µM) indicated that RPV to inhibit the hERG channel. This result is in line with that of the patch clamp study with CHO cells expressing the hERG channel (Study No. TCM278-CPF730).

The potential of orally administered RPV to inhibit *in vivo* trafficking of the hERG channel was evaluated through the occurrence of delayed-onset QT-prolongation in a repeat-dose (16 consecutive days) telemetered guinea pig model (Study No. TCM278-NC327, non-GLP). The dose of RPV (10 mg/kg/day) was selected in a pharmacokinetics study as that giving a C_{max} value of approximately 2 times the human C_{max} at 75 mg RPV once daily (0.466 µg/mL) in a clinical Phase 2b study (C204), which resulted in approximately 10 milliseconds QT prolongation in the TQT study (C131). In telemetered guinea pigs, RPV (10 mg/kg, oral, 16 days) had no effect on ECG parameters, heart rate and body temperature (C_{max} ranged between 0.69-0.91 µg/mL during the dosing period).

In the rabbit arterially-perfused left ventricular wedge model, RPV showed only a marginal potential to induce proarrhythmic effects, including a 6% and 9% prolongation of the QT-interval from baseline at concentrations of 1 and 10 µM (0.37 and 3.7 µg/mL), respectively. At 10 µM only, the assessment of the potential to induce TdP resulted in a marginal score of 0.5 (Study No. TMC278-NC341, non-GLP).

The potential of RPV to inhibit potassium currents I_{Kr}, I_{Ks}, and I_{to} involved in the repolarization phase of the cardiac action potential is probably a contributing factor to the observed clinical QTcF prolongation. However, inhibition of these potassium currents in the cells expressing their channels is a direct concentration-related effect, and can therefore not explain the delayed onset of the QTc prolongation in the clinical TQT study. However, additional clinical studies determined that a daily dose of 25 mg RPV was devoid of clinically relevant QTcF prolongation.

Central Nervous System:

In a modified Irwin test conducted in rats, a single oral dose RPV was administered at doses up to 400 mg/kg (Study No. TMC278-Exp5560, GLP). Apart from a slight reduction in pupil size 2 hours post-dose in all animals, no RPV-related neurological changes or delayed neurotoxicity were observed in this study.

In dogs, RPV administered via oral gavage was evaluated for behavioural effects in both conscious telemetered animals (up to 160 mg/kg, Study No. TMC278-Exp5555, GLP) and in awake instrumented animals (20 mg/kg) via cage-side observations (Study No. TCM278-CPF654, non-GLP). RPV did not produce overt changes in behaviour or locomotor activity.

Respiratory System:

In anaesthetised dogs, intravenous infusion of RPV (5 mg/kg) did not affect respiratory arterial blood parameters during the one hour infusion or for up to 3 hours after the end of infusion (Study No. TMC278-CPF648, non-GLP). Similarly, no effects on respiratory rate and tidal volume were noted in conscious telemetered dogs after a single oral dose of RPV (up to 160 mg/kg, Study No. TMC278-Exp5555, GLP).

TAF:

In vivo safety pharmacology experiments were conducted using TAF as the monofumarate form (GS-7340-02) in 50 mM citric acid. In the *in vitro* hERG assay, TAF as GS-7340-03 was dissolved in DMSO and diluted with HEPES-buffered physiological saline to a final concentration of 0.3% DMSO.

Cardiovascular System:

TAF (as GS-7340-03) was evaluated at concentrations of 1 and 10 µM (free base equivalents [fbe]), and hERG inhibition was not significant. The IC_{50} for the inhibitory effect of TAF on hERG was estimated to be greater than 10 µM (Study No. PC-120-2005, GLP).

Oral administration of TAF (as GS-7340-02) to conscious instrumented male beagle dogs at doses of 30 or 100 mg/kg (24 and 80 mg fbe/kg) did not induce pharmacologic effects on heart rate, systemic blood pressure, or ECGs (Study No. D2000006, GLP).

Central Nervous System:

The effect of TAF on the central nervous system has been examined in GLP Study No. R990188 using male SD rats. Animals were treated with single oral doses of TAF (as the monofumarate form) with doses of 0, 100 or 1000 mg/kg (80 or 800 mg free base equivalents [fbe]/kg). There was no evidence of any effect on the CNS at any dose tested up to 1000 mg/kg.

Gastrointestinal:

SD rats were administered TAF (as GS-7340-02) by oral gavage at doses of 0, 100 or 1000 mg/kg (0, 80 or 800 mg fbe/kg). At the highest dose, the rate of gastric emptying was reduced, although this was not observed at 100 mg/kg (80 mg fbe/kg). A dose of 100 mg/kg was considered to have had no effect on gastric emptying or intestinal motility (Study No. R990187, GLP).

Renal:

The effect of TAF (as GS-7340-02) on the renal system was evaluated in male SD rats following administration of single oral doses of 0, 100, or 1000 mg/kg (80 or 800 mg free base equivalents [fbe]/kg) (Study No. R990186, GLP). Urinary output of calcium was increased at 1000 mg/kg. However, this was correlated with an increase in serum calcium concentration and indicated that the kidneys were functioning

well in order to reduce the serum calcium load. The no-effect dose for a pharmacological effect on the renal system was 1000 mg/kg.

Combination:

FTC and TAF had little effect on vital organ systems in safety pharmacology studies. From the cardiovascular studies with TAF, there is potential for PR interval to be prolonged, as seen in the 39 week dog study at 18/12 mg/kg/day. This change was observed to be associated with decreased weight gain, bone and renal toxicity, and significant decreases in triiodothyronine (T3). In the safety pharmacology study in dogs, however, there was no evidence of PR prolongation or any change in ECG results in doses of up to 1000 mg/kg. Results from the clinical thorough QT study also have revealed no cardiac signal.

RPV has shown a weak potential for QT prolongation in *in vitro* studies, a finding that was not reproduced *in vivo* in non-clinical species. However, a delayed effect was confirmed in a thorough QT study in healthy subjects (Study No. TMC278-TiDP6-C131). At the 25 mg dose of RPV, the observed change in QTcF was not considered clinically relevant, and the combination product is not anticipated to exacerbate the small cardiovascular effect seen with the 25 mg RPV dose.

As there has been a comprehensive program for each of the three components in respect of safety pharmacology, no studies have been conducted with the combination in accordance with CHMP guidance (EMEA/CHMP/SWP/258498/2005). There is sufficient knowledge of the individual components to assess potential overlaps in safety risks, and the results do not warrant additional investigation of the combination.

Pharmacodynamic drug interactions

2.3.3. Pharmacokinetics

Pharmacokinetic studies

The absorption, distribution, metabolism, and excretion of FTC, RPV, and TFV/TAF were evaluated *in vitro* and in a variety of animal models *in vivo*. In addition, the drug-drug interaction profile was also evaluated. The pharmacokinetics of the FTC/RPV/TAF FDC is discussed based on the results of nonclinical studies completed with the individual agents. Given the lack of remarkable effects in the non-clinical studies with the individual agents, no additional pharmacokinetic studies have been conducted for the FTC/RPV/TAF combination.

Methods of analysis

TAF:

The in vivo pharmacokinetic, toxicokinetics, distribution, and excretion of TAF were assessed in mouse, rat, dog, and monkey. The in vitro absorption, metabolism, and drug interaction characteristics of TAF were studied in appropriate model systems. Levels of TAF and TFV in rats and dog plasma and PBMCs were determined using fluorescence derivitization/HPLC. Additional methods to detect levels of TAF and TFV in mouse, rat, rabbit and dog plasma/PMBCs included validated LC/MS/MS methods, and HPLC detection methods. The absorption, distribution, metabolism, and excretion of TAF were assessed in various species following a single oral administration of [14C]TAF, and levels of TAF and its metabolites were measured using LSC, HPLC or LC/MS/MS coupled with flow-through detector (RFD). In vitro determination of TAF levels were

in the main determined by LC/MS/MS, with some LC-radio-profiling. Induction potential of TAF on CYP activity measured mRNA levels using qRT PCR methods.

Absorption

FTC:

No *in vitro* permeability studies have been carried out with FTC, as FTC shows high, dose-independent bioavailability *in vivo* in mice and monkeys. Single-dose pharmacokinetics of FTC has been studied in mice, rats and cynomolgus monkeys. FTC was rapidly and well absorbed with oral bioavailability ranging from 58% to 97% over the dose range of 10 to 600 mg/kg.

The multiple-dose pharmacokinetic parameters for FTC were derived as part of the repeat-dose toxicity studies in mice (80 to 3000 mg/kg/day; Study Nos. TOX109; IUW00701; TOX599; TOX628), in rats (60 to 3000 mg/kg/day; Study Nos. TOX108; TOX097), and monkeys (40 to 2000 mg/kg/day; Study Nos. TOX600; TOX627; TOX032) dosed for periods of 3 days to 104 weeks. There were no significant differences in pharmacokinetics following single and multiple dosing. Exposure to FTC (C_{max} and AUC) increased approximately proportionally with dose and was similar between males and females.

RPV:

The transepithelial permeability of RPV was intermediate in human colon carcinoma-derived (Caco-2) cells (Study Nos. TMC278-TiDP6-JRF [FK4155], TMC278-NC104). Passive transcellular diffusion was proposed as a mechanism for RPV intestinal absorption. RPV was not a substrate of P-glycoprotein (P-gp). However, RPV showed P-gp inhibitory properties with an apparent 50% inhibitory concentration (IC_{50}) of 9.2 µM (3.4 µg/mL). Therefore, inhibition of transepithelial permeation of P-gp substrates by RPV cannot be excluded, but is unlikely to be clinically significant at the intestinal absorption level.

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

After oral administration of RPV (base and HCl forms), peak plasma concentrations (C_{max}) were generally reached rapidly (~1 hour) followed by a decline at lower dose levels, whereas at higher dose levels, the plasma profiles showed a plateau until at least 8 hours in all species. Across the dose range studied and species including humans, plasma concentrations of RPV increased dose-proportionally or more often less than dose-proportionally, due to low solubility. At very high dose levels in animals, there was exposure saturation and no further increase in exposure was seen. Exposure in female mice and rats was generally higher than in males.

TAF:

In vitro: The permeability of TAF was examined using Caco-2 cells (Study No. AD-120-2037). TAF was applied to monolayers at 10, 100, and 1000 µM. TAF showed a dose dependent increase in forward permeability and a decrease in efflux ratio indicating saturable efflux transport. Addition of the efflux transport inhibitor, cyclosporine A (CsA) diminished the efflux ratio and increased the permeability.

Mouse: Both single and repeat dose studies were completed in mice.

In the single dose pharmacokinetic study in mice, TAF/TFV were evaluated following administration of TAF by dosing either GS-7340-02 or GS-7340-03 to male CD-1 mice or GS-7340-03 to both male and female 001178-W mice via oral gavage (Study Nos. AD-120-2014 and AD-120-2016).

Tenofovir exposure increased with the increase in dose and was greater than dose proportional between 10 to 100 mg/kg (Table 1). Gender differences in plasma TFV levels were less than 2-fold in C_{max} and AUC_{0-t} values (Table 2). The pharmacokinetic profiles for the 2 different fumarate forms of TAF were observed to be generally similar.

Table 1. Plasma Pharmacokinetic Parameters Following a Single Dose of GS-7340-02 and GS-7340-03 to Male CD-1 Mice

Test Article	GS-7340-02						GS-7340-03					
Dose (mg/kg)	10		30		100		10		30		100	
Analyte	TAF	TFV	TAF	TFV	TAF	TFV	TAF	TFV	TAF	TFV	TAF	TFV
C_{max} (µg/mL)	5.53	106	NA	440	37.1	1827	NA	85.4	10.3	383	34.7	2152
t_{max} (h)	0.083	0.50	NA	0.25	0.083	0.75	NA	0.50	4.00	0.50	0.25	1.50
$t_{½}$ (h)	NA	NA	NA	NA	NA	NA	NA	5.16	NA	10.1	NA	NA
AUC_{0-t} (ng·h/mL)	NA	455	NA	2005	26.0	10643	NA	493	NA	2477	11.3	10866

NA = not applicable
Source: AD-120-2014

Table 2. Plasma Pharmacokinetic Parameters Following a Single Dose of GS-7340-03 to 001178-W Wild type Mice

Dose (mg/kg)	10				30				100			
Analyte	TAF		TFV		TAF		TFV		TAF		TFV	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
C_{max} (ng/mL)	NA	NA	175	100	8.80	117	615	421	648	280	1988	1733
t_{max} (h)	NA	NA	0.25	0.50	0.083	0.5	0.25	0.25	0.25	0.50	0.50	0.50
$t_{½}$ (h)	NA	NA	9.78	8.20	NA	NA	9.51	10.9	NA	NA	8.04	11.0
AUC_{0-t} (ng·h/mL)	NA	NA	735	354	NA	NA	2639	2053	194	104	10026	7131

NA = not applicable
Source: AD-120-2016

GS-7340-02 was administered by oral gavage for up to 14 days to male and female mice at a dose of 100, 500, or 1000 mg/kg/day (Study No. TX-120-2006). Due to early death for animals given 500 or 1000 mg/kg/day, only the 100 mg/kg/day dose group was evaluated. GS-7340 at 100 mg/kg/day corresponded to a Day 14 C_{max} of 27.1 and 2.89 ng/mL for males and females, respectively; the AUC_{0-24} could not be calculated due to the lack of a distinct elimination phase. GS-7340 rapidly converted to its metabolite, TFV. There were no significant differences in TFV pharmacokinetic profiles between males and females.

Following daily administration of GS-7340-02 to mice via oral gavage for at least 13 weeks at doses of 0, 10, 30, and 100 mg/kg/day, the pharmacokinetic parameters for TAF and TFV were determined (Study No. TX-120-2007). Exposure to TFV increased with the increase in GS-7340-02 dose from 10 to 100 mg/kg/day. The increases in C_{max} and AUC_{0-t} were generally greater than proportional between the 10 to 100 mg/kg/day dose levels. Gender-based differences were less than 2-fold in TFV C_{max} and AUC_{0-t} values. There was no sign

of accumulation of TFV after multiple dosing, and there is rapid and extensive conversion of TAF to TFV after oral administration in mice.

Rat: Both single and repeat dose studies were completed in rats.

In the single dose pharmacokinetic study in rats, the two forms of TAF (GS-7340-02 and GS-7340-03) were again compared, as was the exposure to TFV between TAF and TDF (Study Nos. R990130, AD-120-2015, and R2000065). TAF was rapidly absorbed and generation of the major metabolite TFV was observed with a T_{max} of less than 1 hour (Table 3). TFV exposure increased in a greater than dose proportional manner. There no significant difference in pharmacokinetic parameters between the two forms of TAF, GS-7340-02 and GS-7340-03.

Table 3. Plasma Pharmacokinetic Parameters following a Single Dose of GS-7340-02 and GS-7340-03 to Male Sprague-Dawley Rats

Test Article	GS-7340-02			GS-7340-03		
Dose (mg/kg)	5	25	100	5	25	100
Analyte	TFV	TFV	TFV	TFV	TFV	TFV
C_{max} (µg/mL)	32.5	199	1240	39.3	364	1670
t_{max} (h)	0.667	0.583	0.833	0.583	0.833	0.667
$t_{½}$ (h)	NA	11.2	10.3	NA	7.89	7.85
AUC_{0-t} (ng·h/mL)	122	1395	7771	88.5	1810	9759

In a comparison between exposure of TFV generated due to TAF or TDF (Study No. R20000065), rats were treated orally with a single dose of 400 mg/kg of TAF (GS-7340-02) or TDF. The plasma C_{max} and AUC for TFV were 2- to 3-fold higher with 400 mg/kg TAF compared to 400 mg/kg TDF.

The plasma pharmacokinetic profile of TFV was determined during the course of a 28 day oral gavage toxicity study in adult male and female albino rats following daily administration of either 1.5, 6.25, 25, 100 or 400 mg/kg/day GS-7340-02 (Study No. R990182). A greater than dose proportional increase in exposure was observed. There was no evidence of accumulation.

In a 26-week toxicology study, GS-7340-02 was administered once daily at doses of 0 (vehicle only), 5, 25 and 100 mg/kg/day by oral gavage and plasma pharmacokinetic parameters of TFV were determined on Day 1 and during Weeks 13 and 26 (Study No. TOX-120-001). No consistent differences in plasma pharmacokinetic parameters were found between male and female rats. Mean tenofovir C_{max} and AUC values increased dose proportionally over the dose range of 5 to 100 mg/kg/day. Mean TFV AUC obtained on Day 1 was slightly lower than that measured during Weeks 13 and 26, which suggested that there was a slight accumulation of tenofovir with repeat dosing.

Dog: Both single and repeat dose studies were completed in dogs.

In Study No. 99-DDM-1278-001-PK, the effect on pharmacokinetic parameters due to changes in the stereo configuration, fumarate form, food, and the route of administration was examined. In this study Beagle dogs were administered TAF as a single IV bolus (GS-7340-02 [6.3 mg/kg]), or oral administration (TAF as free base [18.0 mg/kg], its diastereomer GS-7339 [18.0 mg/kg], the mixture GS-7171 [16.0 mg/kg], or GS-7340-02 [4,8, 5.0, and 20 mg/kg under fasted and 5.0 mg/kg under fed conditions]). Following oral administration, TAF and its diasteroisomer were rapidly absorbed and eliminated with a t_{max} of less than 0.5 h and t½ ranging from 0.2-0.9 h. The plasma exposures to the intact prodrugs were similar when TAF or

GS-7339 were dosed separately. However, when the isomeric mixture, GS-7171, was dosed, the exposure to GS-7339 was approximately 3-fold higher than TAF. TFV exposure was similar for both diasteroisomers, although exposure in PBMCs was higher following dosing with TAF than with GS-7339. The effect of food led to a decrease in overall plasma exposure of TFV and TAF (2.5 fold).

When male Beagle dogs were given a single oral dose of 10 mg/kg TAF, there was rapid absorption and elimination, t_{max} was less than 0.5 h and t½ ranged from 0.2-0.9 h. The pharmacologically active metabolite, TFV-DP was the major metabolite in liver achieving a C_{max} of 126 µM at 4.0 hours post-dose.

Following daily oral administration of 8.29 mg/kg TAF for 7 days to male Beagle dogs, the plasma and liver pharmacokinetic profiles were determined on day 1 and 7 (Study No. AD-120-2033). TAF was rapidly absorbed and exhibited a short terminal half-life (t½) of 0.3 hours in plasma on both Day 1 and 7. The rapid disappearance of TAF was accompanied by an increase in TFV. Tenofovir was the major metabolite detected in plasma achieving a maximal plasma concentration (C_{max}) of 1.47 and 2.12 µM on Day 1 and 7, respectively. The pharmacologically active diphosphate metabolite, TFV-DP, was efficiently formed in dog livers achieving concentrations of 242 and 153 µM at 4.0 and 24 hours post-dose on Day 7, respectively.

The plasma PK of TAF and TFV and TFV levels in PBMCs were determined during the course of a 28-day oral gavage toxicity study in adult male and female beagle dogs following daily administration of either vehicle, 0.1, 0.3, 1.0, 3.0, or 10 mg/kg/day GS-7340-02 (Study No. D990175-PK). Repeat dosing at 10 mg/kg/day resulted in nonlinear pharmacokinetics between Days 1 and 28 with TAF median AUC values of 0.454 and 0.985 µg·h/mL, C_{max} values of 582 and 1280 ng/mL, and t½ λz values of 18 and 23 minutes, respectively. The TFV C_{max} values appeared to be linear with increasing dose as well as repeat dosing. The TFV t½ was estimated to be 37 h and substantial accumulation of TFV was observed after repeat dosing. The TFV levels in PBMCs were not linear with increasing dose; however, a linear correlation was observed between TFV levels in PBMCs and corresponding trough plasma concentrations. PBMC concentrations were approximately 100-fold higher than corresponding plasma concentrations.

In a 9-month toxicology study in dog, GS-7340-02 was administered once daily at doses of 0, 2, 6, and 18 mg/kg/day (Study No. TOX-120-002). The dose of 18 mg/kg/day was decreased to 12 mg/kg/day on Day 2 of Week 7 for males and Day 2 of Week 8 for females due to severe clinical signs and reduced body weight and food consumption. The concentrations of GS-7340 and tenofovir in plasma samples and total TFV in Week 39/40 PBMC samples were determined. GS-7340 was rapidly absorbed and converted to tenofovir following oral dose administration, with peak plasma concentrations of GS-7340 and tenofovir occurring at 0.5 and 1 hour post-dose, respectively. GS-7340 was eliminated rapidly from the plasma with a terminal phase half-life of less than 1 hour. The median t½ of tenofovir was estimated to be in the range of 25 to 31 hours on Day 1. The plasma pharmacokinetics of GS-7340 and tenofovir were comparable between male and female dogs after oral administration. Plasma C_{max} and AUC values for TAF increased more than proportionally over the dose range of 2 to 18/12 mg/kg/day. The plasma TFV C_{max} and AUC increased roughly dose proportional. There was some accumulation of tenofovir following repeat dosing (~3-fold). Tenofovir concentrations in PBMCs were measurable at 24-hour post-dose for all dose groups. The median terminal phase half-life of total tenofovir in PBMCs was estimated to be 31 hours (similar to the tenofovir plasma estimate) from the recovery animals with PBMC concentrations measured up to 72 hours. Dose-normalized PBMC mean AUC values of total tenofovir increased more than dose proportionally during Week 39/40.

Monkey:

Single dose pharmacokinetics for TAF and TFV, and TFV in PBMCs was determined using rhesus monkeys administered single oral doses of GS-7340-02 at 0.5, 5.0, and 50 mg/kg (Study No. P2000087). Tenofovir alafenamide and TFV levels increased rapidly with t_{max} values of approximately 0.5 and 1 hour, respectively (Table 4). Levels of TFV in PBMCs were also detected, levels of TFV persisted in PBMCs for up to 96 h and persisted to a higher extent to samples treated with acid phosphatase suggesting that a significant proportion of TFV-related material in PBMCs was in phosphorylated forms (Table 5).

Table 4. Plasma Pharmacokinetic Parameters for TAF And TFV Following a Single Dose of GS-7340-02 to Rhesus Monkeys

GS-7340-02 Dose (mg/kg)	0.5	5	50	0.5	5	50
Analyte	TAF			TFV		
C_{max} (ng/mL)	2.79	125	4143	7.72	161	1326
t_{max} (h)	0.38	0.8	0.5	1	1.33	1.0
$t_{½}$ (h)	0.61	0.23	0.40	4.62	9.92	17.33
$AUC_{0\text{-last}}$ (ng·h/mL)	1.22	95.1	3811	39.9	1037	9934
$AUC_{0\text{-}\infty}$ (ng·h/mL)	2.47	80.0	3846	52.7	1069	10250

Table 5. Concentrations of TFV in PBMCs from Monkeys Dosed with GS-7340-02

	TFV PBMC Levels (ng/10^6 Cells)			
	Without Phosphatase Treatment		With Phosphatase Treatment	
GS-7340-02 Dose (mg/kg)	5	50	5	50
2 h	0.47	17.0	0.73	34.2
24 h	0.06	6.82	0.62	20.1
96 h	BLQ	3.03	0.18	8.68

Following daily oral administration of GS-7340-02 at 0, 3, and 30 mg/kg/day or TFV at 15 mg/kg/day for 28 days, pharmacokinetic profiles of TAF and/or TFV were determined on Day 1, Day 14 and Day 28 (Study No. P2000114-PK). No significant differences in pharmacokinetic parameters were found between males and females. The pharmacokinetic parameters for TFV were dose linear on Day 1 but were greater than dose-linear on Day 28 after oral administration of GS-7340-02. There was no statistically significant accumulation of TFV following repeat dosing of either GS-7340-02 or TFV. The intracellular TFV concentrations in PBMCs were determined from the 30 mg/kg/day GS-7340-02 dose group where 72.3 and 27.2 µg/mL were detected on Day 14 and Day 28, respectively.

FTC / RPV / TAF:

With respect to potential drug interactions within the combination that could affect absorption, FTC and RPV shows high passive permeability and is unlikely to be affected when administered with TAF. While TAF is an efflux substrate in the intestine, absorption is unlikely to be affected by FTC as intestinal efflux transport is not inhibited by FTC. Inhibition of P-gp by RPV observed *in vitro* is unlikely to be clinically relevant as RPV did not affect plasma exposure to P-gp substrates including digoxin and TAF in clinical drug interaction studies (TMC278IFD1001 and GS-US-120-1554). Although formal non-clinical studies of the absorption kinetics of the FTC/RPV/TAF FDC have not been conducted, comprehensive clinical studies on the combination have been performed.

Distribution

FTC:

The protein binding of FTC was very low (<5%) in mouse, rabbit, monkey, and human plasma (Study No. TBZZ/93/0025). The tissue distribution of [^{14}C]FTC was characterised in rats and cynomolgus monkeys after a single oral dose of 200 mg/kg (Study Nos. TOX092 and TOX063, respectively). Distribution was extensive and rapid; levels were detected within 1 h post oral administration. The highest concentration of FTC was found in the kidney and the liver. There was no indication of FTC binding to melanin. Concentrations in CNS tissues were 2-10% of the concentration in plasma. There was no sign of FTC accumulation and elimination was rapid. No radioactivity remained at 72 hours post-dose.

Pharmacokinetic parameters for FTC in pregnant animals appeared to be generally similar to those reported for non-pregnant animals.

RPV:

RPV was extensively bound to plasma proteins in all species and the plasma protein binding was found to be concentration independent. Plasma protein binding values ranged between 99.08% and 99.97% (Study No. TMC278-NC112). RPV was extensively bound to human albumin (99.5% at the physiological protein concentration of 4.3% and irrespective of the RPV concentration) and to lesser extent to α1-acid glycoprotein (48.8% at the physiological protein concentration of 0.07% and a RPV concentration of 1 µg/mL). The rank order of blood to plasma concentration ratio in all species was monkey > dog > rat > man > guinea pig > rabbit > mouse and ranged from 0.96 to 0.58. The distribution of RPV to red blood cells (RBCs) was limited in all species tested.

In pigmented Long Evans rats and pregnant Sprague Dawley rats, the tissue distribution of [^{14}C]RPV base and its metabolites after a single dose was rapid and extensive (Study Nos TMC278-NC108 and TMC278-NC109). The highest concentrations of radioactivity were measured in the liver, adrenal gland, brown fat, and kidney. In pigmented tissues, the radioactivity decreased more slowly than in the other tissues and was still quantifiable 14 days postdose. Tissue to blood AUC_{0-336h} ratios were 146 (uveal tract), 18 (brain meninges) and 15 (pigmented skin). Although levels in pigmented tissues at 14 days postdose still represented about 20% of corresponding peak levels, radioactivity levels decreased from 4 or 24 hours onwards. There was no evidence of undue retention and irreversible binding of RPV and its metabolites to melanin. In pregnant rats (Study No. TCM278-NC109), AUC_{0-8h} values in the placenta and in whole fetuses were 0.95- and 0.64-fold the AUC0–8h value of maternal blood, respectively, suggesting that the placenta is only a partial barrier for RPV and its metabolites.

TAF / TFV:

The extent of binding of TAF to plasma protein was determined using dog and human plasma only (Study No. AD-120-2026). Rat plasma was not included as TAF is highly unstable in rat plasma due to the presence of a high number of esterases. Protein binding of TAF was moderate in dog and human plasma with the percent unbound values of 48.0% and 46.8%, respectively. The *in vitro* values are slightly higher than those observed using *ex vivo* samples from TAF treated humans which ranged from 14 – 23%. For the use in the interaction studies, the percentage of unbound TAF was round up to be 20%.

The protein binding of TFV has been determined in human plasma and serum using centrifugal ultrafiltration (Study No. P0504-00039.1). Percent of unbound TFV was 99.3 ± 3.3% in human plasma, and 92.8 ± 3.6% in human serum. Tenofovir therefore showed very low protein binding in either human plasma or serum.

Extensive tissue distribution studies with TAF were completed using mice, rats and dogs.

Male CD-1 mice were treated with a single oral dose of 100 mg/kg [^{14}C]TAF (Study No. AD-120-2011). Most tissues reached maximum concentration by 1 hour postdose. The tissues showing the highest maximum concentrations of radioactivity, excluding GI tract, included liver, gall bladder, urinary bladder, diaphragm, kidney cortex, kidneys, and kidney medulla. The tissues with the lowest C_{max} values were testis, brain cerebrum, fat (abdominal), spinal cord, and brain medulla. Similar distribution profiles were seen in male C57 Black (pigmented) mice. More persistent exposures in eye lens, eye uveal tract, and eyes were observed in CD57 black mice compared to CD-1 mice, although there was no indication that there was a difference in distribution between pigmented and non-pigmented skin, or that TAF was more preferentially distributed to melanin-containing tissues.

Male SD or Long Evans rats were administered oral 5 mg/kg [^{14}C]TAF (Study AD-120-2020). There was rapid distribution to most tissues, both to pigmented and non-pigmented rats. The tissues showing the highest maximum concentrations of radioactivity included kidney cortex, kidney(s), kidney medulla, and liver. The tissues with the lowest C_{max} values were brain olfactory lobe, seminal vesicle(s), eye vitreous humour, thymus, eyes, testes, and harderian gland for Sprague-Dawley rats and bone, brain olfactory lobe, seminal vesicle(s), fat (abdominal), muscle, eye vitreous humour, and eye(s) for Long Evans rats. As there was no indication that there was any difference in distribution between pigmented and non-pigmented animals, binding to melanin was unlikely.

The distribution of TAF and TFV in pregnant and lactating animals has been evaluated. In pregnant rats, rabbits and monkeys the extent of placental transfer of TAF and TFV was measured during the embryo-fetal developmental studies. In rats, there was a clear increase in TFV exposure with increasing dose of TAF (Study Nos. TX-120-2001 and TX-120-2002). Multiple dosing in the dose-range finding study showed signs of accumulation of TFV, however this was not seen in the definitive study.

In rabbits, there was an increase in exposure to TAF and TFV with increasing dose, with no evidence of accumulation (Study Nos TX-120-2004 and TX-120-2005).

In the monkey, the extent of placental transfer of TFV following subcutaneous administration was determined in pregnant rhesus monkeys (Study No. 96-DDM-1278-005). Placental transfer of TFV appeared to be significant with a fetal/maternal serum concentration ratio of 0.17 ± 0.07 (mean ± SD) at approximately 30 minutes post-dose.

In immature rhesus monkeys (newborn to 12 months old) administered with TFV subcutaneously (30 mg/kg, Study No. 96-DDM-1278-005), C_{max} was higher in younger animals, likely a result of a gradual increase in clearance from birth to 1 year. It is therefore expected that younger monkeys had higher TFV exposure at an equivalent dose. It is likely that newborn monkeys lack the anion transport system responsible for tubular secretion of TFV.

FTC / RPV / TAF:

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

Metabolism

FTC:

FTC is highly metabolically stable *in vitro* and *in* vivo, and is not subject to significant metabolism by CYP enzymes. Generation of a minor (~1%) sulfoxide metabolite (M1 and/or M2) was catalysed by CYP3A4, and inhibitor studies suggested that at least one other enzyme, possibly flavin-containing monooxygenase, may play a role (Study No. 15396 v1). A minor direct glucuronide metabolite, M3, was also detected.

FTC was not extensively metabolised and is eliminated primarily as unchanged drug by renal excretion in mice, rats, and cynomolgus monkeys. Over 90% of the radioactivity in mouse and rat urine and 64% of the radioactivity in monkey urine was unchanged drug. Only trace levels of metabolites were found in faeces (Study Nos. TEIN/93/0015, TEIN/93/0016, TOX063). In all 3 species, metabolism accounted for only a minor percentage of FTC elimination. FTC is subject to Phase I metabolism (oxidation to a diastereomeric sulfoxide) and to direct conjugation (glucuronidation of hydroxymethyl group) as minor metabolic routes.

RPV:

In vitro, the CYP3A4 isoenzyme plays a major role in the biotransformation of RPV. Therefore, some effects of drugs modulating CYP3A4 enzyme activity on plasma concentrations of RPV were expected in humans. Such effects were seen in drug-drug interaction trials with CYP3A4 inducers such as rifampicin and rifabutin, which both decreased the exposure of RPV, and with CYP3A4 inhibitors such as ketoconazole, which increased the exposure of RPV.

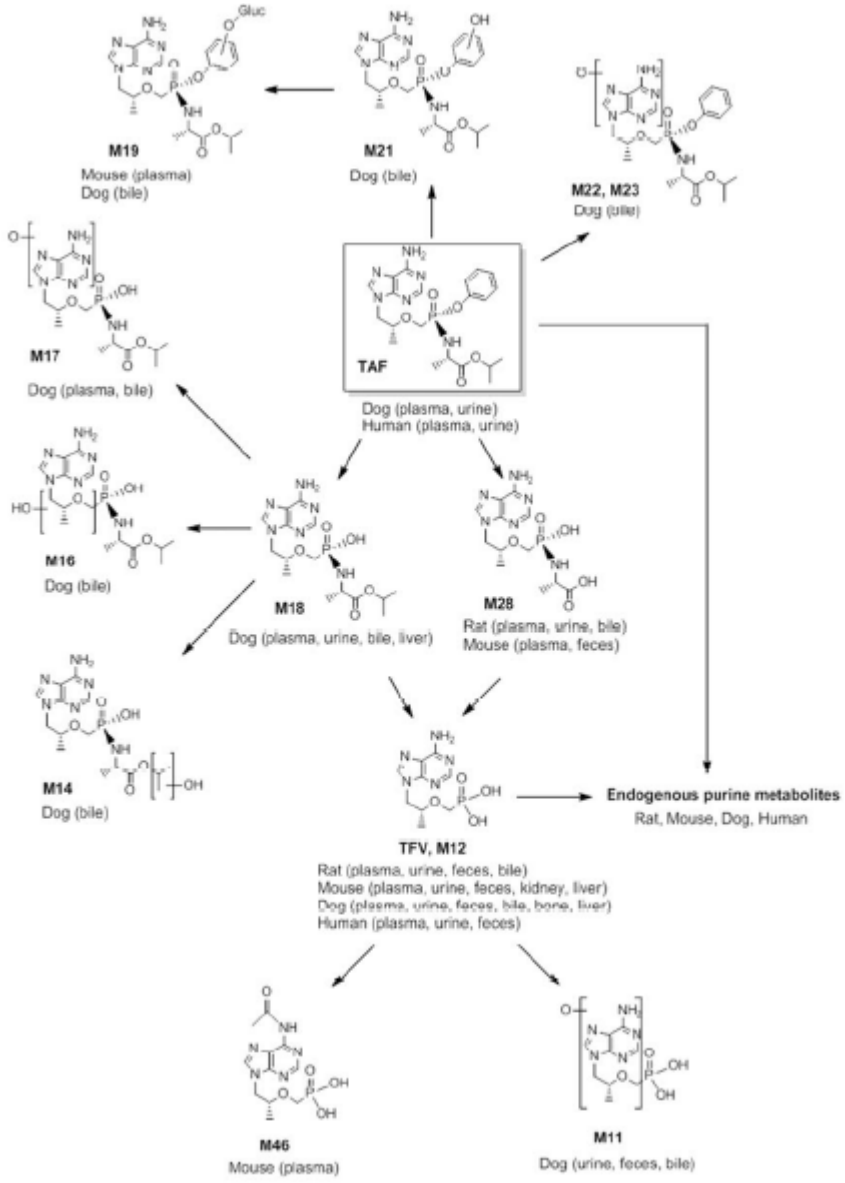
A large number of RPV metabolites were identified in the *in vivo* studies in mice, rats, dogs, and humans (TMC278-NC190, TMC278-NC113, TMC278-NC114, and TMC278-NC157). RPV is metabolized via Phase I and Phase II reactions and the most important pathways are hydroxylation and glutathione conjugation. In mice, oxidation of RPV and, to a lesser extent, glutathione conjugation, were the predominant pathways. In rats, the glutathione conjugation pathway predominated, whereas in dogs and man, oxidation of RPV was predominant. No unique human metabolites were observed. In plasma of animals and human, unchanged RPV was more abundant than all metabolites combined. In mice, the predominant metabolites in faeces were M41 and M42, accounting for up to 18 and 26% of the dose respectively, and M25 in urine (up to 1.6% of the dose, Study No. TMC278-NC190). In rats, M47 was the predominant metabolite (up to 4% of the dose) in faeces. In urine, only M17 and M18 were detected at low levels (1.1 and 0.45% respectively, Study Nos TMC278-NC113 and TMC278-NC145). In dogs, M33, M42 and M44 were the most abundant metabolites in faeces (8.7, 5.3 and 4.3% respectively), and only minor metabolites were detected in urine (Study No. TMC278-NC114). In humans, the predominant faecal metabolite was M42, accounting for 16% of the dose (Study No. TMC278-NC157/TMC278-NC119). In urine, the only Phase I metabolite detected was M30 (0.03% of the dose).

TAF:

Tenofovir alafenamide is subject to intracellular metabolism to TFV, which is further phosphorylated to the anabolites, TFV-MP and TFV-DP with TFV-DP being the pharmacologically active form.

The applicant has proposed a possible metabolism pathway based upon the findings from mice, rats, dogs and humans (Figure 3.4.1). TAF is also subject to intracellular metabolism to TFV, which is further phosphorylated to the anabolites, tenofovir-monophosphate and TFV-DP with TFV-DP being the pharmacologically active form (Figure 3).

Figure 3. Proposed metabolism pathway for TAF



In vitro Metabolism:

The potential for CYP enzymes to metabolise TAF was assessed by incubating TAF with 6 individual bacterially expressed human CYP enzyme preparations co-expressed with human NADPH CYP reductase (Study No. AD-120-2004). Metabolism of TAF was not detected by CYP1A2, CYP2C8, CYP2C9, CYP2C19 or CYP 2D6. Tenofovir alafenamide was slowly metabolised by CYP3A4 at a rate of 1.9 min^{-1} which was 26.6% of the positive control, testosterone.

Intracellular metabolic activation of TAF in PBMCs or other lymphatic tissues involves conversion to TFV by cathepsin A. In contrast to PBMCs, TAF was primarily hydrolysed by carboxylesterase 1 (CES1) in primary hepatocytes. Tenofovir is then further phosphorylated to TFV-DP by cellular nucleotide kinases.

The *in vitro* activation of TAF in human primary hepatocytes was evaluated and compared with that of TDF and TFV (Study No. AD-120-2017). Following a 24-hour continuous incubation of primary hepatocytes with 5 µM TAF, TDF, or TFV, the levels of GS-77938 increased to 1,470, 302, and 12.1 pmol/million cells illustrating that incubation with TAF resulted in 5- and 120-fold higher intracellular levels of GS-77938 compared to TDF and TFV, respectively.

The *in vitro* metabolism of [^{14}C]TFV was studied in dog plasma, in control and induced (Aroclor 1254) rat liver microsomes, and also in dog liver and intestinal S9 fractions (Study No. 96-DDM-1278-003). Tenofovir was recovered unchanged under all conditions: no metabolites were detected in either rat microsomal preparation, with or without the addition of NADPH cofactor. There was no evidence of chiral inversion either.

In vivo Metabolism:

The metabolic profiles of TAF were determined in plasma, urine, faeces, kidney, liver, and nasal turbinate from mice (Study No. AD-120-2012); in plasma, urine, bile, and faeces from rats (Study No. AD-120-2021); and in plasma, urine, bile, faeces, bone, and liver from dogs (Study No. AD-120-2008). The metabolite profiles were also determined in human plasma, urine, and faeces following administration of a single oral dose of [^{14}C]TAF (Study No. GS-US-120-0109). The findings from these studies are summarised in Table 3.4.1 below.

TFV accounted for a majority of drug related material in plasma, urine, and faeces from all species except for human plasma, in which uric acid (M27B) was the predominant metabolite accounting for 73.9% of the total AUC over 96 hours. Uric acid is also detected to a large extent in mouse plasma (19.4%). M18 was the major metabolite in rat bile accounted for 63% of total radioactivity recovered in bile. M18 and its oxidised metabolite, M16 were the major metabolites in dog bile accounted for 29 and 38% of total radioactivity recovered in bile. Various oxidative metabolites were found in dog bile. No metabolites unique to human were observed.

The extent of TFV transformation to TFV-DP was examined in PBMCs, red blood cells (RBCs) and lymph nodes from monkeys (Study No. P2001025). Animals were administered a single dose of 15, 30, or 60 mg/kg of [^{14}C]TFV subcutaneously. TFV was taken up by PBMCs and anabolised to TFV-DP, with intracellular concentrations of the active antiviral anabolite reaching 1.6 µM (60 mg/kg dose group). The half-life of TFV-DP in this experiment was >50 hours. A similar pattern developed in RBCs and lymph nodes. The long intracellular half-life in this respect supports the proposed once daily clinical dosing regimen.

FTC / RPV / TAF:

While RPV is primarily metabolised by CYP3A, TAF and FTC do not interact with drug metabolizing enzymes as inhibitors or inducers at clinically relevant concentrations. Therefore, metabolic drug interactions between these agents are unlikely.

FTC and TAF are analogues of two different nucleosides, cytidine and adenosine, respectively, and do not share a common intracellular metabolism pathway for pharmacological activation through phosphorylation. In experiments where both drugs were incubated together at concentrations higher than achieved in the plasma, the intracellular activation of TFV to its active diphosphate was not negatively influenced by the presence of FTC, and the activation of FTC to FTC-triphosphate, was not negatively affected by the presence of TFV (Study No. PC-164-2002). Also, because FTC and TAF form analogues of different nucleotides, there should be no competition for incorporation by HIV-1 RT and subsequent chain termination. This was confirmed *in vitro* in antiviral assays where strong synergy between FTC and TAF was observed (Study No. PC-183-2004). Similarly, because of the highly restricted substrate specificity of the enzymes catalysing the

phosphorylation of FTC and TFV, inhibition of pharmacological activation by RPV is unlikely and there was no evidence for antagonism in antiviral assays *in vitro*.

Excretion

FTC:

The primary route of elimination of [^{3}H]FTC and [^{14}C]FTC was via renal excretion of parent drug after oral and IV administration in mice, rats, and cynomolgus monkeys, and accounted for 85%, 91% and 41% in mice, rats and monkeys respectively. The majority of the FTC recovered in the faeces after oral administration most likely represents unabsorbed drug, rather than biliary excretion. Although FTC is metabolised to only a minor extent, its metabolites are also excreted via the kidneys.

Excretion into milk has not been evaluated for FTC.

RPV:

In mice, rat, dogs and humans, the predominant route of excretion was as unchanged drug via the faeces, and amounted to 87% to 96%, 93%, 95% and 85% of the administered radioactive dose in mice, rats, dogs and humans, respectively. Only in mice at 20 mg/kg, one metabolite, M42, was the most abundant in faeces. Urinary excretion of radioactivity was less than 4.2% in mice, rats, and dogs, but was slightly higher (6.1%) in humans. In all species, including humans, the amount of unchanged RPV in urine was negligible, and renal clearance of RPV is negligible. RPV was also excreted in the bile in rats (18%-25% of the administered radioactive dose). The amount of unchanged RPV excreted in bile was negligible (about 0.2 % within 24 hours). The biliary excretion study demonstrated that the major part of unchanged RPV in the faeces in rats had not been absorbed.

Excretion into milk has not been evaluated for RPV.

TAF and TFV:

Excretion of oral radiolabelled TAF has been evaluated in mice, rats and dogs.

Mice were administered a single oral dose of 100 mg/kg [^{14}C]TAF (Study No. AD-120-2011). Recovery of radioactivity was 61% from urine and faeces 48 hours post-dose. An average of 41.3 and 27.7% of the administered radioactivity were excreted in faeces and urine, respectively, by 168 hours post-dose.

Bile duct-intact and bile-duct cannulated (BDC) male SD rats were given a single 5 mg/kg oral dose of [^{14}C]TAF (Study No. AD-120-2020). [^{14}C]TAF was rapidly excreted within 24 hours after oral dosing. The mean values of 71.9 and 22.2% of the administered radioactivity were excreted in faeces and urine, respectively, by 168 hours post-dose. The mean overall recovery of radioactivity was 96.7%.

Excretion of radiolabelled TFV was examined following IV administration at doses of 10 or 50 mg/kg to SD rats. Excretion was 85.2 ± 7.63% at 24 hrs, and 92.7% ± 6.77 % by 7 days post-dose in urine. Faecal elimination was 3.18% ± 1.85% by 24 hours, and 4.48% ± 1.89% by 7 days post-dose.

In dogs, the excretion of [^{14}C]TAF was determined after administration of a single 15 mg/kg oral dose of ^{14}C-TAF to bile duct-intact and BDC male dogs (Study No. AD-120-2007). [^{14}C]TAF was readily excreted mostly within 48 hours after oral dosing. The mean values of 37.4% and 35.9% of the administered radioactivity were excreted in faeces and urine, respectively, by 168 hours post-dose. Overall mean recovery of radioactivity was 80.4%.

Excretion of radiolabelled TFV was evaluated in dogs following a single IV dose of [^{14}C]TFV (Study No. 96-DDM-1278-002). The primary route of elimination was via urine, where 70.03% of total radioactivity was recovered. Total faecal recovery of radioactivity was 0.42% of the total dose.

Bile excretion: Bile excretion has been examined in both rat and dog studies following oral administration with radiolabelled TAF. 3.2%, and 2.11% of the administered radioactivity were excreted in faeces, urine, and bile, respectively, by 168 hours post-dose. The mean overall recovery of radioactivity after oral dosing to BDC rats was 99.9%.

The excretion of [^{14}C]TAF was determined following oral administration of a single 15 mg/kg dose of [^{14}C]TAF to male dogs (Study No. AD-120-2007). Mean values of 42.7%, 26.5%, and 14.0% of the administered radioactivity were excreted in faeces, urine, and bile, respectively, through 168 hours post-dose. Based on the radioactivity excreted in urine and bile, a minimum of approximately 41% of the orally administered dose was absorbed. Elimination via biliary excretion appears to be the major route of elimination of [^{14}C]TAF in dogs. The overall recovery of radioactivity in BDC dogs was 86.2%.

Excretion to milk: The extent of TFV excretion in lactating monkeys was evaluated. Milk was obtained from two lactating adult female rhesus monkeys following a single 30 mg/kg subcutaneous dose of TFV (Study No. P2000116). TFV was detected in the milk; the AUC in milk was between 18.6-21.5% of that seen in plasma.

FTC / RPV / TAF:

FTC and TFV are almost exclusively eliminated by renal excretion. While TFV is a substrate for OAT1, OAT3, and MRP4, none of these transporters was inhibited by FTC. RPV is predominantly excreted in faeces. Therefore, interactions within the components of the FTC/RPV/TAF FDC during excretion are considered unlikely.

Pharmacokinetic drug interactions

FTC:

FTC is eliminated, largely unchanged, by renal excretion, and metabolism by CYP3A enzymes plays a minor role in clearance of FTC. It is therefore unlikely that FTC will be a victim of drug interactions, due to inhibition or induction of drug metabolizing enzymes or drug transporters at the intestine or liver. Similarly, it is unlikely that FTC would affect the metabolism of co-administered medications through inhibition or induction.

In vitro data confirmed that FTC was not an inhibitor of activities catalysed by CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A in human hepatic microsomal fractions. FTC also did not show inhibition of the glucuronidation of 7-hydroxycoumarin, a general UGT substrate. FTC did not activate human AhR or PXR at concentrations up to 50 µM (Study No. AD-162-2005). The ability of FTC to affect to action of drug transporters has been explored in a number of *in vitro* studies. A summary of the relevant transporters assessed is listed below in Table 3.6.2 (transporter substrates) and Table 3.6.3 (transport inhibition). These studies indicated that FTC is not a substrate or an inhibitor of any of the transporters tested, except for being a substrate of OAT3.

RPV:

In vitro, RPV was an inhibitor of CYP3A4 (IC_{50} >4.2 µM [1.5 µg/mL]) and CYP2C19 (IC_{50} <0.06 µM [0.021 µg/mL]). Further *in vitro* data indicated a possible inhibitory effect of RPV on the metabolism of substrates of CYP3A4, e.g. clarithromycin (IC_{50} = 2 µM, 0.72 µg/mL), norethindrone (IC_{50} = 3.9 µM, 1.4 µg/mL), and sildenafil (IC_{50} = 1.4 µM, 0.5 µg/mL); and on the metabolism of omeprazole (IC_{50} = 12 µM, 4.3 µg/mL), a

substrate of CYP3A4 and CYP2C19 (Study No. TMC278-NC194). However, no impact was expected from these findings clinically since the mean C_{max} was 0.13 µg/mL (Week 4 to 8) obtained in HIV-infected treatment-naive patients at 25 mg once daily, the recommended dose, and this was confirmed in clinical drug-drug interaction studies performed using substrates of CYP3A4 (atorvastatin, omeprazole, and norethindrone) and a substrate of CYP2C19 (omeprazole).

RPV is also an inhibitor of CYP2C8 and CYP2C9 *in vitro* with Ki values of 10 µM (3.7 µg/mL) and 1.7 µM (0.62 µg/mL), respectively. Taking into account the clinical mean C_{max} of 0.13 µg/mL, inhibition of CYP2C8 and CYP2C9 by RPV was not expected.

The *in vitro* interaction of RPV with the metabolism of sertraline (substrate of multiple CYPs, monoamine oxidase and UDP-GT), paroxetine (CYP2D6), clarithromycin (CYP3A4), sildenafil (CYP3A4), omeprazole (CYP2C19 and CYP3A4), chlorzoxazone (CYP2E1), 17α-ethinylestradiol (Phase II metabolism), S-mephenytoin (CYP2C19), and norethindrone (different isoenzymes) was investigated in a pooled batch of human liver microsomes and the same was done for abacavir (alcohol dehydrogenase) in a pooled batch of human liver cytosol (Study No. TMC278-NC194). RPV seemed to have a significant inhibitory effect (IC_{50} <5 µM) on the metabolism of clarithromycin, sildenafil, S-mephenytoin, and norethindrone and a moderate effect (5 µM< IC_{50} <10 µM) on sertraline, paroxetine, and 17α-ethinylestradiol. Omeprazole metabolism was only poorly inhibited by RPV (IC_{50} 12 µM). RPV did not affect the metabolism of abacavir or chlorzoxazone, as metabolite formation of these compounds was not inhibited (IC50 >30 µM). In summary, RPV may have a possible effect on the *in vivo* metabolism of clarithromycin, sildenafil, S-mephenytoin, and norethindrone. In addition, metabolism of sertraline, paroxetine, and 17α-ethinylestradiol may also be affected by RPV, although likely to a lesser extent.

The potential of RPV to inhibit renal transporters, OCT2, MATE1 and MATE2-K was assessed *in vitro* (Study Nos TMC278-FK10042 and TMC278-FK10420). RPV showed IC_{50} values for OCT2, MATE1, and MATE2-K of 5.46, 7.51, and <0.05 µM, respectively. Since the estimated clinical unbound plasma C_{max} for RPV is 3.5 nM, the effect of RPV on OCT2 and MATE1 is unlikely to be clinically relevant, but it cannot be excluded that RPV would inhibit MATE2-K at clinically relevant concentrations. Renal clearance is, however, negligible for RPV and it is not known what the intracellular RPV concentrations are at the local level of the MATEs' site of action. Metformin is a known substrate for OCT2 and MATEs and co-administration with RPV did not affect the plasma exposure or urine concentrations of metformin (Clinical Study No. TMC278IFD1004). OCT2, MATE1, and MATE2-K are known to be involved in renal secretion of creatinine. Small increases in serum creatinine have been observed in humans treated with RPV, likely due to inhibition of renal transporters for creatinine, but these are not considered to be clinically important.

TAF/TFV:

The potential for TAF to be involved in drug-drug interactions has been assessed in a range of *in vitro* test systems. The potential of TAF or its metabolites to inhibit or induce CYP enzymes and serve as substrates or inhibitors of xenobiotic transporters was assessed. The effect of other drugs, including other antiviral agents that may be co-administered with TAF, on intestinal stability and the absorption potential was also determined. Considering the data generated using *ex vivo* human tissue, the extent of unbound TAF was estimated to be 20% of total exposure.

Inhibition of Cytochrome P450 enzymes and UGT1A1:

The potential for TAF and TFV to inhibit human CYP-mediated drug metabolism was examined *in vitro* using hepatic microsomal fractions and enzyme-selective activities (Study Nos. AD-120-2003 and V990172-104). Inhibition of the following CYP450 enzymes was evaluated, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19,

CYP2D6, and CYP3A. TAF at a concentration of 25 µM was shown to weakly inhibit CYP3A with an IC_{50} ranging from 7.4 to 7.6 µM. TFV did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

In Study AD-120-2040, the potential for TAF to be a mechanism-based inhibitor of human CYP enzymes was investigated. TAF at a concentration of 50 µM had no effect on inhibition to any of the tested isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6). Tenofovir alafenamide did not inhibit UGT1A1 up to 50 µM (IC_{50} > 50 µM) (Study No. AD-120-2006).

Enzymology of Metabolism:

To examine whether TAF may be metabolised by intestinal esterases and/or CYP enzymes following intestinal absorption, the effects of other HIV PIs and CYP inhibitors was explored in Study AD-120-2027. TAF was incubated with HIV-1 PIs (atazanivir or darunavir) or CYP inhibitors (ritonavir or COBI) at concentration of up to 100 µM. The stability of TAF was unaffected by the presence of these CYP inhibitors or PIs.

In order to investigate which enzymes are involved in activation of TAF in human hepatocytes, TAF was incubated alongside known CatA inhibitors (approved hepatitis C virus NS3 inhibitors, telaprevir and boceprevir), CES1 inhibitor (bis-p-nitrophenyl phosphate, BNPP), CYP3A4 and P-gp inhibitor (COBI), or telaprevir and BNPP together (Study No. AD-120-2031). BNPP inhibited the metabolism of TAF in a dose dependent manner. Formation of the active constituent of TAF, TFV-DP was unaffected on co-incubation with telaprevir, boceprevir, or COBI. Combining BNPP and telaprevir resulted in an enhanced level of inhibition. From the results of this study it is implied that TAF is primarily hydrolysed by CES1 and CatA.

Induction Liability:

The ability of TAF to induce CYP enzymes/activity, P-gp or UGT1A1 was examined using cultured human helpatocytes treated with 1, 10, and 100 µM TAF once daily for 3 consecutive days (Study No. AD-120-2032).

There was evidence of cytotoxicity following dosing with 100 µM TAF with reduced CYP activity, but increased mRNA levels. After treatment with 10 µM TAF, the mRNA levels of CYP1A2 and CYP3A4 increased by 3.0- and 8.3-fold which correspond to 3% and 6% of control levels. This demonstrates that TAF has a potential to induce CYP isoenzymes at 10 µM, but this was reduced to little or no induction potential at 1 µM. There was no evidence of a change in induction potential for P-gp or UGT1A1 mRNA.

The potential for TAF to induce human drug metabolising enzymes and drug transporters through the activation of human AhR or human PXR was further evaluated in cell-based systems (Study No. AD-120-2005). At a concentration of 50 µM TAF was only able to activate PXR at 23% of a positive control, rifampicin. This effect reduced to less than 5% with a dose of 15 µM TAF. Activation of AhR was not observed following dosing with 50 µM TAF. TAF is unlikely to activate either PXR or AhR xenobiotic receptors.

Potential for Transporter-Mediated Drug Interactions with TAF and TFV:

The ability of TAF and TFV to affect to action of drug transporters has been explored in a number of *in vitro* studies. A summary of the relevant transporters affected by TAF (and EVG, COBI and FTC) is listed below in Table 3.6.2 (transporter substrates) and Table 3.6.3 (transport inhibition).

TAF:

In terms of inhibiting drug transporters, TAF was unable to inhibit P-gp, BCRP, OAT1, OAT3, and OCT2 (Study No.s. AD-120-2019 and AD-120-2036). Inhibition to OATP1B1, OATP1B3, BSEP, OCT1, and MATE1 was observed but only to a small extent, i.e. at doses that were 200-fold in excess to clinical meaningful exposures. TAF is unlikely to mediate the role of transporter-mediated drug interactions.

In terms of TAF acting as a substrate to drug transporters, TAF has been shown to be a substrate for intestinal efflux transporters, P-gp and BCRP. There is an increase in TAF absorption in the presence of cyclosporine A (CsA) and COBI (inhibitors of P-gp and BCRP) (Study Nos. AD-120-2037 and AD-120-2013). In a study in which dogs were orally administered TAF at 2 mg/kg following untreated or pretreated animals with 75 mg/kg CsA, there was increased exposure to TAF in the CsA pretreated animals, although this had no effect on the overall level of TFV present. The increased TAF plasma exposure led to an increase in levels of TFV-DP detected in PBMCs, suggesting that co-administration of TAF with an efflux transport inhibitor (i.e. COBI) would increase absorption and also result in higher levels of the active anti-viral substance, TFV-DP.

TAF was found to be a substrate for hepatic uptake transporters, OATP1B1 and OATP1B3. Exposure to TAF may be affected by inhibitors of these transporters or genetic polymorphisms that affect the transport activities. Unlike TFV, TAF was not a substrate for renal transporters, OAT1 and OAT3.

TFV:

The route of elimination of TFV is renal excretion by a combination of glomerular filtration and tubular secretion. In order to understand the role of transporters in the renal secretion of TFV and to explore potential drug interactions based on these transport systems, the interactions of TFV with a variety of both uptake and efflux transporters were studied *in vitro*.

Results of *in vitro* transport studies indicate that the active tubular secretion of TFV is mediated by human OAT1 (basolateral uptake) and MRP4 (apical efflux) transporters acting in series in proximal tubules (Study Nos. PC-103-2001, AD-104-2001, AD-104-2002). Human OAT3 may play a secondary role in the tubular uptake of TFV. Neither P-gp nor MRP2 appear to be involved in the efflux of TFV.

As the primary transporter handling the uptake of TFV, OAT1 has been assessed for its potential role in drug interactions between TFV and other renally secreted therapeutics including antibiotics, anti-inflammatory agents, and other antivirals. Under physiologically relevant conditions, none of the tested drugs affected OAT1-mediated transport of TFV, indicating a low potential for renal interactions with TFV due to inhibition of this pathway (Study No. PC-104-2010 and Study No. PC-104-2011).

COBI also shows no detectable inhibition of human OAT1 or OAT3. Similarly, PIs ATV, LPV, and RTV did not exhibit any effect on the active cellular elimination of TFV mediated by the MRP4 efflux pump, and COBI is a very weak inhibitor of MRP4. The results of *in vitro* drug interaction studies indicate that PIs or COBI are unlikely to exert any substantial effect on the renal elimination of TFV in general or result in the accumulation of TFV in renal proximal tubules.

The results from *in vitro* studies investigating the contribution from MRP1 in tubular reabsorption of TFV (Study No. PC-104-2014) indicated that MRP1 is not involved in the reabsorption of TFV at the basolateral membrane of proximal tubule cells.

TFV did not inhibit the activity of human OCT2 or MATE1 (IC_{50} >300 μM), so TFV is unlikely to cause drug interactions through inhibition of these transporters (Study No. AD-104-2012).

FTC, TAF, and TFV do not inhibit any of the transporters tested at clinically relevant concentrations *in vitro*. Therefore, FTC, TAF, and TFV are unlikely to be perpetrators of transporter-mediated drug interactions. Renal excretion of TFV is facilitated by basolateral uptake by OAT1 and OAT3 and apical efflux by the MRP4 efflux transporter. There is no evidence for inhibition of TFV renal excretion by FTC as it shows undetectable inhibition of OAT1, OAT3, and MRP4 *in vitro.*

FTC / RPV / TAF:

While RPV is primarily metabolised by CYP 3A, FTC, TAF and TFV are not clinically relevant substrates, inhibitors, or inducers. In addition, TFV and FTC do not inhibit each other's pharmacological activation through phosphorylation. Thus, the drug interactions through drug metabolizing enzymes within the three compounds are unlikely. However, co-administration of strong inducers or inhibitors of CYP3A may affect exposure to RPV. In addition to the studies described for FTC and TAF, a number of transporter studies were conducted with the STB components, EVG, COBI, FTC, and TFV. Since TFV is the major circulating metabolite for both TDF and TAF, these results are relevant to evaluate the potential for transporter-mediated drug-drug interactions among these components.

Based on the available data FTC, TAF, and TFV are unlikely to be a perpetrator of transporter-mediated drug interactions.

Renal excretion of TFV is facilitated by basolateral uptake by OAT1 and OAT3 and apical efflux by the MRP4 efflux transporter. There is no evidence for inhibition of TFV renal excretion by FTC as it shows undetectable inhibition of OAT1, OAT3, and MRP4 in vitro.

While RPV was found to inhibit P-gp with IC_{50} of 9.2 µM *in vitro*, it is not a clinically relevant inhibitor as exposure of digoxin and TAF was not affected by RPV (Clinical Study No. TMC278IFD1001, GS-US-120-0117, and GS-US-120-1554). As discussed above, inhibition of OCT2 and MATE1 by RPV observed *in vitro* is unlikely to be clinically relevant. In addition, inhibition of MATE2-K by RPV may not result in drug-drug interactions with xenobiotics which are substrates for both MATE1 and MATE2-K. Drug interactions through inhibition of these transporters by RPV within the components of the FTC/RPV/TAF FDC are unlikely as FTC and TAF components of the FTC/RPV/TAF FDC were clinically bioequivalent to the E/C/F/TAF FDC (Clinical Study No. GS-US-336-1159).

2.3.4. Toxicology

FTC toxicology summary

Emtricitabine (FTC) is an NRTI that is marketed as a once-daily capsule (Emtriva 200 mg) and as an oral solution (Emtrival Oral Solution 10 mg/mL) for the treatment of HIV-1 infection. FTC is a synthetic analogue of the naturally occurring pyrimidine nucleoside, 2′-deoxycytidine that is structurally similar to lamivudine (Epivir). Intracellularly, FTC is phosphorylated by cellular enzymes to form the active metabolite, emtricitabine triphosphate.

The general systemic (single and repeat dose) toxicity, genotoxicity, carcinogenicity, reproductive toxicity, and immunotoxicity of FTC have been characterized in a variety of *in vitro* and *in vivo* studies.

The non-clinical toxicity studies demonstrated that FTC was well tolerated after oral dosing for up to one year at doses producing systemic exposure levels in animals much greater than those anticipated in patients treated with the recommended clinical dose.

Treatment-related effects were confined to high-dose groups only and included changes in red blood cell (RBC) parameters, interpreted as a mild, reversible anaemia (mice 1 month, 6 months; rat 3 months; monkey 1 year); changes in various organ weights without any associated adverse histopathological effects in rodents (mouse 1 month, 6 months; rat 3 months), increased urine output (mice 6 months), and soft faeces (monkeys 1 month, 3 months). No observed effect levels (NOELs) could be established for all

treatment-related effects, and in several cases the minor effects observed were reversible after a recovery period.

FTC was not genotoxic or clastogenic. Long-term carcinogenicity studies in mice and rats showed no evidence of carcinogenic potential at exposures greater than 25 times those observed in humans at the therapeutic dose. FTC did not adversely affect reproduction or embryo-fetal development. It was relatively non-cytotoxic to human cells *in vitro*, including bone marrow progenitor cells, and did not produce mitochondrial toxicity.

The impurities and degradation products in the FTC drug substance have been identified and qualified in toxicology studies.

RPV toxicology summary

Rilpivirine (RPV, TMC278) is an NNRTI active against wild type and NNRTI-resistant HIV-1 that is marketed as a once-daily tablet (Edurant 25 mg) for the treatment of HIV-1 infection and is a component of Complera®/Eviplera® (FTC/RPV/TDF). The following convention is applied throughout this module: reference is made to “TMC278” when the hydrochloride (HCl) salt was administered and to “TMC278 base” when the base was administered. The dose or concentration is always given as base equivalent. The analyte in bioanalytical determinations is referred to as “TMC278.”

All *in vivo* studies were done by oral administration, with the exception of the sensitisation and dermal irritation studies. For oral dosing, TMC278 base was dissolved in polyethylene glycol 400 (PEG400) usually with 100 mg/mL citric acid (CA) to improve exposure, with the exception of the rabbit studies in which TMC278 base was suspended in 0.5% (m/v; mass per volume) aqueous hydroxypropyl methylcellulose (HPMC). TMC278 was suspended in 0.5% (m/v) aqueous HPMC in the mouse, rat, and dog studies. In studies in cynomolgus monkeys, the vehicle was 1% (m/v) aqueous HPMC with 0.5% v/v Tween 20.

No formal single-dose studies were conducted and single dose evaluations were part of the initial dose range finding studies or, in the case of mice, part of the bone marrow micronucleus test. The single-dose toxicity of TMC278 in mice, rats, and dogs appeared to be low. The maximal feasible dose did not induce significant toxicity or effects.

Repeat-dose toxicity studies were done in mice as preparation for a 3-month dose range finding carcinogenicity study; in rats for up to 6 months; in non-pregnant rabbits for 5 days as preparation for the dose range finding early embryonic development studies; in dogs up to 12 months; and in immature female cynomolgus monkeys up to 8 weeks as part of the assessment of the effects of TMC278 on juvenile animals. Juvenile rats were used in a 2-week oral dosing study starting on lactation Day 12 (LD 12). The dogs in studies up to 1-month duration are also considered immature. Since the animals were 6.5 to 8 months old at the start of these studies they were not yet sexually mature at the end of the dosing period. Reversibility (after a 1-month recovery period) of the effects of TMC278 on the high dose group was investigated in the 6-month rat study and the 1-month dog study.

The targets of toxicity of TMC278 identified in the repeat-dose studies were: red blood cells (RBCs; mouse, rat, and dog); coagulation (rat); liver (rat and dog); kidneys (mouse and dog); thyroid gland with secondary effects on the pituitary gland (rat); adrenal glands (mouse, rat, dog, and cynomolgus monkey); testes (dog); and ovaries (dog, in immature females with secondary effects on other tissues of the genital tract and on mammary glands). The majority of the induced effects appeared to be completely reversible after a 1-month dose-free period. The effects on thyroid gland and coagulation in rats and on liver and serum alkaline phosphatase (ALP) in dogs showed signs of recovery, but this was not complete at the end of the 1-month

recovery period. A number of targets were affected at the low dose tested in dogs and cynomolgus monkeys preventing establishment of no observed adverse effect levels (NOAELs) in these two species.

TMC278 did not show a potential for genotoxicity in the *in vitro* bacterial reverse mutation (Ames) tests, mouse lymphoma assays or in the *in vivo* mouse bone marrow micronucleus test. No potential for carcinogenicity was concluded in the 2-year studies in mice and rats. The hepatocellular adenomas and carcinomas seen in mice are considered to be induced by liver enzyme induction, an epigenetic mechanism. Similarly, the hepatocellular adenomas and thyroid follicular cell adenomas and carcinomas in rats were also considered to derive as result of liver enzyme induction and a likely associated increased clearance of thyroid hormones leading to a continuous stimulation of the thyroid gland by thyroid stimulating hormone (TSH). No neoplastic lesions associated with the other targets of TMC278 were detected.

TMC278 did not show a teratogenic potential and did not affect fertility, fecundity, early embryonic development, maternal behaviour at parturition and during lactation, or peri- and postnatal development of offspring from dams (rats) treated with TMC278.

Overall, TMC278 had a similar toxicological profile in juvenile or sexually immature rats, dogs, and cynomolgus monkeys as in adult animals. The TMC278-related effects on the female genital tract and mammary glands in dogs at the end of the 1-month studies differed from the effects in longer duration studies in which animals were sexually mature animals at the end of the dosing period. The activation of ovaries in dogs treated with TMC278 in the 1-month studies led to secondary activation noticed in the other parts of the genital tract and mammary glands. These secondary effects occur normally in sexually mature animals during oestrous cycle. Therefore, they were not noted as a difference between TMC278-treated and control animals in longer duration studies. However, in the 1-month study, the control animals were still dormant (i.e., no activation of ovaries and therefore no secondary effects). In the evaluation relative to control animals, the secondary effects were noted. Activation of ovaries was not induced during an 8-week study in immature cynomolgus monkeys at the age of approximately 18 months at the start of the study.

TMC278 tested negative for the potential to cause phototoxicity, skin irritation, and delayed-type hypersensitivity and to induce an immunotoxic effect on the challenge of rats with sheep RBCs. TMC278 was classified as a moderate eye irritant in an *in vitro* test.

The RPV drug substance contains three impurities that were qualified according to ICH Q3A (R2). Two of these, R600682 and R600683, have been evaluated by spiking to the drug substance at a level of 4%. Qualification comprised a bacterial reverse mutation Ames test, a mouse lymphoma assay, and a 1-month oral rat study. The presence of the impurities at 4% did not modify the effects of TMC278 in any of the tests. The third impurity, R289932, is the Z-isomer of TMC278. This isomer was present in all drug substance batches involved in pivotal non-clinical studies at the level of minimally 0.61%. In view of the close structural relationship with TMC278 and the overage between the lowest non-clinical dose (5 mg/kg/day) and the recommended clinical dose of 25 mg once daily, separate qualification of R289932 is not considered relevant. Three further (potential) impurities, T002592, R600646, and R600687, containing structural mutagenic alerts, are present in the drug substance at levels that do not warrant qualification according to ICH Q3A (R2). The mutagenic potentials of the HCl salts of T002592, T002594, and of R600646 and R600687 were tested in an Ames test. Only T002594 showed a mutagenic potential. T002592 is considered a genotoxic impurity. The maximum allowable level of T002592 in a daily dose of 25 mg TMC278 was calculated to be 400 ppm, on the basis of the Threshold of Toxicological Concern (TTC) approach with daily treatment for 1-10 years per ICH M7. The level of T002592 in drug substance and drug product has been controlled at less than 10 ppm.

TAF toxicology summary

Tenofovir alafenamide (TAF) is a prodrug of Tenofovir (TFV). Comprehensive programmes of non-clinical studies have previously been conducted with RPV and FTC in support of marketing authorisations for these medicinal products. As a result, only new data relating to TAF will be discussed in this report, and only brief toxicology summaries have been included below for FTC and RPV.

Tenofovir alafenamide was evaluated in mouse, rat, dog, and non-human primate repeat-dose toxicity studies up to 39 weeks in duration. *In vitro* and *in vivo* genotoxicity studies were conducted. Rat fertility and developmental toxicity studies were conducted, along with developmental and reproductive toxicity studies and a local irritation study in the rabbit. The vehicle for toxicity studies used was 1) 25mM citric acid or 2) 0.5% polysorbate 20, 0.5% carboxymethylcellulose, 0.9% benzyl alcohol or 3) 0.1% (v/v) Tween 20 and 0.1% (v/v) hydroxypropylmethylcellulose (HPMC).

With agreement from the Committee for Medicinal Products for Human Use (CHMP) (EMA/CHMP/SAWP/629722/2012; EMEA/H/SA/2410/1/2012/1), no carcinogenicity studies were conducted due to the lack of TAF exposure in rats and TgRasH2 mice and lower TFV exposure in rats and mice compared to the same studies in which TDF was administered. No peri/postnatal study was conducted based on scientific advice adopted by CHMP (EMA/CHMP/SAWP/ 214541/2013; EMEA/H/SA/2410/1/FU/1/2013/1). As with the carcinogenicity study rationale, there is an inability to measure plasma concentrations of TAF in rats, and TFV exposure after TAF administration was less than that already tested in the TDF peri/postnatal study.

In the development of TAF, 3 forms of the active drug substance were used: GS-7340, synonym for GS-7340 as the free base; GS-7340-02, synonym for GS-7340 as the monofumarate (1:1 molar ratio of free base to fumaric acid), and GS-7340-03, synonym for the hemifumarate (2:1 molar ratio of free base to fumaric acid). The hemifumarate, GS-7340-03 (TAF fumarate) is the selected for final development. It is stated that GS-7340-03 is considered comparable to GS-7340-02 based on physical/chemical properties and both exist as the free base in blood and biological fluids.

Repeat-dose toxicity studies used GS-7340-02. However, the applicant states that any potential effects of the hemifumarate have been evaluated by studies of the monofumarate. The hemifumarate, GS-7340-03 was used in the male and female fertility study, dermal and ocular irritation studies, the local lymph node assay, and a second impurity qualification study.

1 µM TFV (GS-1278) = 0.287 µg/mL

1 ng/mL TFV = 3.48 nM

1 µM TAF (GS-7340) = 0.477 µg/mL

1 ng/mL TAF = 2.10 nM

GS-7340 Equivalents		
mg GS-7340 as the free base (GS-7340)	mg GS-7340 as the hemifumarate (GS-7340-03)	mg GS-7340 as the monofumarate (GS-7340-02)
0.8	0.9	1
4	4.5	5
8	9	10
12	13	15
16	18	20
20	22	25
24	27	30
32	36	40
36	39	45
40	45	50
60	66	75
80	90	100
240	270	300
400	450	500
800	900	1000

The FTC/RPV/TAF FDC contains the same dose of FTC (200 mg) that is currently approved within Emtriva®, FTC/TDF (Truvada®), FTC/efavirenz/TDF (Atripla®), FTC/RPV/TDF (Complera®/Eviplera®) and elvitegravir/cobicistat/FTC/TDF (Stribild®) and the same dose of RPV (25 mg) currently approved within Edurant® and Complera®/Eviplera®. Comprehensive programs of non-clinical toxicology studies with FTC, RPV, and TAF have been completed. Based on the well-characterized toxicity profiles of FTC, RPV and TAF, the low potential for toxicologic interaction noted in the combination toxicology studies with FTC/TDF and the clinical safety data for TVD (Truvada), and other FTC/TDF-containing regimens including FTC/RPV/TDF, the available data demonstrate an acceptable benefit/risk profile for the proposed use of the FTC/RPV/TAF FDC product. In accordance with the CHMP Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005, January 2008), non-clinical safety studies with the FTC/RPV /TAF combination were therefore not conducted.

Single dose toxicity

In male and female Sprague-Dawley rats (5/sex/group) given an oral dose (15 mL/kg) of TAF at 100, 300, or 1000 mg/kg (80, 240, 800 mg/kg free base equivalents [f.b.e.]/kg) followed by a 14-day observation period (study number: R990185) the NOAEL was considered to be 1000 mg/kg.

Male and female beagle dogs (1/sex/group) were given a single oral dose (15 mL/kg) of 30, 90, or 270 mg/kg (24, 72, 216 mg f.b.e./kg) TAF followed by a 14-day observation period (Study number: D990181). In-life observations of salivation, vomiting, reduced activity, tremors, incoordination seen at 270 mg/kg which resolved 2 days following dosing. There was an increase in blood urea nitrogen at 270 mg/kg (present on study Day 2, not study Day 14. Thymus weights were reduced at all doses compared with controls, and thymic atrophy was present in males at 90 and 270 mg/kg. Renal tubular changes characterised by basophilia and/or karyomegaly were present in the male at 270 mg/kg and females at 270 mg/kg and 90 mg/kg. The NOAEL as considered to be 30 mg/kg.

Repeat dose toxicity
Mouse

A two week mouse study was conducted. However, the results were not interpretable due to a large number of confirmed gavage errors and the viscosity of the formulation. These data will not be discussed further.

13-Week GLP Oral Mouse Toxicity Study (study number TX-120-2007)

Crl:CD1(ICR) mice (15/sex/group) were given 10, 30 or 100 mg/kg/day (8, 24, 80 mg f.b.e./kg/day). The vehicle used was 0.1% (v/v) Tween 20 and 0.1% (v/v) hydroxypropylmethylcellulose (HPMC). Reduced body weight gain was seen at 100 mg/kg/day in males and at all doses in females. Reduced food consumption was noted at 30 and 100 mg/kg/day. In the nasal turbinates, an increased incidence and severity of minimal to slight infiltrates of neutrophils in respiratory and olfactory mucosa, and minimal to moderate (100 mg/kg/day only) degeneration of olfactory epithelium was seen in both sexes at all doses. In addition, adverse findings were noted in the nasal turbinates (exudate in the lumen) of both sexes at 30 mg/kg/day and 100 mg/kg/day. Minimal infiltrates and minimal olfactory degeneration were observed at a lower incidence in control animals. Minimal increased apoptosis of the rectum was seen in males and females at 100 mg/kg/day. No NOAEL could be determined. Due to limited concentration data for TAF, AUC values could not be calculated. At week 13, the TFV AUCtau (combined sexes) was 0.213 µg·h/mL at 10 mg/kg/day.

Rat

4-Week Oral Rat Toxicity Study (Study number R990182)

Daily oral administration of GS-7340-02 (15 mL/kg) at 1.5, 6.25, 25, 100, and 400 mg/kg/day (1.2, 5, 20, 80, 320 mg free base equivalents (f.b.e.)/kg/day) to SD rats (10/sex/group) for 28 days resulted in decreased body weight gain, reduced food consumption, decreases in white blood cell (WBC) and RBC parameters, calciuria, decreased bone mineral density (BMD), decreased 1,25 dihydroxy vitamin D3, renal karyomegaly, thymic atrophy, and atrophy of cancellous bone of the femur. Most effects were seen at 400 mg/kg/day group; however, some changes were noted at 25 mg/kg/day with a non-significant decrease in 1,25 dihydroxy vitamin D3 observed at 6.25 mg/kg/day. Based on changes in WBCs, the NOAEL was considered to be 6.25 mg/kg/day (no change in WBC count was observed at doses up to 100 mg/kg/day in the subsequent 26-week rat toxicity study – see below).

26-Week Oral Rat Toxicity Study (Study number TOX-120-001).

Daily oral administration of TAF (GS-7340-02) at 5, 25, and 100 mg/kg/day (4, 20, 80 mg f.b.e./kg/day) to SD rats (15/sex/group) for 26 weeks resulted in minimal renal cortical tubular karyomegaly (100 mg/kg/day) and minimal to slight tibial cancellous bone atrophy (females, 100 mg/kg/day), changes in bone density measurements (100 mg/kg/day) and changes in biochemical markers of bone turnover (25 and 100 mg/kg/day) were also noted. These effects were not observed at 5 mg/kg/day. TAF (GS-7340-02) dose-dependently increase biochemical markers of bone turnover in males and dose-independently decrease serum 1,25-dihydroxy- and 25-hydroxyvitamin D3 in both sexes at 25 and 100 mg/kg/day. It is stated that as the effects (increases in biochemical markers of bone turnover and changes in related hormones) seen at 25 mg/kg/day were minimal, the NOAEL was considered to be 25 mg/kg/day.

Toxicokinetic analysis of plasma samples showed that TAF was rapidly absorbed after oral dosing and was rapidly converted to TFV. No consistent differences in plasma pharmacokinetics were found between the sexes. Tenofovir was eliminated from the plasma with half-lives ranging from 7 to 13 hours. Mean TFV C_{max} and AUC values for combined sex groups increased dose proportionally over the dose range of 5 mg/kg/day to 100 mg/kg/day at each study period.

Rabbits (Study number TX-120-2003)

Daily oral administration of TAF (GS-7340-02) at 20, 50 and 75 mg/kg/day to female rabbits, for 7 days, was generally well tolerated. Plasma exposure to TAF and TFV generally increased with increase in dose level from 20 to 75 mg/kg/day. Values for mean C_{max} and AUC_{0-t} of TFV were generally higher on Day 7 than on Day 1. TAF was rapidly and extensively converted to TFV. The mean TAF AUC_{0-t} on day 7 was not calculated at 20 mg/kg/day (due to values below the lower limit of quantitation of 1.00 ng/mL) and was 0.252 and 1.174 µg·hr/mL at 50 and 75 mg/kg/day, respectively. The mean TFV AUC_{0-t} on day 7 was 2.256, 5.741 and 10.070 µg·hr/mL at 20, 50, and 75 mg/kg/day, respectively.

Dog

4-Week Oral Toxicity Study (Study number: D990175)

Daily oral administration of TAF (GS-7340-02) at 0.1, 0.3, 1, 3, or 10 mg/kg/day (0.08, 0.24, 0.8, 2.4, 8 mg f.b.e./kg/day) (Study number D990175) to male and female beagle dogs (4/sex/group) for 28 days resulted in increased AST in females at 10 mg/kg/day and renal tubular karyomegaly and/or basophilia in both sexes at 10 mg/kg/day and 1 male and 1 female at 3 mg/kg/day. Mean values for bone specific alkaline phosphatase, N telopeptide, parathyroid hormone, 1,25 dihydroxyvitamin D and 25 hydroxy-vitamin D were generally similar across all groups. There were no effects on peripheral quantitative computed tomography-derived bone densitometry parameters (eg, bone mineral content and bone mineral density of the total slice and trabecular and cortical/subcortical compartments). The NOAEL was considered to be 1 mg/kg/day.

At the lower doses, only C_{max} and T_{max} values for TAF were determined as most values were below the lower limit of quantitation of the assay. TAF was rapidly absorbed on Day 1, with median peak values within 0.25 to 0.5 hours of 18.5, 38.7, and 0.582 µg/mL at 1.0, 3.0, and 10 mg/kg/day, respectively. Peak TFV concentrations occurred within 1 hour. At 10 mg/kg/day, Day 28 TFV C_{max} and AUC_{tau} were 0.44 µg/mL and 5.26 µg·h/mL, respectively (males and females combined). Comparisons between Day 1 and Day 28 at 10 mg/kg/day showed potential accumulation upon repeat dosing. Tenofovir in PBMCs was measurable (18.6 µg/mL) after 28 days of 10 mg/kg/day TAF.

39-Week Oral Toxicity Study with a 3 month recovery period (Study number: TOX-120-002).

Male and female beagle dogs were administered daily oral doses (10 mL/kg) of TAF (GS-7340-02) at 2, 6, or 18/12 mg/kg/day (1.6, 4.8, 14.4/9.6 mg f.b.e./kg/day) for 13 weeks (2/sex/group) or 39 weeks (4/sex/group). A dose-related decrease in body weight gain at 39 weeks was seen in all males at all doses and for females at 18/12 mg/kg/day. The dose for the high dose group was reduced from 18 to 12 mg/kg/day on Days 45 and 51, for males and females, respectively, due to the occurrence of severe clinical signs and reduced body weight.

There were two unscheduled deaths (2 males at 18 mg/kg). One of these was considered to be due to a gavage accident. A different male at 18 mg/kg was killed on Day 45 due to deteriorating clinical condition, which was considered to be treatment related. Prior to necropsy, this animal had shown reduced body weight, reduced food consumption, increased AST, globulin levels, triglyceride, cholesterol, total bilirubin, and decreased monocyte and platelet counts. Macroscopically, there was bilateral enlargement of the submandibular lymph nodes, which histologically had slight inflammation and plasmacytosis. Histopathology consisted of mild, mononuclear infiltrate in the ocular posterior uvea; renal cortical tubular degeneration; atrophy of GALT, mesenteric lymph node, and thymus accompanied by an infiltrate of macrophages; mucosal

atrophy of the fundic gland; mucosal hyperplasia of the pyloric gland; and mucosal degeneration and/or regeneration in the cecum and colon.

Increased mean AST (~2.6x compared to control) and total bilirubin (~1.6x compared to control) in dogs administered 18/12 mg/kg/day. No ECG changes occurred at 2 mg/kg/day. At Week 39, a dose-related prolongation of PR interval was observed at 6 (~ +13%) and 18/12-mg/kg/day (~ +24%) groups. TAF reduce heart rate with an associated QT interval prolongation was seen at 18/12 mg/kg/day. According to the Applicant, these changes were associated with decreases in serum triiodothyronine (T3). After the 13-week recovery period, serum T3 values returned to levels similar to the controls.

The applicant states that all bone markers showed age-related decreases. After 3 months, there were some differences noted among mean values for bone formation (skeletal alkaline phosphatase [sALP]) and bone resorption markers (urinary free deoxypyridinoline and N telopeptide) at all doses compared to controls. After 9 months, statistically significant increases in mean values for the bone resorption marker urinary N telopeptide were noted for both sexes at 18/12 mg/kg/day ($p \leq 0.05$), compared to controls. A similar though not statistically significant trend was noted in animals at 6 mg/kg/day, suggesting a dose-related response. No significant changes in free deoxypyridinoline were observed, with no consistent effects (increases) among treated groups. For the formation marker, serum sALP values at all doses were comparable controls except for one male at 18/12 mg/kg/day, which was outside the control ranges (no further details are provided in the non-clinical toxicology summary). At the end of the recovery period, bone marker values returned to below the control range consistent with an age effect and recovery from treatment.

At 18/12 mg/kg/day administered once daily to young beagle dogs for 39 weeks changes in bone densitometry parameters (by dual-energy x-ray absorptiometry [DXA] analysis) considered to reflect primarily effects on bone growth were observed. These changes were considered by the Applicant as secondary to the effects on body weight.

Histopathology changes were noted in the kidneys, eyes, lungs, and spleen after both 13 and 39 weeks. The liver and possibly the adrenal glands were additional target organs identified after 39 weeks. After 13-weeks of treatment, findings of renal cortical tubular degeneration/regeneration and karyomegaly were seen at 6 or 18/12 mg/kg/day; findings after 39 weeks of treatment were similar. These changes were minimal to slight (Grade 1 to 2) at 6 mg/kg/day in both sexes. At 18/12 mg/kg/day severity ranged from mild to moderate (Grade 2 to 3). After 39-weeks of treatment, similar lesions (minimal (Grade 1) karyomegaly and tubular degeneration) were seen in 2 males at 2 mg/kg/day.

A minimal to slight (Grade 1 to 2) infiltration of mononuclear cells in the ocular posterior uvea was noted in some animals at 18/12 mg/kg/day after both treatment periods. Alveolar histiocytosis was present in the lungs after 13-weeks at 18/12 mg/kg/day. Additional pulmonary findings noted following 39-weeks of treatment and consisted of macrophage accumulation with pigment, which was detected predominantly at 18/12 mg/kg/day and in few animals at 6 or 2 mg/kg/day. An infiltration of macrophages laden with pigment was very frequently seen in the splenic white pulp at 18/12 mg/kg/day after both treatment periods. After 39 weeks of treatment, centrilobular hepatocellular cytoplasmic acidophilic inclusions were seen at 18/12 mg/kg/day, pigment deposits in hepatic macrophages and/or sinusoidal cells (Kupffer cells) was seen at 18/12 mg/kg/day. Also, similar pigment deposits in the sinusoidal cells (tissue macrophages) of the adrenal glands were seen in a few animals at 18/12 mg/kg/day. The Applicant states that the cause of the intracellular pigment in tissue macrophages in the lung, liver, spleen, and adrenal is not known, but could represent accumulation of the test article and/or test article metabolite(s) in these cells of the mononuclear phagocyte system. After the 13-week recovery period, test article-related histological changes were still present in the kidneys, lungs, and liver, but were however reduced in incidence and severity.

At 18/12 mg/kg/day, a minimal infiltration of histiocytes was present in some organs (eye [choroid plexus, ciliary body], lung, and spleen) in some animals. In-life ophthalmologic examinations were normal.

The NOAEL after 39 weeks of treatment was considered to be 2 mg/kg/day. Treatment-related findings were completely or partially reversible following a 13-week recovery period.

Toxicokinetic analysis showed that TAF was rapidly absorbed and converted to TFV following oral dose administration, with peak plasma concentrations of TAF and TFV occurring 0.5 and 1 hour after dosing, respectively. The systemic exposure of TAF was dose dependent. Plasma C_{max} and AUC values for GS-7340 increased more than proportionally over the dose range. Plasma C_{max} and AUC, increased roughly in proportion to the administered dose. There was some accumulation of TFV following repeat dosing (approximately 3-fold). There were no gender differences in exposure.

Tenofovir concentrations in PBMCs were measurable at 24 hours after dosing at all doses. The median terminal phase half-life of total TFV in PBMCs was estimated to be 31 hours (similar to the TFV plasma estimate) from the recovery animals with PBMC concentrations measured up to 72 hours. Dose-normalised PBMC mean AUC values of total TFV increased more than dose proportionally during Week 39/40.

Non-human primate

4-Week Oral Rhesus Monkey Toxicity Study (Study number P2000114)

Animals were given TAF (GS-7340-02) at 3 or 30 mg/kg/day (2.4, 24 mg f.b.e./kg/day) or TFV at 15 mg/kg/day. According to the company, there were no adverse in-life effects and no clear test article-related effects on body weight, serum chemistry, plasma chemistry, haematology (including lymphocyte subsets determined by flow cytometry), standard urinalysis parameters, organ weights, and bone-related or histologic parameters. There was 1 death at 30 mg/kg/day TAF, which was not considered test article-related (no further details are provided on the toxicology summary). Kidney, liver and skeletal muscle samples assayed for indicators of mitochondrial integrity showed no effects. The NOAEL for TAF was considered to be 30 mg/kg/day.

The TAF C_{max} values were nonlinear with dose, with greater than expected increases in C_{max} with dose. The TAF AUC_{tau} could only be calculated at 30 mg/kg/day group, with a mean value of 1.03 µg·h/mL and a terminal elimination half-life of 0.335 hours. There were no gender differences in exposure.

Day 28 TFV C_{max} and AUC exhibited slightly greater than proportional increases with increasing dose. Comparison between Days 1 and 28 showed no statistical difference for C_{max} or AUC indicating no change in clearance over time. There were no gender differences in exposure.

Genotoxicity studies

A summary of genotoxicity studies and their results is illustrated in Table 6:

Table 6. Genotoxicity stud y results

Study	Test system	Concentrations/ Concentration range/ Metabolising system	Results
Gene mutations in bacteria – GLP Study number: V990212	TA98, TA100, TA1535, TA1537 & WP2uvrA	100, 333, 1000,3330, 5000 µg/plate +/- S9	Negative
Mouse Lymphoma – GLP Study number: V990213	L5178Y/TK	Up to 5000 µg/mL (4000 µg f.b.e/mL), +/- S9	Negative
Mouse Micronucleus – GLP Study number: M2000113	Male Mouse/CD-1(ICR) BR	500 and 1000 mg/kg (400 and 800 mg f.b.e./kg) & 2000 mg/kg	Negative

TAF was shown to be negative in 2 *in vitro* and one *in vivo* genotoxicity study.

FTC/RPV/TAF combination:

FTC, RPV and TAF are considered non-genotoxic agents. The combination of the three components is therefore not expected to have an altered genotoxicity profile as compared with that of the individual agents.

Carcinogenicity

Based on the scientific advice adopted by the CHMP (EMA/CHMP/SAWP/629722/2012; EMEA/H/SA/2410/1/2012/1), carcinogenicity studies are not required for TAF registration based on the lack of TAF exposure in rats and TgRasH2 mice and lower TFV exposure in rats and mice compared to TDF.

Daily administration of TDF at dose levels of up to 300 mg/kg/day administered for 104 weeks did not reveal any evidence of carcinogenicity in mice. At 600 mg/kg/day, a low incidence of duodenal tumours was observed, possibly related to high local test article concentration in the gastrointestinal tract. This is adequately reflected in section 5.3 of the SmPC. In rats, daily administration of TDF at dose levels up to 300 mg/kg/day did not reveal any evidence of carcinogenicity.

Reproduction Toxicity

Fertility and early embryonic development

Oral Fertility and General Reproduction Toxicity Study of TAF in Sprague-Dawley Rats (Study number TX-120-2012).

Male and female Crl:CD(SD) rats 20, 80, or 160 mg free base equivalent (f.b.e.)/kg/day (22, 90, 180 mg GS-7340-03/kg/day) TFV (GS-7340-03). Males were necropsied after at least 10 weeks of dosing, the reproductive organs were weighed followed by assessment of sperm motility and total concentration. Male and female reproductive performance was evaluated based on results of confirmation of mating and pregnancy. There were some effects on male body weight at 80 and 160 mg/kg/day and female at 160 mg/kg/day throughout the study.

There were no differences in premating oestrous cycles. There were no test article-related differences in male or female reproductive parameters. There were no test article-related effects on the uterine and fetal

parameters and no significant differences in female reproductive organ weights. There was a slight increase in absolute testis weight (significant increase (9%) in the adjusted mean of the left testis only) at 160 mg/kg/day. This was considered by the Applicant to be test article-related, but not adverse, as there were no other reproductive organ weight or functional reproductive effects. There were no test article-related effects observed on mean epididymal sperm motility or on sperm concentration. The NOAEL for male and female toxicity was 80 mg/kg/day. The TAF NOAEL for reproductive and early embryonic toxicity was 160 mg/kg/day.

Embryo-fetal development

Oral Embryo-Fetal Development Study of TAF in Rats (Study number: TX-120-2002)

Four groups of 25 pregnant female Crl:CD(SD) rats were given daily doses of TAF (GS-7340-02), by oral gavage, from gestation day (GD) 6 to 17, inclusive. Targeted dose levels were 0 (vehicle control), 25, 100 and 250 mg/kg/day. Dose formulation analysis showed that each 5 mg/kg/day animal was administered a GS-7340-02 concentration of 3.85 mg/mL instead of 5 mg/mL for 5 to 8 days between GD 10 and 17, providing a daily dose of 19.3 mg/kg/day (77% of targeted dose) on these days. Dose formulation analysis showed that each 20 mg/kg/day animal was administered a GS-7340-02 concentration of 12.9 mg/mL instead of 20 mg/mL for 4 to 7 days between GD 6 and 12, providing a daily dose of 64.6 mg/kg/day (65% of targeted dose) on these days.

At 250 mg/kg/day, a statistically significant decrease in the number of animals noted with incomplete ossification of the interparietal and hyoid bones was noted at 250 mg/kg/day. Other minor skeletal anomalies were comparable in incidence to controls. At this dose group, body weights, body weight gains and food consumption were significantly decreased during the treatment period. On GD 21, the mean body weight of the 250 mg/kg/day group was 10% lower than that of the controls. Mean corrected body weights (body weight on GD 21 minus gravid uterus weight) and mean corrected body weight gains (body weight gain on GD 6 to 21 minus gravid uterus weight) were also lower at 250 mg/kg/day, with the corrected mean body weights also 10% lower than controls on GD 21. Fetal weights (males, females and sexes combined) were decreased dose dependently and remained within the range of historical control data. However, fetal weights at 250 mg/kg/day were at the lower extreme of this range. The incidences of fetal major malformations, minor external, visceral and skeletal anomalies were not affected by TAF. Sternebrae variants (1 to 4 and 5 and 6) were increased at 250 mg/kg/day.

In summary, at 250 mg/kg/day, there was decreased fetal body weight associated with some delays in the rate of ossification. There was no evidence of embryo-lethality or teratogenicity attributed to TAF in this study. The maternal TAF NOAEL and the TAF NOAEL for embryo-fetal development were both considered to be 100 mg/kg/day, which resulted in GD17 AUC_{0-t} values of 17.4 and 0.2 µg·hr/mL for TFV and TAF, respectively.

Plasma concentrations of TAF were all below the lower limit of quantitation at 25 mg/kg/day. Exposure to TAF increased with the increasing dose from 25 to 250 mg/kg/day. Exposure to TFV increased with the increase in TAF dose from 25 to 250 mg/kg/day.

Oral Embryo-Fetal Development Study of TAF in Rabbits (TX-120-2005)

TAF (GS-7430-02) was administered by oral gavage to time-mated F0 generation female rabbits (20 main study females per group and 3 toxicokinetic females per group) at 0 (vehicle control), 10, 30 and 100

mg/kg/day. Lower body weight gains were noted at 100 mg/kg/day for the first week following treatment initiation. Lower food intake was noted at 100 mg/kg/day from GD 8 to 24. Three animals at this dose consumed less than 30 g for at least 4 days during the dosing period. There were no TAF-related macroscopic changes. The number of corpora lutea, implantation sites, live fetuses, dead fetuses, resorptions, the sex ratio and the pre- and post-implantation losses were not affected. There was no effect of TAF on fetal weights. The incidence of major malformations, minor external, visceral, skeletal anomalies and common skeletal variants were not affected by TAF.

Exposure to TAF increased when increasing dose (10 to 100 mg/kg/day). The increases in C_{max} were greater than proportional between 10 to 100 mg/kg/day and the increases in AUC_{0-t} were greater than proportional between 30 to 100 mg/kg/day on GD 20. Exposure to TFV increased with increasing TAF doses from 10 to 100 mg/kg/day. The increases in C_{max} and AUC_{0-t} were roughly proportional between the 10 to 100 mg/kg/day. Accumulation of TFV was observed after multiple dosing.

Concentrations of TFV were higher than concentrations of TAF, indicating that TAF was extensively converted to TFV. The TAF NOAEL for maternal toxicity was 30 mg/kg/day (AUC_{0-t} = 1.1 and 5.0 µg·h/mL for TAF and TFV, respectively) and the TAF NOEL for embryo-fetal development was 100 mg/kg/day (AUC_{0-t} = 11.0 and 27.3 µg·h/mL for TAF and TFV, respectively.

Prenatal and postnatal development, including maternal function

Based on the scientific advice adopted by CHMP(EMA/CHMP/SAWP/214541/2013; EMEA/H/SA/2410/1/FU/1/2013/1), a peri/postnatal study in rats is not required for TAF registration due to the lack of TAF exposure in rats and lower TFV exposure compared to TDF.

In a rat peri-and postnatal reproduction toxicity study conducted with TDF, the maternal NOEL 50 mg/kg/day. Higher doses (150, 450, and 600 mg/kg/day) resulted in adverse clinical observations, reductions in body weight gain during gestation, and increases in body weight gain during lactation; and the 450 and 600 mg/kg/day dosages reduced gestation and lactation feed consumption values. The developmental NOEL for TDF was considered to be 150 mg/kg/day, as higher doses (≥450 mg/kg/day) resulted in increased peri/postpartum pup mortality, reduced pup survival, and reduced pup body weights. The NOEL for general toxicity of TDF in the F1 generation was 50 mg/kg/day, as a result of mortality, reduced body weights and/or food consumption in the 150, 450, and 600 mg/kg/day dose groups. The F1 generation male and female NOEL for behavioural, reproductive, and developmental toxicity of TDF was 150 mg/kg/day due to the effects on sexual maturation that were observed at doses of 450 and/or 600 mg/kg/day.

Local Tolerance

In a bovine corneal opacity and permeability assay (BCOP) TAF (GS-7340-03) elicited an *in vitro* irritancy score of 21.0 ± 8.7 with a 4-hour incubation and was predicted to be a non-corrosive/non-severe eye irritant.

In a dermal irritation study in rabbits animals were given a single 4 hour, semi-occlusive, dermal administration of approximately 0.5 g of TAF (GS-7340-03 and were observed for 4 days (Study number: TX-120-2011). No local dermal reaction was observed in any animal throughout the duration of the study. The Primary Irritation Index was calculated to be 0.0; TAF was classified as a ‘non-irritant’.

2.3.5. Ecotoxicity / environmental risk assessment

Full ERAs have been provided for FTC and RPV. The applicant has also conducted a full ERA for TAF in the overall assessment for the FDC. Using default values for Fpen, the PEC surface water values for FTC, RPV and TAF are all above the action limit of 0.01 µg/L; hence a full (Phase II) assessment was performed. In Phase II, Fpen refinement for the three substances has been made based on sales forecasts.

The studies on transformation in water/sediment systems (OECD 308) show that all three active substances (FTC, RPV and TAF) are very persistent considering the DT50 values in sediment (FTC > 1000 days, RPV > 1000 days, TFV: 303 days at 12°C), water (FTC: 209/81 days at 12°C) and soil (RPV: 213.3 d at 12°C). Furthermore FTC forms persistent transformation products M-3 (RT 2.7 min) and M-6 (RT 3.5 min) in sediment. In compliance with the current OECD 305 guideline, a normalisation of the BCF values to a lipid content of 5% is required to enhance the comparability of results. For RPV, the lipid normalized BCF values are below 2000, and RPV is therefore not expected to bioaccumulate. The overall conclusion of the ERA confirms that the FTC/RPV/TAF combination poses an acceptable risk to the environment.

Emtricitabine

The results of the environment risk assessment of FTC are summarised in the Table 7.

Table 7. Summary of main study results

Substance (INN / Invented Name): Emtricitabine / Odefsey			
CAS-number (if available): 143491-57-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD107	-0.693 – -0.670	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log *K*ow	-0.693 – -0.670	not B
	BCF	Not required	not B
Persistence	DT50 or ready biodegradability	DT50 (dissipation) 36-151 days; DT50 (degradation) > 100 days. No significant metabolites formed	
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, refined	1.2 (F*pen* 0.012)	□g/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	*Kd* sludge =12.9 L.kg-1	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} (dissipation) 36-151 days; DT_{50} (degradation) > 100 days; No significant metabolites formed. % shifting to sediment =>10% AR associated with sediment from Day 7	Sediment toxicity assessment is triggered

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	110	mg.L-1	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	110	mg.L-1	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	6.10	mg.L-1	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	≥ 1000	mg.L-1	Sewage microorgnisms
Phase IIb studies					
Sediment dwelling organism	OECD 218	NOEC	38	mg/kgd wt	*Chironomus riparius* normalised for 10% OC 200 mg.kgdwt -1)

Tenofovir alafenamide

The results of the environment risk assessment of TAF are summarised in the Table 8.

Table 8. Summary of main study results

Substance (INN/Invented Name): Tenofovir alafenamide (as environmentally relevant TFV) / Odefsey			
CAS-number (if available): 1392275-56-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD107	-3.8 – -4.3	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log *K*ow	-3.8 – -4.3	not B
	BCF	Not required	not B
Persistence	DT50 or ready biodegradability	DT50 (degradation) 10.4-32.7 days; Water DT50 (dissipation) 2.0-3.5 days Three significant metabolites formed	P
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, refined	0.07 µg/L (F*pen* 0.012)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc ads soil 351 - 1091 L.kg-1 Koc des soil 968 - 2791 L.kg-1 KF ads sludge 6.0 - 21 L.kg-1 KF des sludge 16 - 62 L.kg-1	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 (degradation) 10.4-32.7 days; Water DT50 (dissipation) 2.0-3.5 days; Three significant metabolites formed. >10% AR associated with sediment from Day 7	Sediment toxicity assessment is triggered

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	32	mg.L-1	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	mg.L-1	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	≥10	mg.L-1	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg.L-1	Sewage microorganisms
Phase II b studies					
Sediment dwelling organism	OECD 219	NOEC	290	mg/kg dwt	*Chironomous riparius* normalised for 10% OC 17.06 mg.kgdwt-1

Rilpivirine

The results of the environment risk assessment of RPV are summarised in the Table 9.

Table 9. Summary of main study results

Substance (INN/Invented Name): RPV/ Odefsey					
CAS-number (if available): 500287-72-9					
PBT screening		**Result**			**Conclusion**
Bioaccumulation potential- log K_{ow} (D_{ow})	OECD 123	log K_{ow} 4.66			Potential PBT
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log D_{ow}				
	BCF	$BCF_{low\ dose}$ = 122.8 – 159.5 $BCF_{high\ dose}$ = 113 - 135			
Persistence	DT_{50} or ready biodegradability	DT_{50} = 321 days			
Toxicity	NOEC or CMR	$NOEC_{fish}$ = 20 µg/L			
PBT-statement :	RPV is persistent into the environment				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0015 µg/L (refined on the basis of sales forecasts)	µg/L			< 0.01 threshold
Other concerns (e.g. chemical class)					
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{OC,ads}$ soil =34179 – 89476 $L.kg^{-1}$ $K_{OC,des}$ soil =45816 – 166761 $L.kg^{-1}$ $K_{d,ads}$ sludge =5502 - 7207 $L.kg^{-1}$ $K_{d,des}$ sludge =8560 – 8665 $L.kg^{-1}$			
Ready Biodegradability Test	OECD 301	Not available			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	>10% AR associated with sediment from Day 7 $DT_{50,\ System}$ (deg.) = 307 – 321 days $DT_{50,\ Water}$(dis.) = 1.2 – 1.3 days			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC (72 h)	≥22 $µg.L^{-1}$	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC (21 day; repr.)	≥32 $µg.L^{-1}$	mg/L	

Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	≥20 µg.L^{-1}	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC (3 h; respiration) EC_{20}, EC_{50}	≥1000 mg.L^{-1} not calculated	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	$BCF_{low\ dose}$ $BCF_{high\ dose}$	137.2 □5.8 125.6 □6.(		
Aerobic and anaerobic transformation in soil	OECD 307	DT_{50}	DT_{50} 135 - 198 days (normalised to 12 °C)		
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	≥100 mg.kg^{-1}	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	≥1000 mg.kg^{-1}	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	≥1000 mg.kg^{-1}	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	≥1000 mg.kg^{-1}	mg/kg	
Sediment dwelling organism	OECD 218	NOEC	≥100 mg.kg^{-1}	mg/kg	

2.3.6. Discussion on non-clinical aspects

The toxicology profiles of FTC and RPV have already been well-characterised previously.

Prolonged PR intervals (approximately 13% to 24%) with associated QT interval prolongation were noted in the 39 week dog study with TAF. No PR prolongation or any change in ECG results occurred in the safety pharmacology study that evaluated a TAF dose up to 100 mg/kg or in the clinical TQT study.

At 18/12 mg/kg/day in dogs (39 week dog study), a minimal infiltration of histiocytes was present in some organs (eye [choroid plexus, ciliary body], lung, and spleen). The posterior uveitis seen at 18/12 mg/kg/day occurred at 3.7- and 17-fold higher exposure to TAF and TFV, respectively, than that observed in human subjects administered a 25-mg dose of TAF. In-life ophthalmologic examinations were normal in this study. There were no test article-related effects on ophthalmic exams or microscopic exams of ocular tissue observed in repeat-dose toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), non-human primates (4 weeks) or in the 4-week dog toxicology study. It is unlikely that these findings would translate into a concern regarding the ocular safety of TAF and were probably due to the poor condition of these animals during the in-life phase of the study. However, there was one adolescent with uveitis considered to be drug-related by the investigator. A brief description of these ocular findings is included in section 5.3 of the SmPC.

Adverse degenerative (olfactory) and acute inflammatory (infiltrate neutrophil) changes in the nasal mucosa were noted in mice given TAF for 13 weeks. Given that these findings were not seen any other species or rats for longer durations of administration, it can be agreed that these findings probably do not pose a clinical risk.

In the rat fertility and reproductive toxicology study, an increase in absolute testis weight was seen at 160 mg/kg/day. This was considered by the applicant to be test article-related but not adverse as there were no effects on other reproductive organ weights or reproduction. Sternebrae variants were increased at 250 mg/kg/day in the rat embryo-fetal development study (the NOEL was considered to be 100 mg/kg/day [84

mg/kg/day achieved]). There were no effects seen the embryo-fetal development study in rabbits. Given no that peri/postnatal study was conducted with TAF, the product literature should contain the reproductive findings seen with TDF (i.e. reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses) or this omission otherwise justified using relative exposures of TFV and TFV-DP after TAF exposure.

Overall, TAF showed a similar toxicity profile as tenofovir disoproxil fumarate (TDF). The kidney and bone findings seen in the rat and dog toxicology are known toxicities of TFV.

The combination of FTC, RPV and TAF is not anticipated to exacerbate known toxicities or lead to new toxicities. Comprehensive non-clinical safety databases on these drugs, including combination toxicity studies with FTC and TDF, strongly indicate that further toxicological investigations are unlikely to yield new data relevant to humans. Further studies of longer duration with the combination are not warranted because of the lack of significant overlapping toxicities, and the use of additional animals that would be required to obtain such information.

Concerns raised on the ERA have been adequately addressed by the applicant, and the overall conclusion of the ERA confirms that the FTC/RPV/TAF combination poses an acceptable risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

No major concerns have been identified from the nonclinical data. The initial concerns relating the ERA have been adequately addressed.

2.4. Clinical aspects

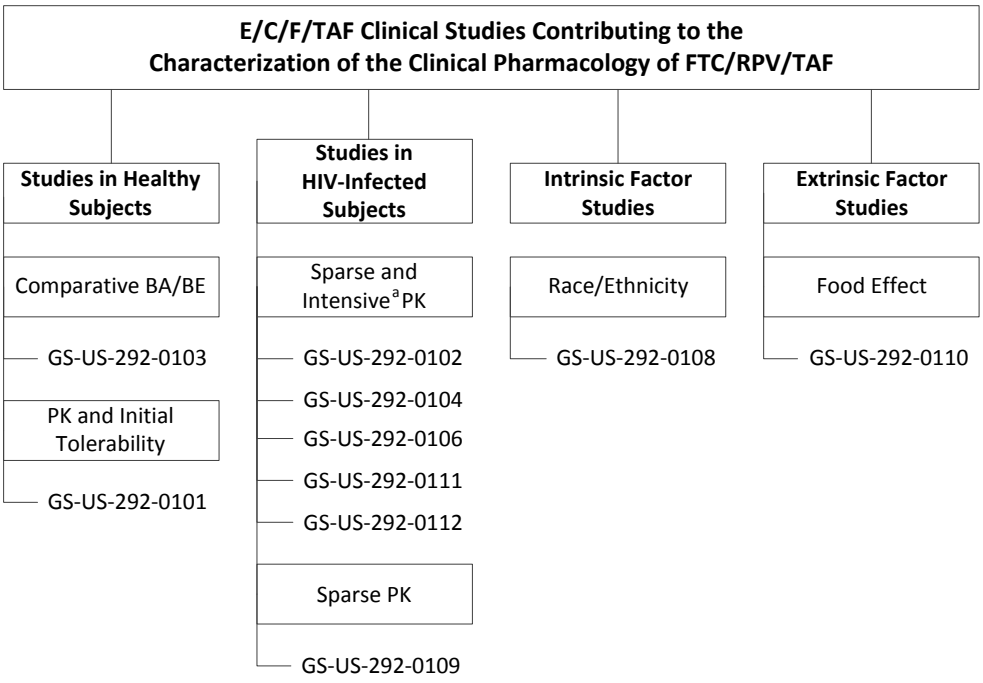
2.4.1. Introduction

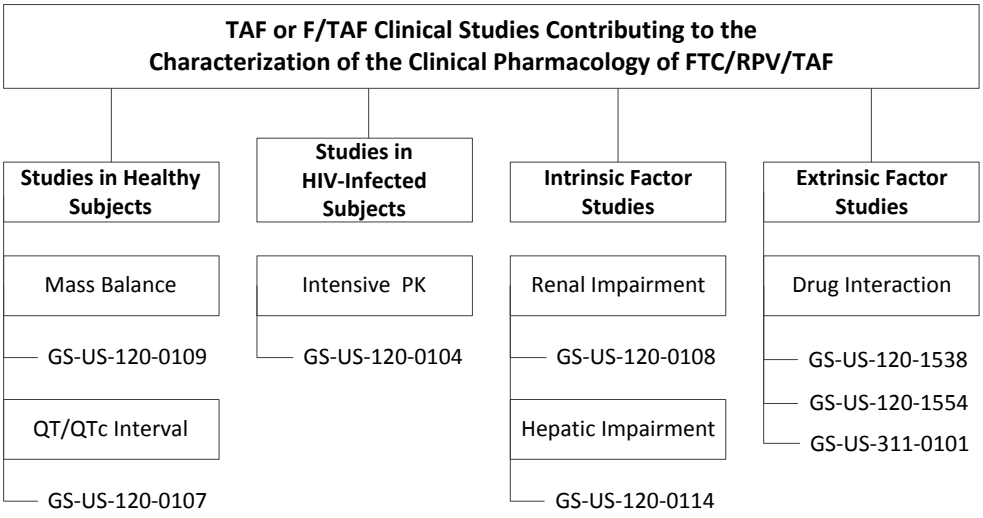
The F/R/TAF tablet provides a single tablet regimen (STR) for treatment of HIV infection. All doses reported below refer to the TAF content of the various formulations (and not the equivalent dose of the hemifumarate). The commercial F/R/TAF FDC film-coated tablets were used in the pivotal bioequivalence study and the other two new Phase 1 studies.

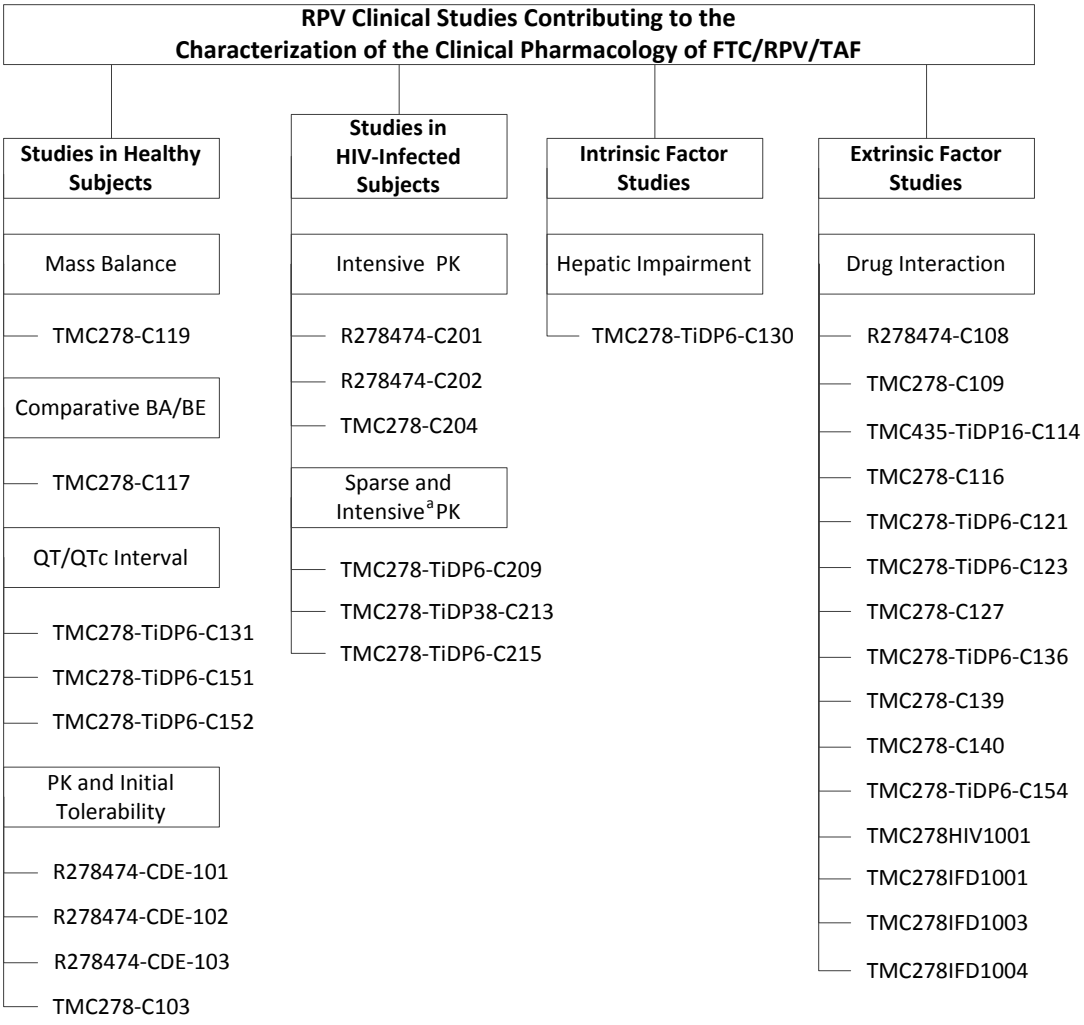
Overview of studies

Study	Study Description	Test Treatment(s)		Reference Treatment(s)
		Dose/Formulation	n	
GS-US-366-1159	Phase 1 study to evaluate the BE between the FTC/RPV/TAF and E/C/F/TAF FDCs and between the FTC/RPV/TAF FDC and the 25-mg RPV tablet (Edurant) in healthy subjects	**FTC/RPV/TAF** 200/25/25-mg tablet	95	**RPV** 25-mg tablet **E/C/F/TAF** 150/150/200/10-mg tablet
GS-US-366-1651	Phase 1 study to evaluate the effect of food on TAF, RPV, and FTC exposure following administration of FTC/RPV/TAF in healthy subjects	**FTC/RPV/TAF** 200/25/25-mg tablet	60	Not applicable

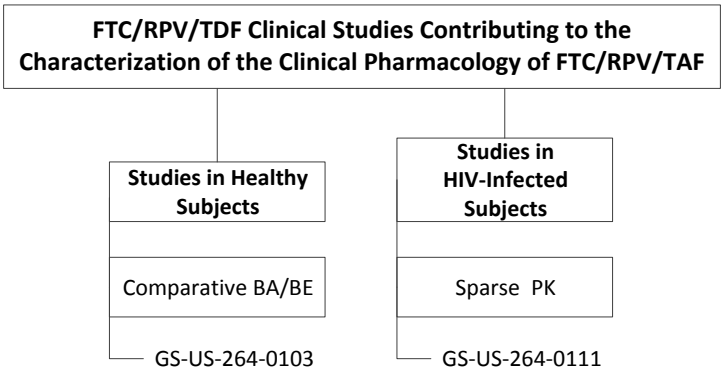
Study	Study Description	Test Treatment(s)		Reference Treatment(s)
		Dose/Formulation	n	
GS-US-366-1689	Phase 1 study to evaluate the DDI potential between the FTC/RPV/TAF and LDV/SOF FDCs in healthy subjects	**FTC/RPV/TAF** 200/25/25-mg tablet + **LDV/SOF** 90/400-mg tablet	42	**FTC/RPV/TAF** 200/25/25-mg tablet **LDV/SOF** 90/400-mg tablet
GS-US-120-1554	Phase 1 study to evaluate the DDI potential between RPV and TAF in healthy subjects	**TAF** 25-mg tablet (CM1306B2) **RPV** 25-mg tablet **TAF** 25-mg tablet (CM1306B2) + **RPV** 25-mg tablet	34	


E/C/F/TAF Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of FTC/RPV/TAF
Studies in Healthy Subjects
Comparative BA/BE
GS-US-292-0103
PK and Initial Tolerability
GS-US-292-0101
Studies in HIV-Infected Subjects
Sparse and Intensive[a] PK
GS-US-292-0102
GS-US-292-0104
GS-US-292-0106
GS-US-292-0111
GS-US-292-0112
Sparse PK
GS-US-292-0109
Intrinsic Factor Studies
Race/Ethnicity
GS-US-292-0108
Extrinsic Factor Studies
Food Effect
GS-US-292-0110


TAF or F/TAF Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of FTC/RPV/TAF
Studies in Healthy Subjects
Mass Balance
GS-US-120-0109
QT/QTc Interval
GS-US-120-0107
Studies in HIV-Infected Subjects
Intensive PK
GS-US-120-0104
Intrinsic Factor Studies
Renal Impairment
GS-US-120-0108
Hepatic Impairment
GS-US-120-0114
Extrinsic Factor Studies
Drug Interaction
GS-US-120-1538
GS-US-120-1554
GS-US-311-0101



An additional DDI study with carbamazepine (GS-US-311-1387) was submitted during the evaluation.



GS-US-264-0103	Phase 1 study to evaluate the BE between the FTC/RPV/TDF FDC and the 25-mg RPV tablet (Edurant) in healthy subjects	**FTC/RPV/TDF Formulation 3** 200/25/300-mg tablet **FTC/RPV/TDF Formulation 4** 200/25/300-mg tablet	35	**FTC** 200-mg capsule **RPV** 25-mg tablet **TDF** 300-mg tablet
GS-US-264-	Phase 2b study to evaluate	**FTC/RPV/TDF**	49	Not applicable

0111	the efficacy and safety of FTC/RPV/TDF after switching from EFV/FTC/TDF in virologically suppressed, HIV-infected subjects	200/25/300-mg tablet		

In addition, the following studies were submitted including the study in adolescents from which additional follow-up information was provided during the evaluation:

HIV-Infected, ART-Naive, Adolescent Subjects			
GS-US-292-0106	Phase 2/3, open-label	E/C/F/TAF FDC (N = 48) PK sub-study: N = 24	Week 48 efficacy, PK, and safety

C213 (PAINT)	Phase 2 PK, safety, and efficacy in ART-naive, HIV-infected adolescents	25 mg commercially available RPV tablet	Background regimen of AZT, ABC or TDF in combination with 3TC or FTC

TAF fumarate (GS-7340-03; the hemifumarate form) was selected for further clinical development from early in-vitro and in-vivo studies.

GCP

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

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

2.4.2. Pharmacokinetics

Absolute bioavailability

- Absolute bioavailability has not been determined for TAF but the applicant estimates that this is ~ 40% in the absence of P-gp inhibition or induction.
- FTC-110 demonstrated that the absolute bioavailability of FTC is 93%.
- The absolute bioavailability of RPV has not been documented.

Effect of a P-gp inhibitor on TAF and TFV concentrations

GS-US-292-0101 was an open-label crossover study that compared two formulations of E/C/F/TAF each containing 25 or 40 mg TAF monofumarate with Stribild (STB) and **TAF 25 mg alone**. Dosing was for 12 days with 2-day washouts and after a meal of 550-650 kcal and 25-30% fat.

Following administration of E/C/F/TAF 25 mg vs. TAF 25 mg administered alone the TAF AUC_{last} and Cmax were ~2.2 and 2.3-fold higher, respectively, while TFV AUC_{tau} and Cmax were ~3.1 and 3.7-fold higher, respectively. Mean TFV exposures (AUC_{tau} and Cmax) following TAF alone were ~90% lower compared with those achieved after STB. For FTC there was bioequivalence between the E/C/F/TAF formulations and STB.

GS-7340 PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Cohort 1				
EVG/COBI/FTC/GS-7340 Formulation 1 (25 mg) (Test) vs. GS-7340 (25 mg) (Reference)	N=19	N=19		
AUC_{last} (ng•h/mL)	552.1 (40.5)	242.4 (42.4)	221.78	199.99, 245.95
C_{max} (ng/mL)	506.9 (54.2)	215.4 (55.0)	222.62	187.11, 264.87
Cohort 2				
EVG/COBI/FTC/GS-7340 Formulation 2 (25 mg) (Test) vs. GS-7340 (25 mg) (Reference)	N=18	N=18		
AUC_{last} (ng•h/mL)	558.7 (28.6)	244.9 (34.0)	230.93	205.52, 259.50
C_{max} (ng/mL)	472.4 (57.4)	210.8 (43.7)	223.01	188.40, 263.97

TFV PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Cohort 1				
TFV, EVG/COBI/FTC/GS-7340 Formulation 1 (25 mg) (Test) vs. EVG/COBI/FTC/TDF (Reference)	N=19	N=19		
AUC_{tau} (ng•h/mL)	834.9 (17.6)	3737.3 (22.3)	22.62	21.39, 23.91
C_{max} (ng/mL)	65.9 (50.9)	444.7 (28.9)	14.02	12.20, 16.11
C_{tau} (ng/mL)	28.1 (20.3)	73.2 (25.1)	38.93	36.54, 41.47
EVG/COBI/FTC/GS-7340 Formulation 1 (25 mg) (Test) vs. GS-7340 (25 mg) (Reference)	N=19	N=19		
AUC_{tau} (ng•h/mL)	834.9 (17.6)	273.4 (23.5)	306.92	290.34, 324.45
C_{max} (ng/mL)	65.9 (50.9)	16.3 (24.8)	367.68	319.98, 422.50
C_{tau} (ng/mL)	28.1 (20.3)	9.4 (25.9)	301.52	283.03, 321.22
Cohort 2				
TFV, EVG/COBI/FTC/GS-7340 Formulation 2 (25 mg) (Test) vs. EVG/COBI/FTC/TDF (Reference)	N=18	N=18		
AUC_{tau} (ng•h/mL)	897.8 (12.7)	4089.6 (21.7)	22.47	21.11, 23.91
C_{max} (ng/mL)	71.9 (57.3)	505.3 (27.1)	13.54	11.62, 15.77
C_{tau} (ng/mL)	31.3 (15.0)	81.6 (22.2)	39.13	36.46, 41.99
EVG/COBI/FTC/GS-7340 Formulation 2 (25 mg) (Test) vs. GS-7340 (25 mg) (Reference)	N=17	N=18		
AUC_{tau} (ng•h/mL)	897.8 (12.7)	300.3 (13.4)	299.23	281.25, 318.37
C_{max} (ng/mL)	71.9 (57.3)	17.5 (15.1)	370.45	318.17, 431.34
C_{tau} (ng/mL)	31.3 (15.0)	10.5 (16.7)	300.33	279.91, 322.24

Influence of food

GS-US-311-1386 was an open-label crossover study that evaluated the effect of food on F/TAF tablets. Dosing was on days 1 and 8 with a single F/TAF 200/25 mg tablet in the fasted state or after a high-calorie/high-fat meal of approximately 800 kcal and 50% fat. Administration of F/TAF under fed conditions resulted in a slightly lower TAF Cmax and delayed Tmax (by 30 min). In contrast the GLSM ratios for TAF AUCs were ~175% (90% CI ~165, 188) for the fed vs. fasted state. TFV was not measured in this study. As expected, FTC AUCs were unaffected by food, although slightly lower, and Cmax was clearly reduced.

Compared to GS-US-292-0110, which assessed the PK of TAF after dosing E/C/F/TAF 10 mg STR under fasted and fed conditions (including the same meal type as above), the effect of food on TAF was greater after dosing with 200/25 mg F/TAF. The difference was thought to reflect a lesser effect of food on TAF absorption in the presence of P-gp inhibition by COBI.

GS-US-366-1651 was a randomised, single-dose, 2-period, crossover, food-effect study that used F/R/TAF (200/25/25 mg) FDC tablets. Meals tested were ~600 kcal and 27% fat (B) and ~800-1000 kcal and 50% fat (C). There was intensive post-dose sampling after each dose up to 240 h.

- TAF AUC_{last} increased by 45% and 53% (moderate-fat and high-calorie, high-fat conditions, respectively) vs. dosing in the fasted state. This magnitude of effect of the high fat meal on TAF plasma exposure was less for the F/R/TAF tablet compared with the F/TAF tablet (above).
- There was no important effect of food on FTC but Tmax was delayed by 1 h and Cmax reduced.
- RPV AUC_{inf} increased by ~13% with treatment B and 73% with treatment C vs. dosing in the fasted state. Both Edurant and Eviplera are recommended to be taken with a meal.

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

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

Bioequivalence studies to support the F/R/TAF formulation

GS-US-311-1088 was an open-label crossover study in which subjects received F/TAF (200/25 mg) and FTC 200 mg + TAF 25 mg. Dosing was after completion of a 600 kcal and 27% fat meal. Bioequivalence was demonstrated for each of TAF and FTC. The CSR states that TFV levels were not reported due to failure of the incurred sample reliability measure. The bioanalytical report states that the QCs spiked with GS-7340 plus TFV showed conversion of GS-7340 to TFV so the method did not control conversion effectively, particularly when the GS-7340:TFV ratio was high.

GS-US-311-1473 was a large (>100 subject) open-label crossover study which compared F/TAF (200/25 mg) with E/C/F/TAF 10 mg. Dosing was after completion of a 600 kcal and 27% fat meal. Bioequivalence was demonstrated for each of TAF (i.e. between 25 mg in F/TAF and 10 mg in E/C/F/TAF) and FTC. TFV was not measured.

GS-US-366-1159 is the pivotal bioequivalence study supporting this application. This was an open-label 3-way crossover study in which subjects received single doses of the following in randomised order and with 12-day washout periods:

A: FTC/RPV/TAF (200/25/25 mg) FDC tablet

B: RPV 25 mg tablet

C: E/C/F/TAF (150/150/200/10 mg) FDC tablet

All dosing was within 30 minutes after the start of a standardised breakfast containing ~600 kcal and 27% fat and within 5 minutes of meal completion. Bioequivalence criteria were met for each of FTC, RPV and TAF. Plasma TFV was not measured in this study.

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

GS-US-264-0103 was a 3-way crossover study that provides data on co-administration of RPV and FTC with TDF compared to two test formulations of the FTC/RPV/TDF FDC. This study did not include separate dosing with each constituent but it does provide TFV and FTC plasma levels on dosing with RPV that can be compared with the typical range observed with other FTC/TDF-containing presentations. All dosing was within 5 minutes of completing a standardised breakfast (400 kcal and 13 g fat). Bioequivalence criteria were met except for RPV Cmax after the F4 test formulation.

To put these data for TFV and FTC into context, the assessor compared plasma exposures to TFV and FTC that were provided by the applicant during the assessment of Stribild, which is also taken with food due to effects on EVG and COBI. The TFV AUC and Cmax values documented above fall within the range observed in prior studies in healthy subjects and HIV-infected patients treated with Stribild. The FTC AUC and Cmax resemble the values observed in healthy subjects given Truvada.

Excretion and metabolism

In GS-US-120-0109 healthy male volunteers received a single TAF 25 mg capsule containing 24.15 mg TAF plus 100 µCi [0.85 mg] radiolabeled [14C]TAF after a standardised breakfast. The total mean (± SD) recovery of [14C]radioactivity in faeces plus urine (n=7) was 84.4% (± 2.45%). The percent of radioactive dose recovered from faeces was 47.2% (± 4.62%) and the percent recovered from urine was 36.2% (± 5.62%).

Quantifiable levels of [14C]radioactivity were observed in whole blood for up to 360 h post-dose in most subjects but quantifiable levels of TAF were observed in plasma for up to 6 h post-dose and then remained BLQ. TAF was extensively metabolised with only 1.41% (± 0.561%) of the total radioactive dose appearing in urine as TAF and no radioactive TAF was detected in faeces. TFV accounted for 99% of the radioactivity recovered in faeces and 86% of the radioactivity recovered in urine. At 2 h post-dose the predominant species was TAF, accounting for 72.6% of the total [14C]radioactivity quantified. At 24 to 48 h post-dose the predominant species was uric acid, accounting for 97.6% of the total [14C]radioactivity quantified. Low quantities of other metabolites were formed including xanthine, hypoxanthine and adenine (identical to the endogenous products of purine metabolism).

For pooled urine a mean of 25.8% (± 5.50%) of the radioactive dose was quantified, within which the predominant species was TFV (M12), accounting for 22.2% (± 4.47%). All other metabolites appeared in trace amounts and none exceeded 2% of the administered dose of radioactivity. For pooled faeces a mean of 31.7% (± 10.5%) of the radioactive dose was quantified, within which the predominant species was TFV (M12), accounting for 31.4% (± 10.4%). Two unidentified metabolites appeared in trace amounts.

Pharmacokinetics in target population

POPPK analyses were performed for TAF and TFV using PK data collected from E/C/F/TAF studies as reported in full in the previous assessment reports. Since the applicant proposed use of F/R/TAF from the age of 12 years and 35 kg the PK data from the E/C/F/TAF study GS-US-292-0106 and the RPV study C213 (PAINT; which previously supported the Edurant variation II/17G) were provided. Plasma exposures to TAF, TFV, FTC and RPV were concluded to be comparable between adults and adolescents.

The POPPK predicted values were also comparable between adolescents and adults.

Pharmacokinetics of emtricitabine, and tenofovir alafenamide in antiretroviral-naïve adolescents and adults

	Adolescents Emtricitabine +tenofovir alafenamide			Adults Emtricitabine +tenofovir alafenamide		
	FTCa	TAFb	TFVb	FTCa	TAFc	TFVc
AUCtau (ng•h/mL)	14,424.4 (23.9)	242.8 (57.8)	275.8 (18.4)	11,714.1 (16.6)	206.4 (71.8)	292.6 (27.4)
Cmax (ng/mL)	2,265.0 (22.5)	121.7 (46.2)	14.6 (20.0)	2,056.3 (20.2)	162.2 (51.1)	15.2 (26.1)
Ctau (ng/mL)	102.4 (38.9)b	N/A	10.0 (19.6)	95.2 (46.7)	N/A	10.6 (28.5)

FTC = emtricitabine; TAF = tenofovir alafenamide; TFV = tenofovir, N/A = not applicable

Data are presented as mean (%CV).

a n = 24 adolescents (GS-US-292-0106); n = 19 adults (GS-US-292-0102)

b n = 23 adolescents (GS-US-292-0106, population PK analysis)

c n = 539 (TAF) or 841 (TFV) adults (GS-US-292-0111 and GS-US-292-0104, population PK analysis)

Impaired renal function

<u>TAF study GS-US-120-0108</u>

A single 25 mg dose of TAF was administered to 14 subjects with severe renal impairment (15 ≤ CrCL ≤ 29 mL/min) and 13 matched controls.

In severe renal impairment there was a 92% (< 2-fold) higher mean plasma TAF AUC_{inf}, 92% higher AUC_{last} and 79% higher Cmax. Correspondingly the mean plasma TAF CL/F was lower (61,717.8 mL/h vs. 117,633.1 mL/h, respectively, p = 0.003) but the half-life was not statistically significantly different. At 1 and 4 h the mean percent unbound TAF was not different between those with severe renal impairment (20.0% and

14.2%) vs. controls (20.1% and 13.6%). Approximately 0.117 mg TAF (0.47% of the dose) was excreted in urine in renally impaired subjects vs. ~0.500 mg (2.00%) in controls with renal clearance of 4.2 mL/min and 35.8 mL/min, respectively.

In severe renal impairment there was much higher (about 5-6-fold) plasma exposure to TFV vs. controls with lower plasma and renal clearance but no significant difference in half-life. TFV plasma protein binding at 2 and 24 h was not different between groups (e.g. 99.2% vs. 98.9% at 24 h). Approximately 30% vs. 24% of the dose was excreted in urine. The plasma TFV exposures (mean TFV AUCinf 2073.8 ng•h/mL vs. 342.6 ng•h/mL for controls) were within or below the TFV exposure ranges of subjects with normal renal function taking TDF 300 mg once daily

E/C/F/TAF study GS-US-292-0112

This open-label study in HIV-infected patients with $eGFR_{CG}$ in the range 30-69 mL/min included an intensive PK/PD sub-study.

- TAF PK parameters were consistent with data obtained from HIV-infected patients with normal renal function in E/C/F/TAF studies as well as from healthy subjects (AUC_{last} 244.8 ng*h/mL). Exposure to TAF was numerically higher in those with baseline $eGFR_{CG}$ < 50 vs. ≥ 50 mL/min but it was less than the mean AUC_{last} (510.6 ng*h/mL) in subjects with $eGFR_{CG}$ 15-29 mL/min in GS-US-120-0108.
- TFV plasma levels were higher in those with screening $eGFR_{CG}$ 30 to 69 mL/min compared to the HIV-infected patients in E/C/F/TAF studies (mean TFV AUCtau 552.7 ng*h/mL vs. 326.2, 311.8 and 286.2 ng*h/mL; see section 2.1.8 above) but well below the TFV exposure in those with $eGFR_{CG}$ 15-29 mL/min in GS-US-120-0108 (mean AUCinf 2073.8 ng*h/mL) and after TDF-containing regimens. As expected, exposure to TFV was higher in those with baseline $eGFR_{CG}$ < 50 vs. ≥ 50 mL/min.
- FTC plasma levels were higher in those with screening $eGFR_{CG}$ 30 to 69 mL/min compared to the Phase 2 E/C/F/TAF patients (mean AUC_{tau} 20,968 ng*h/mL vs. 11,714.1 ng*h/mL).

Impaired hepatic function

TAF study GS-US-120-0114

This was an open-label study in which single doses of 25 mg TAF were administered after completion of a moderate-fat meal (600 calories, 27% fat). The plasma exposure parameters of TAF and TFV were considered to be comparable between subjects with mild hepatic impairment and matched controls. The lower exposures vs. controls were not considered to be clinically relevant. In those with moderate hepatic impairment the plasma exposure parameters for TAF were slightly higher and exposures to TFV were slightly lower vs. matched controls. The differences observed were not considered to be clinically relevant. TAF plasma protein binding at 1 and 4 h post-dose showed a mean unbound TAF range from 16% to 19% in mild hepatic impairment and from 14% to 23% in moderate hepatic impairment. TFV plasma protein binding at 2 and 24 h post-dose showed a mean unbound TFV of > 99% in mild or moderate hepatic impairment. For TAF and TFV binding was similar to controls.

Race

In the E/C/F/TAF study GS-US-292-0108 after multiple dosing:

- The AUCs of all analytes were lower in Japanese vs. Caucasian subjects.
- For FTC the lower bounds of the 90% CI were well below 80% for AUC_{tau} and C_{tau}.

- For TAF the lower bound of the 90% CI was well below 80% for AUC_{last}.
- For TFV the lower bounds of the 90% CI were well below 80% for AUC_{tau} and C_{tau}.

Interactions

In vitro

- At TAF concentrations up to 25 µM all IC_{50} values were > 25 µM except for CYP3A4. TAF showed weak inhibition of CYP3A-mediated oxidation of midazolam or testosterone with IC_{50} values of 7.6 or 7.4 µM, respectively.
- At 10 µM TAF the mRNA levels of CYP1A2 and CYP3A4 increased by 3.0- and 8.3-fold, which correspond to 3% and 6% of the induction levels observed with respective positive controls. TAF showed little or no potential for CYP induction at clinically relevant concentration (1 µM).
- TAF did not inhibit UGT1A1 up to 50 µM.
- There was no significant induction of P-gp and UGT1A1 mRNA on exposure to TAF.
- TAF showed weak inhibition of OATP1B1, OATP1B3, BSEP, OCT1 and MATE1 but none was inhibited by 50% at 100 µM TAF, which is approximately 200-fold Cmax in plasma.
- TAF is a substrate for P-gp and BCRP. An increase in TAF absorption was observed in the presence of efflux transport inhibitors CsA or COBI. Co-administration of TAF with efflux inhibitors may potentiate antiviral efficacy by increasing TFV-DP levels in PBMCs.
- TAF is also a substrate for OATP1B1 and OATP1B3. Exposure to TAF may be affected by inhibitors of these transporters or genetic polymorphisms affecting activities.
- TAF was not a substrate for OAT1 and OAT3.
- At 50 µM TAF the extent of activation of PXR was only 23% of the maximal effect of rifampicin and 15 µM TAF demonstrated activation of < 5% of the maximal induction elicited by rifampicin.
- TAF did not activate AhR up to 50 µM, the highest concentration tested.
- TFV at 100 µM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1 or CYP3A.
- The active tubular secretion of TFV is mediated by human OAT1 (basolateral uptake) and MRP4 (apical efflux) transporters acting in series in proximal tubules. Human OAT3 may play a secondary role in the tubular uptake of TFV.
- Under physiologically relevant conditions, none of the tested drugs affected OAT1-mediated transport of TFV.
- TFV did not inhibit the activity of human OCT2 or MATE1 (IC50 > 300 µM).

In vivo

GS-US-311-0101 - F/TAF with Efavirenz [EFV] and TAF with COBI

Although F/R/TAF is not anticipated to be given with these agents the effects of co-administration are of interest for assessing the wider risk of DDIs.

- FTC/TAF (40 mg) plus EFV resulted in no clinically relevant changes in FTC, TFV or TAF AUCs compared with FTC/TAF (40 mg) dosed alone based on the pre-defined acceptance criteria. The TAF and TFV Cmax values were lower on co-administration but the differences were not considered to be clinically meaningful.
- Co-administration of TAF 8 mg plus COBI 150 mg resulted in substantially higher TAF and TFV exposures relative to TAF 8 mg dosed alone. The applicant ascribed the effect to COBI-mediated inhibition of P-gp-mediated intestinal secretion of TAF.

GS-US-311-1387 – F/TAF with carbamazepine

The study evaluated the effect of steady-state carbamazepine (CBZ) on the PK of TAF and TFV. Subjects received a single dose of F/TAF (200/25 mg) and a second dose with CBZ at steady-state (titrated from 100 mg twice daily to 300 mg twice daily over 20 days) with food. When co-administered with CBZ 300 mg at steady-state, TAF AUC_{inf}, AUC_{last} and C_{max} decreased by approximately 54%, 55% and 57%, respectively, compared with administration of F/TAF FDC alone. A lesser decrease in TFV exposure was observed on co-administration such that AUC_{inf}, AUC_{last} and C_{max} decreased by approximately 23%, 25%, and 30%, respectively.

GS-US-311-1387: Statistical Comparisons of TAF and TFV Pharmacokinetic Parameter Estimates Between F/TAF FDC Administered with Steady-State CBZ and F/TAF Alone

	GLSM		
	CBZ 300 mg Twice Daily + F/TAF 200/25 mg (Test) (N = 22)	F/TAF 200/25 mg (Reference) (N = 26)	GLSM Ratio (%) (90% CI) Test/Reference
TAF PK Parameter			
AUC_{last} (h*ng/mL)	92.08	204.61	45.00 (39.66, 51.06)
AUC_{inf} (h*ng/mL)	103.81[a]	224.68[b]	46.21 (39.68, 53.81)
C_{max} (ng/mL)	87.80	204.59	42.92 (35.87, 51.35)
TFV PK Parameter			
AUC_{last} (h*ng/mL)	157.05	208.91[c]	75.18 (71.39, 79.17)
AUC_{inf} (h*ng/mL)	185.06[d]	239.47[b]	77.28 (73.51, 81.24)
C_{max} (ng/mL)	4.96	7.13[c]	69.61 (65.18, 74.34)

a n = 13, b n = 23, c n = 24, d n = 21

The CBZ trough concentrations confirmed that steady state was reached well before day 26. The effect of co-administration on CBZ and its metabolite was not formally assessed in this study. However, Day 25 and 26 plasma levels are reported and do not indicate any important differences.

GS-US-120-1538

This was an open-label study to evaluate co-administration of TAF with oral and IV midazolam in which subjects were dosed as follows after standard breakfasts.

- TAF had no significant effect on plasma MDZ or 1'OH-MDZ after oral dosing based on 90% CI that fell within 80, 125%. The 90% CI for MDZ AUCs were slightly higher on co-administration (did not span 100%) but the metabolite was not similarly affected.
- TAF had no significant effect on plasma MDZ or 1'OH-MDZ after IV dosing based on 90% CI that fell within 80, 125% but the 90% CI for MDZ and metabolite AUCs did not span 100%.
- There was 25% to 30% decrease in TAF Cmax (25% to 30%) after co-administration with oral or IV MDZ, which the Company proposed may reflect an effect of MDZ on gastrointestinal motility. The AUCs were also slightly lower on co-administration but relatively less affected (~10-15% decreases).

GS-US-120-0117 – Single doses of TAF + RPV

This was an open-label crossover study to evaluate co-administration of TAF with rilpivirine (RPV), which is primarily metabolised by CYP3A but is not expected to induce or inhibit CYP3A4 or P-gp at 25 mg QD.

- Plasma TAF was unaffected by RPV in that all 90% CI fell within 80, 125% and spanned 100%.
- The TFV Cmax and AUC were slightly higher on co-administration with 90% CI around AUC ratios that did not span 100% and with a Cmax ratio of 118.1 and 90% CI 107.3, 130.
- The RPV Cmax and AUCs were slightly lower on co-administration with lower bounds of the 90% CI just below or at 80%. C_{last} (at 120 h) was not affected (9.2 ng/mL vs. 10 ng/mL) and mean concentrations did not diverge at earlier time points.

GS-US-120-1554 – Multiple doses of TAF + RPV

This was an open-label study in two cohorts who received 14 days of either TAF 25 mg or RPV 25 mg and all subjects also received both together after standardised breakfasts.

- Plasma PK parameters for TAF were unaffected by co-administration.
- For TFV the 90% CI fell within 80, 125% but all exceeded 100%.
- The RPV AUC was unaffected by co-administration whilst Cmax was slightly lower and Ctau was slightly higher.

GS-US-366-1689 - F/R/TAF plus sofosbuvir (SOF) and ledipasvir (LDV)

This was an open label, multiple-dose, 3-way cross-over study to evaluate the potential for interactions between the F/R/TAF FDC and SOF, its metabolites (GS-566500 and GS-311007) or LDV. All dosing was with food.

Co-administration with LDV/SOF did not notably affect the PK of FTC, RPV or TAF. Compared to FTC/RPV/TAF alone co-administration led to increases in TAF and TFV AUC_{tau} of 32% and 75%, respectively. TFV Cmax was increased by 62% and C_{tau} by 85% but there was no effect on TAF Cmax. Co-administration with F/R/TAF did not notably affect the PK of LDV or SOF (including its metabolites GS-566500 or GS-331007).

The applicant discussed that the increase in TFV (the major TAF metabolite) exposures of approximately 75% was consistent with the mechanistic understanding of the interaction between the P-gp inhibitor LDV and the P-gp substrate TAF. It was pointed out that the mean TFV AUC_{tau} on co-administration (467 ng*hr/mL) is approximately 5 times lower than TFV exposure following dosing with TDF (AUC_{tau} 2290 ± 690 ng*hr/mL). As such, the differences in overall TFV exposure following administration of LDV/SOF+FTC/RPV/TAF vs.

FTC/RPV/TAF alone were not considered to be clinically relevant and no dose adjustment of FTC/RPV/TAF is proposed when it is co-administered with LDV/SOF.

2.4.3. Pharmacodynamics

TAF is predominantly hydrolysed to TFV by Cathepsin A (CatA) cleavage in target lymphoid cells. TFV (a monophosphate) is then metabolised to TFV diphosphate (TFV-DP), which is a competitive inhibitor of HIV-1 RT. In T-cells, macrophages and PBMCs TAF EC50 values ranged from 3 to 14 nM. The in-vitro activity of TAF against HIV-1 is 100- to 600-fold greater than TFV and 4- to 6-fold greater than TDF. For TAF intracellular activation pathways in lymphoid cells and tissues, refer to Figure 1.

Since TAF is a pro-drug of TFV it is affected by the same resistance associated mutations (RAMs). In-vitro studies indicated that TAF and TFV have similar propensities to select for mutational resistance and that EC_{50} values are affected to a similar extent by various mutations and combinations of mutations. However, the applicant postulated that the in-vivo resistance profile may differ when dosing with TAF or TDF since the level of TFV-DP achieved after TAF is significantly higher than that after TDF.

Viral breakthrough experiments were conducted using known TDF-resistant HIV-1 isolates in MT-2 cells to model the impact of the higher TFV-DP concentrations. These experiments were conducted at a higher multiplicity of infection (MOI) compared to typical EC_{50} assays; the EC_{50} values for TAF and TFV were 0.02 and 5 µM, respectively. The cells were incubated in the presence of TAF or TFV (concentrations were equivalent to the EC_{95} [estimated at 10 × EC_{50}] with a 5-fold increase for TAF) followed by HIV-1 infection. After 4 or 5 days of incubation cultures were scored for viral breakthrough (i.e., CPE) and the procedure was repeated every 4 to 5 days for up to 4 weeks. TAF inhibited viral breakthrough for the duration of the experiment for 9/11 viruses but viral breakthrough was only inhibited for 2/11 viruses in the presence of TFV. However, breakthrough of viruses with 5 TAMs was not prevented by TAF or TFV.

TAF monotherapy and other data on the PK-PD relationship

GS-120-1101

Study Title: A Phase 1/2 Randomized, Double-Blind, Active-Controlled, Dose Escalation Study of the Safety, Tolerance, Pharmacokinetics, and Antiviral Activity of GS-7340-02 in Antiretroviral-Naïve Patients Who Are Chronically Infected with HIV-1

This study explored the antiviral activity of TAF (50 mg and 150 mg QD as the monofumarate) vs. TDF during 14 days monotherapy in 30 ARV-naïve patients (27 male) with plasma HIV-1 RNA ≥ 15,000 copies/mL and CD4 cell count ≥ 200 cells/mm^3 at screening. TFV was detectable within PBMCs earlier, more consistently, and at greater concentrations after TAF vs. TDF. DAVG1, 2 and 3 were all significantly greater in the TAF groups compared to TDF but there was no significant difference between the TAF doses.

GS-US-120-0104

Study Title: A Phase I Randomized, Partially-Blinded, Active and Placebo-Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-7340 Monotherapy in Subjects with HIV-1

TAF monotherapy was compared to TDF and placebo over 10 days in patients with HIV-1 RNA > 2000 copies/mL, CD4 counts ≥ 200 cells/mm^3 and without use of ARVs within 90 days. Randomisation (2:2:2:1:2) was to TAF at 8, 25 or 40 mg or to TDF 300 mg or placebo. At steady state, the mean TFV AUC_{tau} after TAF

doses were 97%, 86% and 79% lower, respectively, vs. the mean after TDF dosing and Cmax values were 98%, 94% and 89% lower, respectively.

The peripheral blood mononuclear cell TFV-DP concentrations were highly variable but the mean AUCtau was similar between TAF 8 mg and TDF 300 mg and was ~ 7-fold and ~ 25-fold higher after 25 mg and 40 mg doses of TAF, respectively. The antiviral effect of GS-7340 8 mg was similar to that of TDF 300 mg. There were statistically significantly greater decreases in viral load with 25 mg and 40 mg TAF doses compared to TDF 300 mg. The first phase decay slopes for plasma HIV-1 RNA in the TAF 25 mg and 40 mg groups were also significantly steeper than for TDF 300 mg.

Table 10. Time-Weighted average change from baseline up to Day 11 (DAVG11) in plasma HIV-1 RNA (Full analysis set)

	GS-7340 (8 mg) (N=9)	GS-7340 (25 mg) (N=8)	GS-7340 (40 mg) (N=8)	TDF (300 mg) (N=6)	Placebo (N=7)
Baseline					
Mean (SD)	4.51 (0.369)	4.52 (0.377)	4.34 90.4770	4.96 (0.308)	4.24 (0.780)
95% CI	(4.23,4.79)	(4.21,4.84)	(3.95,4.74)	(4.63,5.28)	(3.52,4.96
Median	4.50	4.64	4.44	4.90	4.32
Q1-Q3	4.41,4.79	4.45,4.73	4.08,4.73	4.76,5.13	3.79,4.77
Min, Max	3.78,4.96	3.69,4.87	3.42,4.83	4.60,5.45	2.81,5.27
Pairwise p-values					
p-value vs placebo	0.46	0.45	0.77	0.054	
p-value vs TDF	0.052	0.061	0.033		
p-value vs GS-7340 (40mg)	0.53	0.49			
p-value vs GS-7340 (25mg)	0.96				
DAVG11					
Mean (SD)	-0.67 (0.265)	-0.94 (0.254)	-1.14 (0.226)	-0.45 (0.340)	0.13 (0.391)
95% CI	(-0.88,-0.47)	(-1.15,-0.72)	(-1.33,-0.95)	(-0.81,-0.09)	(-0.23,0.49)
Median	-0.76	-0.94	-1.08	-0.48	-0.01
Q1,Q3	-0.86,-0.57	-1.12,-0.76	-1.35,-0.97	-0.57,-0.34	-0.03,0.01
Min, Max	-0.97,-0.24	-1.13,-0.54	-1.46,-0.84	-0.94,0.11	-0.08,1.01
Pairwise p-values					
p-value vs placebo	0.001	0.001	0.001	0.038	
p-value vs TDF	0.22	0.017	0.006		
p-value vs GS-7340 (40mg)	0.003	0.13			
p-value vs GS-7340 (25mg)	0.075				

The PK/PD relationships between TAF and TFV plasma exposures and antiviral activity were explored using a maximum (PD) effect (E_{max}) model. The TAF AUC fitted well with an E_{max} model, with an E_{max} of ~1.7 to 1.8 log_{10} decline from baseline and the EC_{50} for AUC of ~32 ng•h/mL. A similar fit/E_{max} estimate was obtained using TAF C_{max}, which was somewhat expected given its brief plasma half-life and the resulting contribution of the C_{max} to the overall AUC. Upon comparison of antiviral activity with 40 mg and previous data with 150 mg (GS-120-1101), TAF 25 mg was expected to provide near-maximal activity (~1.7 to 1.8 log_{10} copies/mL). Plasma TFV exposure, which was substantially lower with TAF versus TDF, did not correlate with antiviral activity.

GS-US-292-0104 and 0111

Phase 3 E/C/F/TAF studies provided intracellular TFV-DP concentrations following administration of TAF vs. TDF (i.e., E/C/F/TAF vs. STB) in HIV-infected patients. There was a >4-fold higher intracellular concentration of TFV-DP (based on the AUC_{tau} GLSM ratio) when TAF was given vs. TDF.

The PK/PD analysis sets included all ARV-naïve patients who received a dose of E/C/F/TAF and had at least one TAF or TFV PK parameter (AUC_{tau} or C_{max}) estimated from the POPPK analysis. Virologic success was uniformly high across TAF AUC_{tau} quartiles with no trends in exposure-response relationship observed.

Table 11. Virologic success rates at Week 48 across quartiles of TAF exposure (TAF PK/PD analysis set)

TAF AUC_{tau} Quartile (ng•h/mL)	Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) (%) (N = 135)
47.2 to 140.2	96.3[a]
140.5 to 184.8	92.6
184.9 to 229.7	94.8
230.8 to 1869.3	91.9

These results based on TAF 10 mg when given with COBI (or other agent with similar PK effects on TAF) are of relevance to the unboosted dose of TAF 25 mg, which was concluded to provide near maximal antiviral efficacy in the monotherapy study.

The data were also used to explore the exposure-safety relationships in these two studies, focusing on diarrhoea and nausea (very common), vomiting and GI/abdominal pain (common).

- For diarrhoea and GI/abdominal pain, both the TAF and TFV exposure was comparable regardless of the presence or absence of either of those symptoms and no exposure-AE trends were observed.
- For nausea and vomiting, the TFV exposure was comparable regardless of the presence or absence of either of those symptoms with no exposure-AE trends noted. Logistic regression analysis showed a trend between the highest TAF exposure and the presence of these AEs (nausea correlated with the highest 4% of TAF exposure; vomiting correlated with the highest 19% of TAF exposure). No trend was observed between TAF exposure and severity.
- Across all TAF and TFV AUC_{tau} quartiles, the percentage change from baseline at Week 48 in BMD was comparable; no trends in exposure-changes in BMD were noted.
- Across all TAF and TFV AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable; no trends in exposure-changes in serum creatinine were noted.

GS-US-311-1089

Further data on intracellular TFV-DP concentrations were provided from an ongoing study GS-US-311-1089 in which patients who are virologically suppressed on regimens containing FTC/TDF either switch to F/TAF or stay on FTC/TDF and are followed for 48 weeks. The report is based on trough blood samples collected at Week 4 (20 to 24 h post-dose). Overall, F/TAF resulted in intracellular TFV-DP concentrations >4-fold those observed with FTC/TDF.

Table 12. GS-US-311-1089: Statistical Comparisons of Intracellular PBMC TFV-DP Concentrations Between F/TAF and FTC/TDF (PBMC PK Analysis Set)

	Intracellular PBMC TFV-DP Concentration (pg/10^6 cell)	
	F/TAF (N = 308)	FTC/TDF (N = 271)
Geometric Mean (95% CI)	14.2 (12.6, 16.0)	3.4 (3.0, 3.8)
GLSM	14.1	3.3
TAF/TDF GLSM Ratio (90% CI) x 100%	424.62 (370.26, 486.97)	

Further breakdowns according to co-administered agents, noting the variable denominators, showed:

- A very clear difference between co-administration with EFV vs. other agents.
- Lower values with DRV/r and LPV/r compared to ATV/r.

Pharmacodynamic interactions with other medicinal products or substances

TFV is presented for clinical use as a nucleotide analogue, i.e. it is already monophosphorylated. The effects of combination of TFV with other agents that require intracellular phosphorylation has been investigated in in-vitro studies. Combination with ABC did not change the rates of phosphorylation of either compound to the triphosphate (active) forms.

The anti-HIV-1 activity of TAF in combination with a broad panel of representatives from the major classes of approved anti-HIV agents was evaluated in HIV-1 IIIB infected MT-2 cells. TAF exhibited moderate to high synergistic effects (synergy scores from 41 to 131) when combined with any of the N(t)RTIs or NNRTIs. None of the drug combinations containing TAF exhibited antagonistic antiviral effects. The combination of FTC, RPV and TFV demonstrated synergistic antiviral activity in cell culture.

Secondary pharmacology

GS-US-120-0107 was a TQT study that evaluated single doses of 25 mg and 125 mg TAF. Pharmacokinetic parameters for TAF and TFV following single oral doses of 25 or 125 mg TAF were approximately proportional to dose. The lower bound of the 2-sided 90% CI for the mean difference between moxifloxacin and placebo was > 5 ms at 2 post-dose time points (3 and 4 h) establishing assay sensitivity. At these respective time points the actual changes were -1.4 and +4.1 ms for moxifloxacin compared to -12.9 and -7.1 ms for placebo.

For the primary analysis, TAF was concluded to have no QTcF prolongation effect as the upper bounds of the 2-sided 90% CIs for the mean difference between 25 mg and 125 mg TAF and placebo were below 10 ms at each time point after dosing. Small negative changes in QTcF were observed at both doses. Analyses of secondary endpoints (QTcB, QTcN and QTcI) were consistent with the primary analysis.

In the categorical analyses no subject had a treatment-emergent absolute QTc interval > 500 ms or a change from pre-dose baseline QTc > 60 ms with any correction factor following any treatment. No subject had a treatment-emergent absolute QTc interval > 480 ms or a change from pre-dose baseline > 30 ms following either dose of TAF.

2.4.4. Discussion on clinical pharmacology

Doses of TAF, FTC and RPV in F/R/TAF

The evidence to support selection of 25 mg TAF once daily in the absence of an inhibitor or inducer of P-gp comes from the monotherapy studies. Doses of 25 mg and 40 mg TAF achieved effects on viral load similar to those of 50 mg and 150 mg in the preliminary study, suggesting a plateau effect from ~25 mg upwards and superiority over TDF 300 mg. It was clear that 8 mg TAF was not an appropriate dose. Doses between 8 and 25 mg were not studied.

The peripheral blood mononuclear cell TFV-DP concentrations were highly variable across dose groups and time points in the monotherapy and other studies in which data were generated. Differences among studies are expected given the technical challenges associated with the assessment of intracellular nucleotide levels, including TFV-DP in PBMCs. For example, there is currently no GLP standard for PBMC collection, and haemolysis during sample collection may adversely affect quantification. Accurate counting of PBMCs is also technically difficult and PBMCs are variably contaminated with RBCs, which can contain significant quantities of nucleotide analogues. Additionally, dephosphorylation may occur during cell collection and isolation. Potential variances in the application of PBMC processing procedure at different clinical trial sites may contribute to the observed differential TFV-DP concentrations.

However, within any one study it seems that the quantitative differences in TFV-DP concentrations between TDF and TAF treatment groups are most likely real even if the absolute values reported differ between studies due to the inherent variance in the technical assessment of TFV-DP levels. It is notable then that in the monotherapy study the intracellular PBMC concentrations of TFV-DP were ~ 7-fold and ~ 25-fold higher after 25 mg and 40 mg doses of TAF, respectively, vs. TDF. Thus there was a lack of linearity with dose. Despite this apparent difference in intracellular TFV-DP the 40 mg dose of TAF did not have a superior antiviral effect to 25 mg. Since the antiviral effect should carry more weight, the TAF monotherapy studies support a conclusion that doses lower than 25 mg should not be pursued and that increasing the dose beyond 25 mg is unlikely to achieve a greater antiviral effect.

To further support the selection of the 25 mg TAF dose the applicant provided the results of E_{max} modelling. The models gave an E_{max} of ~1.7 to 1.8 $\log_{10}$ decline in viral load from baseline. The EC_{50} approximated to a TAF AUC of ~32 ng•h/mL. After 10 days dosing with TAF 25 mg alone the mean and median TAF AUC_{last} values were 115 and 109 ng.h/mL, respectively. It was concluded that 25 mg TAF will provide near maximal activity. It is important to note that there was no relationship detected between plasma TFV and antiviral activity.

The observation of higher levels of TFV-DP in PBMCs after dosing with TAF 25 mg compared to TDF 300 mg is not mechanistically explained. However, TAF is a more stable prodrug than TDF and it is more efficiently loaded into PBMCs (including lymphocytes and other HIV-target cells), although the mechanism of cell uptake is not known. Due to its poor cellular permeability, plasma TFV does not meaningfully contribute to intracellular levels of TFV-DP in patients receiving F/R/TAF. This is supported by the kinetic profile of TFV-DP in PBMCs since TFV-DP accumulates rapidly after dosing, when plasma TAF levels are still high, and are maintained based on its long intracellular half-life. Additionally, the TAF AUC fitted well with an Emax model but TFV exposure did not correlate with antiviral activity.

The slight deviation from dose proportionality in TAF and TFV plasma levels observed in the negative TQT study for 25 vs. 125 mg TAF over the 5-fold range tested suggests that uptake of TAF into cells and conversion to TFV was not easily saturable.

There is no evidence to suggest that substitution of TDF with TAF in the FDC will increase the risk of selection of resistance. Also, in-vitro studies with FTC and TAF indicated synergy, suggesting no intracellular interference in formation of their respective phosphorylated active moieties.

Overall, the applicant's rationale for pursuing a TAF dose of 25 mg once daily in the absence of a P-gp inhibitor can be supported. Based on the multiple dose DDI study that showed no interaction between TAF 25 mg and RPV 25 mg, the known lack of interaction potential of FTC, and the bioequivalence study that compared F/R/TAF with Edurant, the selection of the licensed doses of FTC and RPV in the F/R/TAF FDC is supported. The resulting FDC differs from the approved FDC Eviplera only in substitution of TDF with TAF.

The doses of FTC and RPV in the proposed F/R/TAF FDC are those approved in the standalone presentations and also in the approved FDC Eviplera. A lack of interaction between TAF and RPV was shown in the multiple dose DDI study. A definitive study that compares F/R/TAF with each component dosed alone has not been conducted but FTC does not have any potential to affect exposures to TAF, TFV or RPV.

Effect of food

After dosing the F/R/TAF FDC with food the TAF AUC_{last} was increased by 53% (high-calorie/high-fat; AUC_{last} 312 vs. 201 ng.h/mL fasted). The magnitude of effect of the high fat meal on TAF was less than that observed after dosing with the F/TAF tablet under similar conditions (75%) in another study (GS-US-311-1386; AUC_{last} 235 fed vs. 134 ng.h/mL fasted). Although these data come from two different studies the actual TAF AUC_{last} values were notably lower for F/TAF vs. F/R/TAF when each was dosed with or without food. It is also relevant to note that the food effect study for E/C/F/TAF (GS-US-292-0110) showed only a small effect of a similar meal on TAF AUC_{last} (240 vs. 206 ng.h/mL fasted) in the presence of a strong P-gp inhibitor (COBI). In addition, it is interesting that the TAF AUC_{last} value in the fasted state after dosing with E/C/F/TAF (10 mg TAF) is very close to that observed in the fasted state for F/R/TAF (25 mg TAF) and, again, notably higher than after dosing F/TAF (25 mg) in the fasted state.

The magnitudes of effect of food on TAF AUCs when dosed as F/R/TAF vs. F/TAF and the differences in actual AUC values in each of fed and fasted states could suggest that RPV dosed at 25 mg does have some inhibitory effect on gut P-gp, which increases TAF absorption. In this regard it should be noted that the DDI study that concluded no effect of RPV on P-gp was conducted with digoxin, which is not the most sensitive substrate.

After dosing with F/R/TAF, the RPV AUC_{inf} increased by ~13% with the moderate fat meal and 73% with the high fat meal vs. dosing in the fasted state. However, the effect on TAF AUC_{last} was not very different between the two types of meal (44% vs. 53%). These data do not suggest that there is a relationship between the systemic exposure to RPV and TAF exposure but this does not rule out an underlying effect of RPV on P-gp-mediated TAF absorption in the gut.

Both Edurant and Eviplera are recommended to be taken with a meal and the SmPC recommends that F/R/TAF is also taken with a meal. This recommendation is considered appropriate. It is relevant to note that the pivotal bioequivalence study was conducted with all dosing after a meal of ~600 kcal and 27% fat, which is the moderate fat meal tested in the F/R/TAF food effect study. This design could seem to be acceptable but it remains the case that the bioequivalence criteria may not have been fully met if this study had been conducted in the fasted state or after a high fat meal.

As expected from prior data, there was no important effect of food on FTC. Therefore the recommendation to dose F/R/TAF with food is driven by the RPV and TAF content of the FDC.

Bridging to the E/C/F/TAF and RPV efficacy data

The pivotal study to bridge the efficacy observed with E/C/F/TAF and RPV in the ART-naïve to F/R/TAF (200/25/25 mg) was conducted with all dosing in the fed state after standard moderate fat meals. The requisite bioequivalence criteria were met. The TAF AUC_{last} values were 250 and 238 ng.h/mL for F/R/TAF and E/C/F/TAF, respectively. These values are very similar to those reported above after dosing each FDC with the same moderate fat meal type in the food effect studies.

These data were generated in healthy subjects. Therefore it is pertinent to observe that in the POPPK analysis based on the E/C/F/TAF studies the applicant concluded that HIV disease status did not have an effect on TAF exposure and was not a statistically significant or clinically relevant covariate. The estimated TAF AUC_{last} values were 250 ng.h/mL for healthy subjects vs. 206 ng.h/mL for HIV-infected patients, noting that patients were to take E/C/F/TAF with food. In the additional integrated *ad hoc* PK analysis in the F/TAF dossier, from which the applicant again concluded that there was no clinically relevant difference in TAF exposure between healthy subjects and HIV-infected patients, the estimated TAF AUC_{last} was 127 ng.h/mL for TAF 25 mg. This resembles the value observed with this dose in the TAF monotherapy studies.

There are no patient PK data available as yet after dosing with the F/R/TAF FDC although such data will be collected and reported from two ongoing studies in which virologically suppressed patients switch to F/R/TAF. There were too few patients treated with F/TAF 25 mg + RPV in GS-US-311-1089 to substantiate patient plasma levels and intracellular TFV-DP with this combination regimen.

During the procedure several questions were raised regarding the validity of bridging efficacy on the basis of bioequivalence as described above. In the Phase 1 study GS-US-292-103 plasma TAF was very slightly lower on dosing with Genvoya but the plasma TFV AUC was lower after dosing with F/TAF 25 mg. This finding, which remains mechanistically unexplained, suggested an effect of COBI on the compartmental disposition of TFV.

- The finding raised a question regarding the basis for extrapolation of efficacy from Genvoya to F/TAF regardless of the third agent co-administered (i.e., including F/R/TAF).
- It also raised a question regarding the CNS levels of TFV-DP that may be achieved with F/TAF, and, hence, the efficacy of various TAF-containing regimens (including F/R/TAF) against HIV within the CNS.

The applicant responded to these concerns during the procedure and the questions were referred to the SAG Viral Diseases. When considering these issues the following observations have some relevance.
To ascribe the difference in TFV plasma levels that was observed when TAF was administered with or without COBI to a differential effect on the whole body distribution of TFV would require that systemic concentrations of COBI are sufficient to exert effects on relevant transporters outside of the gut.

In vitro, COBI inhibits the transporters P-gp, BCRP, MATE1, MRP-2, OATP1B1 and OATP1B3. Its effect on plasma exposures to substrates of P-gp and/or BCRP via inhibition at the gut level is clear. There are modest changes in TFV exposure when TDF (a known substrate of P-gp) is given with inhibitors of intestinal P-gp, including COBI and RTV. In addition, COBI is predicted to inhibit intestinal BCRP and MRP2 at concentrations theoretically achievable in the intestinal lumen following a 150 mg oral dose. The results of a study to evaluate whether MRP2 or BCRP could contribute to the intestinal efflux transport of TDF were submitted during the evaluation of the Tybost dossier and indicated that this could occur. However, in the context of plasma TFV levels after oral administration of TAF, it should be noted that TFV is not a substrate for P-gp, MRP2 or BCRP and its renal elimination should not be affected by COBI based on the calculated $C_{max,u}/IC_{50}$ ratios.

Regarding the potential for systemic effects on other transporters it is clear that COBI reaches sufficient concentrations to inhibit MATE1 in the kidney, with consequent effects on serum creatinine. It is also predicted to have weak to modest effects resulting in increased exposures to OATP1B substrates. In the

interaction study with digoxin, in which Cmax and AUC_{0-last} increased but AUC_{inf} remained unchanged on co-administration, there was a numerical decrease in the digoxin t1/2 from 38 to 30 h, which was unexpected in light of the calculations described above suggesting that COBI would not reach sufficient systemic concentrations to inhibit renal P-gp and so affect elimination of digoxin in urine. This effect on t1/2 remains unexplained and in a small DDI study it may not represent a true difference.

Overall, existing knowledge regarding COBI and its effects on transporters, as well as the substrate profile of TFV, do not explain the modest difference in TFV plasma levels observed when TAF was given with and without COBI to healthy subjects. There is no clear basis for concluding that the difference truly reflects different whole body distribution of TFV when TAF is administered with or without COBI.

TFV is not the active moiety but is the moiety associated with adverse renal and bone effects. Since TFV plasma levels were slightly lower for F/TAF 25 mg vs. TAF 10 mg given with COBI there is no reason to expect a worse safety profile for F/TAF when used without COBI compared to Genvoya. In addition, the safety data from GS-US-311-1089, in which subjects either switched to TAF or remained on TDF, each with FTC and a wide range of third agents (including PI/r combinations), indicated that the safety profile for TAF-treated patients vs. TDF-treated patients was consistent with observations made in the Phase 3 Genvoya studies that compared Genvoya with Stribild.

The issue was whether the supposed difference in whole body distribution of TFV in the presence and absence of COBI could bring into question the validity of bridging F/R/TAF to the Genvoya Phase 3 efficacy data by means of TAF bioequivalence. Thus, to consider whether the durable anti-viral activity observed so far in plasma when dosing TAF as part of Genvoya, accompanied by lack of any signal for neurocognitive disorders caused by HIV-1 in the CNS, would apply when dosing TAF within other ART regimens, including F/R/TAF.

As part of this concern regarding bridging of efficacy, it was questioned whether CNS penetration of TAF and formation of the active moiety TFV-DP in brain parenchyma could be different in the presence vs. absence of COBI. In addition, it was questioned whether control of HIV-1 within the CNS could vary depending on the third agent used with F/TAF. On this latter theme, and in relation to the well-recognised concerns regarding the efficacy of RPV 25 mg QD, it was questioned whether patients taking this FDC could be at particular risk of HIV-related neurocognitive disorders. Thus, several issues culminated in a series of questions that covered both the efficacy of F/TAF when used with third agents other than EVG/co, including but not limited to RPV, and the associated potential for HIV-1 neurocognitive disorders to occur.

With regard to the brain levels of the active moiety (TFV-DP) when TAF is given orally, the theoretical concern is that systemic levels of inhibitors of transporters known to be located at the BBB (including P-gp, BCRP and MRP-4) could suffice to have a clinically important impact. Hence, if COBI or RTV were to exert some inhibition of these transporters at the BBB, the efflux of their substrates from the brain might be reduced. TAF is a substrate of P-gp and BRCP but TFV is not a substrate of either of these transporters. Theoretically brain parenchyma concentrations of TAF and TFV-DP could be relatively higher when TAF is dosed with vs. without COBI or RTV.

TFV and TAF poorly penetrate into the CSF, likely resulting in concentrations well below EC_{50} for HIV reverse transcriptase. However, as reported by Kalvass *et al*. (2013) in a review conducted by the ITC, transport processes at the blood-CSF barrier can be functionally different than those at the BBB. For example, P-gp and BCRP secrete substrates into the CSF at the blood–CSF barrier, but at the BBB they act as efflux transporters pumping substrates into blood. In contrast, MRP4 acts as an efflux transporter at both the BBB and the blood–CSF barrier. The authors point out that effects on the activity of BCRP or MRP4 at the BBB are not likely to result in clinically relevant effects. As elaborated by the authors, drug detection and drug

concentrations in CSF may not provide an accurate reflection of concentrations in brain parenchyma. CSF concentrations are often not representative of unbound brain concentrations for substrates of P-gp, BCRP and/or MRP4. Furthermore, TFV-DP is the active moiety but it is formed only within cells. Hence it cannot be assumed that TAF and TFV levels measured in CSF necessarily correlate with inhibition of HIV-1 replication by TFV-DP within the brain.

Kalvass *et al*. (2013) also discuss uptake transporters at the BBB. In light of the possibility that COBI could have effects on other (as yet untested or unrecognised transporters) this potential effect of COBI cannot be ruled out but it would only be important whenever TAF was a sensitive substrate.

In the switch study GS-US-311-1089 there were no differences in efficacy or safety of F/TAF when used with a boosted PI or unboosted third agents, including no signal for neurocognitive disorders. However, the demonstration of efficacy in a population in which HIV-1 replication is already profoundly suppressed may not be relevant to initiation of treatment in the ART-naïve. In addition, only 3 patients received F/TAF+RPV in this switch study.

During the review of F/R/TAF the applicant provided interim and blinded data on virologic failures in two ongoing studies in which patients who are virologically suppressed on Atripla or Eviplera are randomised to switch or not switch to F/R/TAF (GS-US-366-1160 and GS-US-366-1216). So far there have been very few virologic rebounds but, as for GS-US-311-1089, these interim switch study efficacy data cannot *per se* overcome the theoretical concerns that have been raised.

HIV-1 replication in the CNS is thought to occur in perivascular macrophages and/or microglia within the brain parenchyma. In patients with cognitive impairment, HIV-1 RNA in the CSF is derived primarily from enriched perivascular macrophages and migrating monocytes. Although plasma TFV exposures with TAF are ~90% lower vs. TDF, intracellular TFV-DP levels are typically 4- to 7-fold higher. Theoretically it may be that TAF is able to load migrating monocytes more effectively than TDF prior to entry into the CNS.

Neuro-symptomatic replication of HIV-1 in the CNS (in which CSF HIV-1 RNA is higher than in plasma) does occur but appears to be rare and is mostly documented anecdotally via case reports or series. In reported cases of concurrent virologic failure in the CSF and plasma it is not possible to determine whether plasma virologic failure followed CSF virologic failure or *vice versa*. Generally the evidence supports a conclusion that clinically significant escape replication of HIV-1 in the CNS is extremely unlikely to occur when there is successful suppression of plasma HIV-1 RNA regardless of the regimen used and the predicted CNS penetration of the active moieties. In addition, there is only a very remote possibility that escape replication in the CNS would lead to failure to control plasma HIV-1 RNA levels.

In summary, although there remains a theoretical possibility that the presence of a P-gp inhibitor as part of an overall TAF-containing ART regimen could affect entry of TAF into the brain and, thus, TFV-DP levels, the overall picture at present suggests that this is a remote possibility. CSF levels of TFV or TAF cannot be regarded as highly predictive of TFV-DP in the brain. Brain penetration in nonclinical studies may poorly predict the human situation. There is at least a theoretical possibility that use of TAF rather than TDF could improve on levels of TFV-DP achieved in the CNS replicating sites.

The general experience with the more highly effective ART regimens that have become available especially in the last decade support a conclusion that effective and sustained virologic suppression in plasma is associated with CSF virologic suppression or, at least, only asymptomatic and usually temporary detection of HIV-1 RNA in CSF. There no reason to believe that rates of plasma virologic failure or CSF virologic failure are more likely to occur with regimens containing TAF vs. otherwise identical regimens containing TDF. Thus, F/R/TAF should exert similar activity to Eviplera when used in accordance with identical restrictions and

warnings and there is no good reason to expect that the risk of escape HIV-1 replication in the brain is any greater with the former vs. the latter.

The SAG concurred with a conclusion that F/TAF should pose no difference vs. Truvada in control over HIV replication in plasma and in the CNS when each is given with the same third agent, including RPV.

Co-administration of TAF with inhibitors and inducers of P-gp

There is incomplete overlap between inhibitors and inducers of each of CYP3A and P-gp and the magnitude of effect of any one agent can vary according to the co-administered substrate.

The results of the DDI study with F/TAF and carbamazepine reported during the procedure shows that the effect of P-gp inducers on TAF is an important issue to be mentioned. In line with the Edurant SmPC, F/R/TAF is contraindicated for use with several agents that are known to induce CYP3A due to potential lack of efficacy resulting from lower RPV levels. These agents are also to some extent inducers of P-gp, although this is not specified in section 4.3. However, section 4.5 acknowledges that medicinal products that strongly affect P-gp activity may lead to changes in TAF absorption, including a lowering of TAF by P-gp inducers. Therefore the issue seems to be adequately covered in the SmPC.

It was clear from GS-US-292-0101 that even after co-administration of 25 mg TAF with a strong P-gp inhibitor (COBI) the plasma TFV levels were markedly below those attained after dosing with TDF.

Due to the overlap (although incomplete) between P-gp and CYP3A inhibitors it should be noted that the Edurant SmPC acknowledges that CYP3A inhibitors may increase RPV plasma levels but no dose adjustment is required. Therefore it seems that the RPV plasma levels reached were not anticipated to be associated with important safety issues. On the other hand, using F/TAF 25 mg in the presence of well-recognised *potent* inhibitors of P-gp could lead to chronic exposure to plasma TFV that is well above that observed in the E/C/F/TAF and other studies that support beneficial safety effects (including the switch study GS-US-311-1089). It is not known whether longer-term exposure to plasma TFV levels well below those seen with TDF yet above those observed in the Phase 3 studies that provide the critical safety data for TAF vs. TDF could translate into a safety profile that more resembles TDF than TAF.

For F/TAF there is the option of using 10 mg TAF when it is given with potent P-gp inhibitors. In the D180 responses on F/TAF the applicant agreed that F/TAF 10 mg should be the dose used when the FDC is given with ciclosporin, ketoconazole and itraconazole. Since dose adjustment is not possible using F/R/TAF the only option seems to be to state that use with agents such as the triazoles and ciclosporin should be “not recommended” in the table in section 4.5.

Other DDI issues

F/R/TAF represents a single treatment regimen for HIV and therefore co-administration with other ART should not occur. This is stated in section 4.4 of the SmPC.

Other issues for TAF pharmacokinetics

The applicant has not been able to identify the mechanism of uptake of TAF into PBMCs. If there were to be any reason why TAF uptake into PBMCs was reduced to a level below that achieved with TDF 300 mg there would have to be a concern for efficacy. During the assessment of E/C/F/TAF and F/TAF the applicant provided additional argumentation supporting a conclusion that TAF uptake into cells is not associated with a specific transporter.

The applicant has concluded that TAF is primarily hydrolysed by CatA in PBMCs. Cathepsin A is a ubiquitously expressed multifunctional enzyme with deamidase, esterase and carboxypeptidase activities and is encoded by the CTSA gene. Genetic polymorphisms in CatA have been described, some of which can result in depressed enzymic activity. The potential for human polymorphisms in CatA to affect conversion of TAF to TFV was addressed during the procedure and seems to be remote. In-vitro studies did not suggest significant inhibition of the conversion step by HIV protease inhibitors (known to inhibit CatA) but during review of the E/C/F/TAF dossier the applicant acknowledged that the HCV PIs telaprevir and boceprevir could have an effect intracellularly and the SmPC was amended such that co-administration with these agents is not recommended. The same advice has been included in the F/R/TAF SmPC. The applicant commits to review newly marketed HIV or HCV PIs for any possibility that they could exert a similar effect on TAF conversion.

After TAF is converted to TFV it is proposed that metabolism proceeds via the purine catabolic pathway. This includes formation of uric acid. In the metabolite profiling study with TAF uric acid levels in pooled plasma increased over time and reached a maximum at 72 h. TAF was undetectable by the 6-h time point, indicating that the depurination reaction proceeded even after TAF was depleted from plasma. The applicant considered that in theory complete inhibition of the depurination pathway could result in increase of plasma TFV levels up to 4-fold. Even under these conditions, the plasma TFV levels would be lower than those after administration of TDF (300 mg). Since the depurination reaction is likely to occur after TAF is converted to TFV, potential induction of this pathway should not affect the TAF levels and, therefore, not affect efficacy which is mainly delivered by intact TAF. On this basis the applicant concluded that clinically important DDIs associated with the depurination pathway are unlikely.

TAF is slowly metabolised by CYP3A4 *in vitro*, which is inhibited by COBI. However, given the rapid rate of hydrolysis of TAF to form TFV it is thought to be unlikely that CYP3A4 plays a significant role in the activation of TAF.

Special populations

The SmPC recommends no dose adjustment in adult patients with estimated creatinine clearance ≥ 30 mL/min or with Class A or B hepatic impairment. Treatment should not be initiated if CrCL is < 30 mL/min and is not recommended in patients with Class C severe hepatic impairment due to lack of data. The Emtriva (FTC) SmPC requires lengthening of the dose interval when CrCL falls below 50 mL/min, which cannot be achieved using the F/R/TAF FDC. However, based on GS-US-292-0112, it was agreed that the data support use of FTC in patients with mild or moderate impairment of renal function without dose adjustment. Since this advice does not conflict with the RPV recommendations, the advice in the SmPC for F/R/TAF is acceptable regarding use in renal and hepatic impairment categories.

2.4.5. Conclusions on clinical pharmacology

TAF was selected for development specifically because it had potential to be active with much lower TFV plasma levels and hence improved safety vs. TDF. Thus, selection of the TAF dose could not be based on matching plasma profiles of TFV achieved with TAF vs. those observed with TDF. The TAF dose in F/R/TAF provides plasma TAF levels comparable with those obtained when 10 mg TAF is given with a strong P-gp inhibitor as part of E/C/F/TAF. F/R/TAF provides plasma levels of RPV bioequivalent to those achieved on dosing RPV alone under similar dosing conditions (i.e. after a standard moderate fat meal).

2.5. Clinical efficacy

2.5.1. Dose response studies

There were no dose-finding studies with F/TAF or F/R/TAF since the dose of TAF was identified from the monotherapy studies and modelling.

2.5.2. Main studies

The anticipated efficacy of F/RTAF is primarily based on PK bridging to the E/C/F/TAF and RPV Phase 3 studies in ART-naïve patients as described in the table below. The two Eviplera switch studies may be viewed as supportive. Data from the two adolescent studies (GS-US-292-0106 and C213) are notable because the F/R/TAF FDC is proposed for use from 12 years of age.

Data up to Week 48 were provided from the F/TAF switch study GS-US-311-1089 but very few patients received RPV as the third agent so they are of limited relevance. During the procedure blinded virologic failure rates were provided from two ongoing studies in which virologically suppressed patients remained on Atripla or Eviplera or switched to F/R/TAF. These switch studies are not in the overview of clinical studies table.

Overview of clinical studies

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented
E/C/F/TAF Studies			
HIV-Infected, ART-Naive Adult Subjects			
GS-US-292-0104	Phase 3, R DB study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC (N = 435) STB (N = 432)	Week 48 efficacy, PK, and safety
GS-US-292-0111	Phase 3, R DB to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC (N = 431) STB (N = 435)	Week 48 efficacy, PK, and safety
GS-US-292-0102	Phase 2, R DB to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB Open-label extension phase allowed crossover from STB to E/C/F/TAF after Week 48 and enrollment of virologically suppressed adults who had received a DRV+COBI-containing regimen in GS-US-299-0102*	Randomized phase: E/C/F/TAF FDC (N = 112); STB (N = 58) Open-label extension phase: Continued on E/C/F/TAF FDC (N = 105) Switch to E/C/F/TAF FDC (N = 161) from STB (N = 53) from D/C/F/TAF (N = 70) from DRV+COBI+TVD (N = 38)	Week 48[b] efficacy, PK, and safety
HIV-Infected, Virologically Suppressed Adult Subjects			
GS-US-292-0109	Phase 3, open-label switch study from a TDF-containing regimen to E/C/F/TAF FDC	Switch to E/C/F/TAF FDC (N = 959) Stay on TVD+3rd Agent (N = 477)	Week 48 efficacy and safety
HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment			
GS-US-292-0112	Phase 3, open-label	E/C/F/TAF FDC (N = 248)	Week 24 efficacy and safety
HIV-Infected, ART-Naive, Adolescent Subjects			
GS-US-292-0106	Phase 2/3, open-label	E/C/F/TAF FDC (N = 48) PK substudy: N = 24	Week 24 efficacy, PK, and safety
RPV Studies			
HIV-Infected, ART-Naive Adult Subjects			
C209 ECHO	Phase 3, randomized, double-blind	RPV + FTC/TDF (N = 346) EFV + FTC/TDF (N = 344)	Week 48 and 96 efficacy and safety

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented
C215 THRIVE	Phase 3, randomized, double-blind	RPV + background regimen of 2 N(t)RTIs (N = 340) EFV + background regimen of 2 N(t)RTIs (N = 338) FTC/TDF subset RPV + FTC/TDF (N = 204) EFV + FTC/TDF (N = 202)	Week 48 and 96 select[c] safety FTC/TDF subset: Week 48 and 96 efficacy and select[c] safety
HIV-Infected, ART-Naive Adolescent Subjects			
C213 PAINT	Phase 2, open-label, adolescents aged 12 to < 18 years.	RPV + investigator-selected background regimen of 2 N(t)RTIs (N = 36)	Week 48 efficacy, PK, and safety
Eviplera Studies			
HIV-Infected, Virologically Suppressed Adult Subjects			
GS-US-264-0111	Phase 2b, open-label switching from EFV/FTC/TDF STR to FTC/RPV/TDF (Eviplera)	Eviplera Group: (N = 49)	Week 48 efficacy, PK, and safety
GS-US-264-0106	Phase 3, randomized, open-label, in virologically suppressed, HIV-1 infected subjects.	Eviplera Group: (N = 317) Stay on Baseline Regimen (SBR) Group: 24 weeks, then switched to Eviplera for 24 weeks (N = 152) Total Eviplera Group: The Eviplera group +the Delayed Switch Group (N = 469)	Week 48 efficacy and safety

TVD = Truvada® (FTC/TDF).

a Subjects included in the Safety Analysis Set

b The randomised phase was 48 week;

c FTC/TDF with RPV subsets from Studies C209 and C215 provide data for RPV+ FTC+TFV prodrug

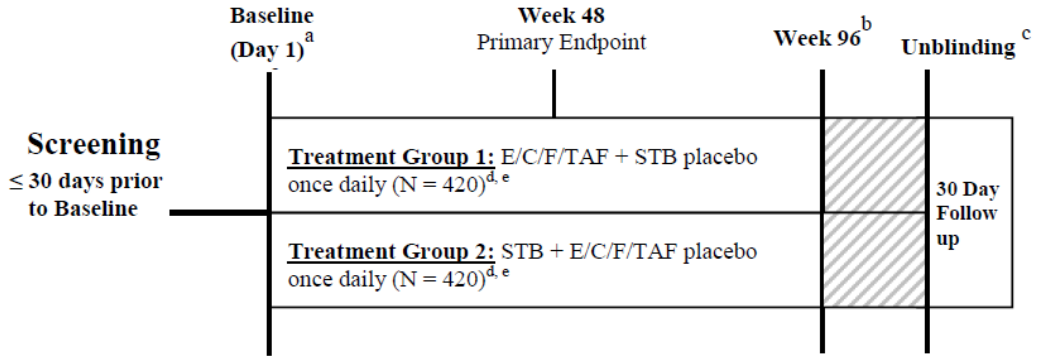
Summary of the main efficacy studies to which F/R/TAF is bridged

GS-US-292-0104 and 0111

Study Titles: Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment- Naive Adults

The two double-blind studies in ART-naïve patients were of the same design as summarised in Figure 4.

Figure 4. Study design



a Following the baseline visit, subjects returned for study visits at Weeks 2, 4, 8, 12, 16, and 24 and then every 12 weeks through Week 96.
b Subjects will continue to attend visits every 12 weeks following Week 96 until treatment assignments are unblinded.
c Once Gilead provides unblinded treatment assignments to the investigators, all subjects will return to the clinic (preferably within 30 days) for an unblinding visit. At the unblinding visit all subjects will discontinue their blinded study drugs and will be given an option to participate in an OL rollover study. Subjects who do not wish to participate in the OL rollover study will discontinue their blinded study drugs and will return for a 30 Day Follow-up visit following the unblinding visit.
d Subjects who have discontinued study drugs prior to the unblinding visit will not be eligible for the OL rollover study; these subjects will be asked to continue attending the scheduled study visits through the unblinding visit and discontinue the study after the unblinding visit.
e E/C/F/TAF and matching placebo were administered orally, 1 tablet, once daily with food at approximately the same time each day. STB and matching placebo were administered orally, 1 tablet, once daily, with food at approximately the same time each day

The main inclusion criteria were:

- Aged ≥ 18 years with plasma HIV-1 RNA ≥ 1000 copies/mL at screening
- No prior use of any approved or investigational ARV except the use for PrEP or PEP up to 6 months prior to screening
- Screening genotype report must have shown sensitivity to EVG, FTC and TDF
- Normal ECG or no clinically significant abnormalities
- $eGFR_{CG}$ ≥ 50 mL/min
- AST and ALT ≤ 5 × ULN and total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin
- Absolute neutrophil count ≥ 1000/mm3; platelets ≥ 50,000/mm3; haemoglobin ≥ 8.5 g/dL
- Serum amylase ≤ 5 × ULN (or > 5 × ULN but with lipase ≤ 5 × ULN)

Randomisation using IVRS or IWRS was 1:1 to E/C/F/TAF or STB and was stratified by:

- HIV-1 RNA level (≤ 100,000, > 100,000 to ≤ 400,000 copies/mL, > 400,000 copies/mL)
- CD4 count (< 50 cells/μL, 50 to 199 cells/μL, ≥ 200 cells/μL)
- Region (US vs. ex-US)

Virologic outcome was categorised as follows:

- Virologic success - last available HIV-1 RNA < 50 copies/mL in the Week 48 analysis window while on assigned treatment

- Virologic failure - any of:

  a) Last available HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window

  b) No on-treatment HIV-1 RNA data in the Week 48 analysis window and last available on-treatment HIV-1 RNA ≥ 50 copies/mL

  c) Non-study ARV added between the first dose and last on-treatment HIV-1 RNA within the
- Week 48 analysis window
- No virologic data in the Week 48 analysis window
- Suboptimal virologic response = < 1 $\log_{10}$ reduction in HIV-1 RNA from baseline and ≥ 50 copies/mL at the Week 8 visit, confirmed at a scheduled or unscheduled visit following Week 8.
- Virologic rebound = after achieving HIV-1 RNA < 50 copies/mL, there is ≥ 50 copies/mL confirmed at any scheduled or unscheduled visit.

Objectives

The primary objective was to evaluate the efficacy of E/C/F/TAF vs. STB in HIV-infected, ART naive adults based on HIV-1 RNA < 50 copies/mL at Week 48. The details of the assay(s) used to measure HIV RNA are not reported but virological responses are reported at the < 50 and < 20 copies/mL level.

A sample size of 840 patients randomised 1:1 (420 per group) was planned to achieve at least 95% power to assess a non-inferiority margin of 12% applied to the difference in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the FDA snapshot algorithm) between 2 groups. It was assumed that each treatment would elicit a response rate of 0.85. The significance level was 1-sided alpha of 0.025.

Two interim IDMC analyses were conducted prior to the primary analysis. An alpha penalty of 0.00001 was applied for each interim analysis so the primary efficacy hypothesis of non-inferiority of E/C/F/TAF vs. STB was tested with a 1-sided, 0.02499 alpha level. The Week 48 primary efficacy analysis used the FAS. The baseline stratum weighted difference in the response rate and its 95.002% CI were calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion.

Based on planned Week 48 interim analyses conducted after all randomised patients had completed the Week 48 study visit or had prematurely discontinued. It was planned that data would be combined across studies to assess efficacy, including an assessment of superiority of E/C/F/TAF over STB. After Week 96, patients will continue to take their blinded study drugs and attend visits every 12 weeks until treatment assignments are unblinded, at which point all patients will return for an unblinding visit and will be given the option to participate in an open-label (OL) rollover study to receive E/C/F/TAF.

GS-US-292-0109

Study Title: A Phase 3, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects

Objectives

The primary objective of this study was as follows:

- To evaluate the noninferiority of switching to a TAF-containing FDC relative to maintaining TDF-containing regimens in virologically suppressed, HIV-infected subjects as determined by having HIV-1 RNA < 50 copies/mL at Week 48 FDA snapshot algorithm

The secondary objectives of this study were as follows:

- To determine the safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine BMD at Week 48
- To determine the safety of the 2 treatment groups as determined by the change from baseline in serum creatinine at Week 48

GS-US-292-0112

Study Title: A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

This open-label study was primarily designed to assess the safety profile of E/C/F/TAF in HIV-infected patients with stable renal impairment ($eGFR_{CG}$ 30-69 mL/min) at Week 24. Enrolment was in 2 cohorts:

- **Cohort 1**: switched to E/C/F/TAF from an existing ARV regimen on which they had HIV-1 RNA < 50 copies/mL for at least 6 months or they had successfully completed GS-US-236-0118.
- **Cohort 2**: ARV-naïve with plasma HIV-1 RNA ≥ 1000 copies/mL

All subjects received E/C/F/TAF once daily with food. Selection criteria were similar to those for Phase 3.

In Cohort 1 the majority was male (79.3%) with median age 58 years (63 were ≥ 65 years). Most (65.3%) were taking TDF-containing regimens prior to the switch. The baseline median CD4 count and CD4% were 632 cells/µL and 34.7%, respectively. Overall, 97.5% had baseline HIV-1 RNA < 50 copies/mL and 2.5% had ≥ 50 to ≤ 100,000 copies/mL. The majority acquired HIV via homosexual sex (52.1%), 74.4% were asymptomatic and 14.0% had AIDS. Overall, 33.1% had eGFRCG < 50 mL/min, 63.6% had eGFRCG 30-59 mL/min, 42.3% had clinically significant proteinuria (UPCR > 200 mg/g) and 48.9% had clinically significant albuminuria (UACR ≥ 30 mg/g). Dipsticks showed that 9.5% had Grade 2, 23.1% had Grade 1 and 67.4% had no proteinuria. In Cohort 2 only 6 patients were enrolled.

Following the completion of all patients to Week 48 there were no clinically relevant differences in virologic success rates between subgroups (age, sex, race, region, or study drug adherence rate) for Cohort 1. The virologic success rate for those aged ≥ 65 years was 85.7% (54/63). The percentages with < 20 copies/mL at Week 48 using the FAS were 90.1% for Cohort 1 (baseline eGFRCG < 50 mL/min 88.8%; baseline eGFRCG ≥ 50 mL/min 90.7%) and 6/6 in Cohort 2. In Cohort 1, 2 patients (0.8%) had virus that showed resistance to multiple drug classes. One had the same resistance documented in an historic genotype and the other appeared to have had reinfection with a resistant virus.

Results

Efficacy outcomes for the F/TAF studies

Table 13. Virologic outcomes of studies GS US 292 0104, GS US 292 0111 at Week 48 and Week 96 a, and GS US 292 0109 at Week 48a

	Treatment-naïve adults in studies GS-US-292-0104 and GS-US-292-0111[b]				**Virologically suppressed adults in study GS-US-292-0109**	
	Week 48		**Week 96**		**Week 48**	
	E/C/F/TAF (n = 866)	**E/C/F/TDF(n = 867)**	**E/C/F/TAF (n = 866)**	**E/C/F/TDF (n = 867)**	**E/C/F/TAF (n = 959)**	**Baseline regimen (n = 477)**
HIV-1 RNA < 50 copies/mL	92%	90%	87%	85%	97%	93%
Treatment difference	2.0% (95% CI: -0.7% to 4.7%)		1.5% (95% CI: -1.8% to 4.8%)		4.1% (95% CI: 1.6% to 6.7%, p < 0.001[c])	
HIV-1 RNA ≥ 50 copies/mL[d]	4%	4%	5%	4%	1%	1%
No virologic data in Week 48 or 96 window	4%	6%	9%	11%	2%	6%
Discontinued study drug due to AE or[e]	1%	2%	1%	2%	1%	1%
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[f]	2%	4%	6%	7%	1%	4%
Missing data during window but on study drug	1%	< 1%	2%	1%	0%	<1%
HIV-1 RNA < 20 copies/mL	84%	84%	82%	80%		
Treatment difference	0.4% (95% CI: -3.0% to 3.8%)		1.5% (95% CI: -2.2% to 5.2%)			
Proportion (%) of patients with HIV-1 RNA < 50 copies/mL by prior treatment regimen[d]						
EFV/FTC/TDF					96%	90%
FTC/TDF plus boosted atazanavir					97%	92%
E/C/F/TDF					98%	97%

a Week 48 window was between Day 294 and 377 (inclusive); Week 96 window was between Day 630 and 713 (inclusive).

b In both studies, patients were stratified by baseline HIV-1 RNA (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL), by CD4+ cell count (< 50 cells/µL, 50-199 cells/µL, or ≥ 200 cells/µL), and by region (US or ex US).

c P-value for the superiority test comparing the percentages of virologic success was from the CMH (Cochran-Mantel-Haenszel) test stratified by the prior treatment regimen (EFV/FTC/TDF, FTC/TDF plus boosted atazanavir, or E/C/F/TDF).

d Included patients who had ≥ 50 copies/mL in the Week 48 or 96 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

e Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

f Includes patients who discontinued for reasons other than an AE, death, or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

Table 14. GS-US-292-0112: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	Cohort 1: Switch			Cohort 2: ART-Naive
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)	Total (N = 6)
Virologic success at Week 48[a]; n (%)				
HIV-1 RNA < 50 copies/mL	72 (90.0)	150 (96.2)	222 (91.7)	6 (100.0)
95% CI[b]	81.2% to 95.6%	87.4% to 96.1%	87.5% to 94.9%	54.1% to 100.0%
Virologic failure at Week 48[a]; n (%)	0	3 (1.9)	3 (1.2)	0
HIV-1 RNA ≥ 50 copies/mL	0	1 (0.6)	1 (0.4)	0
Discontinued study drug due to lack of efficacy	0	1 (0.6)	1 (0.4)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA >= 50 copies/mL[c]	0	0	0	0
Added new ARV	0	1 (0.6)	1 (0.4)	0
No virologic data in Week 48 window[a]; n (%)	8 (10.0)	9 (5.6)	17 (7.0)	0
Discontinued study drug due to AE/death	5 (6.3)	2 (1.2)	7 (2.9)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[c]	1 (1.3)	6 (3.7)	7 (2.9)	0
Missing data during window but on study drug	2 (2.5)	1 (0.6)	23 (1.2)	0

a Week 48 window is between Day 294 and 377 (inclusive).

b The 95% CIs for virologic success rate in each cohort and baseline eGFR category was obtained using Exact method.

c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

CD4 cell counts remained stable during treatment with E/C/F/TAF for Cohort 1 and increased in Cohort 2 with a mean change from baseline to Week 48 of 152 [SD 152.3] cells/µL.

Rilpivirine studies

TMC278-C209 and TMC278-C215 studies

Study Titles: C209: A Phase III, randomized, double-blind trial of TMC278 25 mg qd versus efavirenz 600 mg qd in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive HIV-1 infected subjects

C215: A Phase III, randomized, double-blind trial of TMC278 25 mg q.d. versus efavirenz 600 mg q.d. in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors in antiretroviral-naive HIV-1 infected subjects.

Objectives

The primary objective of this trial was to demonstrate non-inferiority of treatment with RPV when administered as 25 mg once daily compared with control (EFV 600 mg once daily) in regard to the proportion of virologic responders (plasma viral load < 50 HIV-1 RNA copies/mL, according to the TLOVR algorithm) at 48 weeks in ARV treatment-naive HIV-1 infected adult subjects, with a maximum allowable difference of 12%.

Diagnosis and Main Criteria for Inclusion

Adult subjects with a viral load ≥ 5000 copies/mL, who were ARV treatment-naive, who had HIV-1 susceptible to the FTC/RTF at screening, and in whom the genotype of HIV-1 exhibited no NNRTI RAMs at screening were eligible for the trial.

Study GS-US-264-0111

Study Title: A Phase 2b Open-Label Pilot Study to Evaluate Switching from a Regimen Consisting of an Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) Single Tablet Regimen (STR) to Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) STR in Virologically-Suppressed, HIV-1 Infected Subjects

Objectives

The primary objective of this study was as follows:

- To evaluate the efficacy of Complera/Eviplera after switching from EFV/FTC/TDF (ATR) at baseline in maintaining HIV-1 RNA < 50 copies/mL at Week 12
- The secondary objectives of this study were as follows:
- To evaluate the safety and tolerability of Complera/Eviplera over 24 and 48 weeks
- To evaluate the efficacy of Complera/Eviplera after switching from EFV/FTC/TDF at baseline in maintaining HIV-1 RNA < 50 copies/mL at Week 24 and Week 48
- To explore the PK of RPV after switching from EFV

Diagnosis and Main Criteria for Inclusion

Subjects were HIV-1 infected adults receiving a first ARV regimen consisting of EFV/FTC/TDF for ≥ 3 months at screening, had maintained plasma HIV-1 RNA concentrations at undetectable levels (at least 2 measurements) while on treatment according to the local assay being used for ≥ 8 weeks prior to screening, had RNA < 50 copies/mL at the screening visit, and had decided on a change of regimen due to EFV intolerance. Subjects were also required to have adequate renal function and, prior to starting Complera/Eviplera, a genotype and no known resistance to any of the study agents at any time in the past, including but not limited to, the reverse transcriptase mutations K65R, K101E/P, E138G/K/Q/R, Y181C/I/V, M184V/I, and H221Y.

Study GS-US-264-0106

Study Title: A Phase 3b Randomized, Open-Label Study to Evaluate Switching from Regimens Consisting of a Ritonavir-boosted Protease Inhibitor and Two Nucleoside Reverse Transcriptase Inhibitors to Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) Fixed-dose Regimen in Virologically Suppressed, HIV-1 Infected Patients

Objectives

The primary objective of this study was to evaluate the noninferiority of Complera/Eviplera relative to regimens consisting of a PI/r and 2 NRTIs in maintaining HIV-1 RNA < 50 copies/mL at Week 24.

The secondary objectives of this study were as follows:

- To evaluate the change from baseline in fasting lipid parameters (total cholesterol, LDL and HDL cholesterol, and triglycerides) over 24 and 48 weeks
- To evaluate the safety and tolerability of each treatment over 24 and 48 weeks
- To evaluate the change from baseline in CD4+ cell count in each treatment group at 24 and 48 weeks

Diagnosis and Main Criteria for Inclusion

The study included adult HIV-1 infected subjects currently receiving ARV therapy consisting of a PI/r and 2 NRTIs continuously for ≤ 6 months preceding the screening visit. Subjects had plasma HIV-1 RNA concentrations (at least 2 measurements) at undetectable levels (according to the local assay being used) for ≤ 6 months prior to the screening visit and had HIV RNA < 50 copies/mL at the screening visit. Subjects had to be on their first or second ARV drug regimen; if on their second regimen, must not have had HIV-1 RNA ≥ 50 copies/mL at the time of the change in ARV drugs nor ever experienced 2 consecutive HIV RNA ≥ 50 copies/mL after first achieving HIV RNA < 50 copies/mL. Subjects were required to have adequate renal function defined as having an eGFR ≥ 70 mL/min according to the CG formula. Subjects must have had no previous use of any approved or experimental NNRTI drug for any length of time, and must have had hepatic transaminases (AST and ALT) ≤ 5 x upper limit of normal, with no proven or suspected acute hepatitis in the 30 days prior to study entry. A genotype was required prior to starting initial ARV therapy, and subjects must have had no known resistance to any of the study agents at any time in the past including, but not limited to the reverse transcriptase (RT) resistance mutations K65R, K101E/P, E138G/K/R/Q, Y181C/I/V, M184V/I, or H221Y.

Efficacy outcomes for the rilpivirine studies

RPV Studies C209, C215, and Pooled Data (FTC/TDF Subset Populations)

Table 15. Virologic outcomes of randomised treatment of studies TMC278-C209 and TMC278-C215 (pooled data for patients receiving rilpivirine hydrochloride or efavirenz in combination with FTC/TDF) at Week 48 (primary) and Week 96

	RPV + FTC/TDF (n = 550)	EFV + FTC/TDF (n = 546)	RPV + FTC/TDF (n = 550)	EFV + FTC/TDF (n = 546)
	Week 48		Week 96	
Overall response (HIV-1 RNA < 50 copies/mL (TLOVR[a]))[b]	83.5% (459/550)	82.4% (450/546)	76.9% (423/550)	77.3% (422/546)
By baseline viral load (copies/mL)				
≤ 100,000	89.6% (258/288)	84.8% (217/256)	83.7% (241/288)	80.8% (206/255)
> 100,000	76.7% (201/262)	80.3% (233/290)	69.5% (182/262)	74.2% (216/291)
Non-response				
Virologic failure (all patients)	9.5% (52/550)	4.2% (23/546)	11.5% (63/550)[c]	5.1% (28/546)[d]
By baseline viral load (copies/mL)				
≤ 100,000	4.2% (12/288)	2.3% (6/256)	5.9% (17/288)	2.4% (6/255)

	RPV + FTC/TDF (n = 550)	EFV + FTC/TDF (n = 546)	RPV + FTC/TDF (n = 550)	EFV + FTC/TDF (n = 546)
	Week 48		Week 96	
> 100,000	15.3% (40/262)	5.9% (17/290)	17.6% (46/262)	7.6% (22/291)
Death	0	0.2% (1/546)	0	0.7% (4/546)
Discontinued due to adverse event (AE)	2.2% (12/550)	7.1% (39/546)	3.6% (20/550)	8.1% (44/546)
Discontinued for non-AE reason[e]	4.9% (27/550)	6.0% (33/546)	8% (44/550)	8.8% (48/546)

EFV = efavirenz; RPV = rilpivirine

a ITT TLOVR = Intention to treat time to loss of virologic response.

b The difference of response rate at Week 48 is 1% (95% confidence interval -3% to 6%) using normal approximation.

c There were 17 new virologic failures between the Week 48 primary analysis and Week 96 (6 patients with baseline viral load ≤ 100,000 copies/mL and 11 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the Week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.

d There were 10 new virologic failures between the Week 48 primary analysis and Week 96 (3 patients with baseline viral load ≤ 100,000 copies/mL and 7 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the Week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.

e e.g. lost to follow up, non-compliance, withdrew consent.

Studies in paediatrics

GS-US-292-0106

Study Title: A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents

This open-label study was conducted in ARV-naïve HIV-infected adolescents (aged 12 to < 18 years) with body weight ≥ 35 kg, plasma HIV-1 RNA ≥ 1000 copies/mL, CD4 cell counts > 100 cells/µL and eGFR ≥ 90 mL/min/1.73 m2 (Schwartz formula) at screening. Viruses were to be sensitive to TFV, EVG and FTC based on genotyping at screening. All patients received E/C/F/TAF QD with food.

In Part A: 18 to 24 patients (at least 6 aged 12 to < 15 years and 6 aged 15 to < 18 years) were to be enrolled to evaluate steady-state intensive PK at Week 4 (see Pharmacokinetics).

In Part B: The remaining patients (up to the planned total of 50 across Parts A and B) were enrolled to evaluate the safety and antiviral activity of E/C/F/TAF.

The completed Week 24 analyses showed that 90% (45/50) had < 50 copies/mL. There was no virologic resistance to E/C/F/TAF detected.

The mean (SD) increase from baseline in CD4 cell count at Week 24 was 191 (175.2) cells/µL

Table 16. GS-US-292-0106: Virologic Outcome at Week 24 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	E/C/F/TAF (N=50)
Virologic Success at Week 24[a]; n (%)	
HIV-1 RNA < 50 copies/mL	45 (90.0)
Virologic Failure at Week 24[a]; n (%)	4 (8.0)
HIV-1 RNA >= 50 copies/mL	3 (6.0)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[b]	1 (2.0)
Added New ARV	0
No Virologic Data in Week 24 Window[a]; n (%)	1 (2.0)
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[b]	1 (2.0)
Missing Data During Window but on Study Drug	0

a Week 24 window is between Day 140 and 195 (inclusive).

b Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

Study TMC278-C213: A Phase II, open-label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of TMC278 in antiretroviral-naïve HIV-1 infected adolescents aged 12 to <18 years.

The study population consisted of boys and girls, aged ≥12 to <18 years, weighing ≥32 kg, with documented chronic HIV-1 infection who were treatment naïve at screening. Patients' HIV-1 plasma viral load at screening was ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL for Part 1b and Part 2 of the study. For Part 1a, patients with a screening viral load ≥ 5,000 HIV-1 RNA copies/mL were allowed.

Main exclusion criteria were: NNRTI resistance at screening or from historical data available in the source documents; any currently active Acquired Immunodeficiency Syndrome (AIDS) defining illness; any active clinically significant disease; Risk factors for QTc prolongation.

Objectives

The objectives of Part 1 of this study were:

- to evaluate the steady-state pharmacokinetics of RPV 25 mg qd in patients aged ≥12 to <18 years;
- to evaluate short-term safety and antiviral activity of RPV in this age group.

The objectives of Part 2 of this study were:

- to evaluate long-term safety and efficacy over a 24- and 48-week treatment period of RPV;
- to evaluate immunologic changes (as measured by CD4+ cell parameters) over a 24- and 48-week treatment period of RPV;

- to assess the evolution of viral genotype and phenotype over a 24- and 48-week treatment period of RPV;
- to evaluate pharmacokinetics (by means of population pharmacokinetics) and pharmacokinetic-pharmacodynamic relationships for safety and efficacy of RPV;
- to evaluate treatment adherence as measured by the Study Adherence Questionnaire for Children and Teenagers.

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population Week 48			
Descriptive statistics and estimate variability	Treatment group	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load ≤100000 copies/mL	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load >100000 copies/mL
	Number of subject	36	28	8
	Virologic Response HIV-1 RNA <50 copies/mL, TLOVR, n (%)	26 (72.2%)	22 (78.6%)	4 (50.0%)
	95% CIs	[54.8% - 85.8%]	[59.1% - 91.7%]	[15.7% - 84.3%]
	Virologic failure never suppressed initial lack of response rebounder *Discontinued due to AE* *Discontinued due to reason other than AE*	8 (22.2%) 4 (11.1%) 1 (2.8%) 4 (11.1%) 1 (2.8%) 1 (2.8%)	5 (17.9%) 2 (7.1%) 0 3 (10.7%) 0 1 (3.6%)	3 (37.5%) 2 (25.0%) 1 (12.5%) 1 (12.5%) 1 (12.5%) 0
Notes	Rilpivirine resistance mutations were observed in 62.5% (5/8) of subjects with virological failure. In 4 of those 5 subjects, NRTI resistance was observed as well.			
Analysis population and time point description	Intent to treat population, sensitivity analyses Week 48			
Descriptive statistics	Treatment group	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load ≤100000 copies/mL	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load >100000 copies/mL

	Virologic Response HIV-1 RNA <50 copies/mL, n (%)						
	Snapshot	N= 36	26 (72.2)	N= 28	22 (78.6)	N= 8	4 (50.0)
	NC=F	N= 36	26 (72.2)	N= 28	22 (78.6)	N= 8	4 (50.0)
	Observed	N= 29	26 (89.7)	N= 25	22 (88.0)	N= 4	4 (100)
	CD4+ cell count mean change from baseline						
	NC=F	201.2 (32.87)		214.5 (38.85)		154.5 (59.47)	
	N=total number of subjects, n=number of responders.						
Analysis population and time point description	Summary Statistics of Individual Population PK Model-Derived Parameters of RPV 25 mg qd in Adolescents and Adults (Week 48 Analysis)						
PK analysis	mean±SD (range)	Adolescents (C213)		Adults (pooled Phase 3)			
	N	34		679			
	C_{0h}, ng/mL	84±39 (7 - 202)		80±37 (1.45 - 300)			
	AUC_{24h}, ng.h/mL	2391±991 (417 – 5166)		2397±1032 (482 – 8601)			
	N=number of subjects with data						

Ongoing Studies with F/R/TAF

Two Phase 3b studies (GS-US-366-1160 and GS-US-366-1216) are currently ongoing with the F/R/TAF FDC and will provide post-approval data on use in HIV-1 infected patients who are virologically suppressed on their current regimen.

GS-US-366-1160 is a randomised (1:1), double-blind Phase 3b study in which virologically-suppressed patients do or do not switch from Atripla (EFV/FTC/TDF) to F/R/TAF. The primary analysis will consist of a non-inferiority evaluation of switching to F/R/TAF vs. continuing on Atripla based on proportions with HIV-1 RNA <50 copies/mL at Week 48 (as defined by the FDA snapshot analysis). Interim unaudited data reported that the study was fully enrolled with 875 patients and the median study drug duration as of 14 December 2015 was 12.3 weeks. Virologic success (HIV-1 RNA < 50 copies/mL, missing treated as failure) at Week 12 per blinded preliminary data of both treatment groups combined was 97% (855/874) and there were no discontinuations due to lack of efficacy. Treatment-emergent AEs leading to study drug discontinuation occurred in 11 patients (1.3%), none of whom had evidence of virologic failure at the time of discontinuation.

GS-US-366-1216 is a randomised (1:1), double-blind Phase 3b study in which virologically-suppressed patients do or do not switch from Eviplera to F/R/TAF. The primary analysis will consist of a non-inferiority evaluation of switching to F/R/TAF vs. continuing on Eviplera based on proportions with HIV-1 RNA < 50 copies/mL at Week 48 (as defined by the FDA snapshot analysis). Based on interim unaudited data the study was fully enrolled with 630 patients and the median study drug duration as of 14 December 2015 was 14.7 weeks. Virologic success (HIV-1 RNA < 50 copies/mL, missing treated as failure) at Week 12 per blinded preliminary data of both treatment groups combined was 98.3% (619/630) and there were no discontinuations due to lack of efficacy. Treatment-emergent AEs leading to study drug discontinuation occurred in 2 patients (0.3%), neither of whom had evidence of virologic failure at the time of discontinuation.

2.5.3. Discussion on clinical efficacy

Dose of TAF within F/R/TAF

The Phase 2 and 3 E/C/F/TAF studies vs. STB evaluated the use of TAF with other highly active agents to which patients' viruses were known to be susceptible. The design of these studies, while appropriate for patient care, cannot provide definitive evidence that the TAF dose within these highly active regimens was necessarily sufficient. The critical data to support the dose in the FDC come from the monotherapy studies (with doses ranging from 8 to 150 mg), the Emax modelling and the PK data. Taking into account the apparent lack of any negative interaction between TAF and RPV, the use of 25 mg TAF when combined with FTC and RPV can be supported. The discussion of pharmacokinetics further considers the basis for bridging efficacy from Genvoya and Edurant studies to F/R/TAF.

Indicated population for F/R/TAF

Phase 2 results suggested that STB might be better than E/C/F/TAF in those with the highest baseline viral loads (but only 20% had >100,000 c/mL) and lowest CD4 counts (but < 5% had < 200 cells/µL). One Phase 3 study (0104) essentially showed no difference between treatments in these subgroups. In the other study (0111) the differences in percentages (E/C/F/TAF vs STB) were -3.1% (95% CI: -12.8% to 6.5%) for baseline HIV-1 RNA > 100,000 copies/mL and -6.4% (95% CI: -20.8% to 8.0%) for baseline CD4 cell count < 200 cells/µL. After further exploration of the data pooled across Phase 2 and 3 studies the applicant concluded that the apparent differences between treatments for the subgroups were driven by non-virologic reasons for non-success (e.g. missing data or study drug discontinuation due to AEs, deaths or other reasons). These arguments were accepted for Genvoya.

Moreover, updated week 96 efficacy results were provided for these studies (0104 and 0111) and are reflected in section 5.1 of the SmPC.

Nevertheless, it is appropriate that the proposed indication for use of F/R/TAF is restricted to patients with ≤ 100,000 HIV-1 RNA copies/mL due to the conclusions drawn from the RPV Phase 3 studies. In addition, the SmPC conveys the major findings from the RPV studies, including the high rate of emergent RAMs in viruses from treatment failures.

Use of F/R/TAF in adolescents

The E/C/F/TAF study, included the updated results, was assessed as part of the application dossier for Genvoya. The viral response rate in the 48 adolescents studied was high and similar to that in adults. Emergence of viral resistance was not observed.

In contrast, the viral response rates at Week 24 and 48 (75% and 72%) in the 36 adolescents enrolled into the RPV study C213 were, if anything, slightly lower than observed in the adult Phase 3 studies. In common with the adult studies there was lower efficacy as viral load increased and 6/8 failures at Week 48 had evidence of emergence of NNRTI resistance mutations. There were no further virologic failures between weeks 48 and 96. At Week 48 72.2% (26/36) were virologic responders. These results are described under the heading Paediatric population in section 5.1 of the SmPC. The warning statement agreed as a result of the variation to add use in adolescents to the Edurant SmPC has been carried over into the F/R/TAF SmPC.

Lack of efficacy data with F/R/TAF

Unfortunately the applicant's two ongoing studies with F/R/TAF are both switch studies (one from Atripla and one from Eviplera), so that the question of primary efficacy will not be addressed. Nevertheless, supportive

efficacy data and very useful safety data will come from these two studies. Thus far the blinded data suggest very high rates of maintenance of viral suppression.

2.5.4. Conclusions on the clinical efficacy

F/R/TAF provides plasma levels of RPV bioequivalent to those achieved on dosing RPV alone under similar dosing conditions (i.e. after a standard moderate fat meal). Therefore the contribution of RPV to the efficacy of F/R/TAF could be presumed to be similar to that exerted when it is combined with FTC/TDF, including administration as the FDC Eviplera. In Phase 3 studies with RPV in combination with FTC/TDF or with other NRTIs, the viral suppression rates have been lower than observed with E/C/F/TAF, especially in the subset with the highest baseline viral loads, with emergence of NNRTI RAMs in a substantial proportion of virological failures. However, the F/R/TAF SmPC recommends dosing with food and restricts use to patients with viral loads < 100,000 c/mL.

2.6. Clinical safety

The safety of the FTC/RPV/TAF (200/25/25 mg) FDC is based on the established safety of E/C/F/TAF (150/150/200/10 mg), Edurant (RPV 25 mg), and Complera/Eviplera (FTC/RPV/TDF 200/25/300 mg) using a pharmacokinetic bioequivalence bridge between FTC/RPV/TAF and E/C/F/TAF (for the FTC/TAF component) and between FTC/RPV/TAF and Edurant (for the RPV component). The safety of E/C/F/TAF, Edurant, and Complera/Eviplera has been established in the following HIV-infected patient populations:

- Antiretroviral therapy (ART)-naive subjects: E/C/F/TAF pivotal Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 and the randomized phase of Phase 2 Study GS-US-292-0102; RPV pivotal Phase 3 Studies C209 and C215
- Virologically suppressed subjects: E/C/F/TAF Phase 3 Study GS-US-292-0109 and the open-label extension phase of Phase 2 Study GS-US-292-0102; Complera/Eviplera Phase 2b Study GS-US-264-0111 and Phase 3b Study GS-US-264-0106
- Subjects with mild to moderate renal impairment: E/C/F/TAF Phase 3 Study GS-US-292-0112
- ART-naive adolescent subjects: E/C/F/TAF Phase 2/3 Study GS-US-292-0106; RPV Phase 2 Study C213

The applicant provided a summary of safety containing all the information related to E/C/F/TAF, F/TAF, RPV and FTC/RPV/TDF.

Section 4.8 of the SmPC is based on the two E/C/F/TAF studies vs. STB in the ART-naïve and the two pivotal RPV studies in the ART-naïve plus post-marketing experience from Eviplera. The table in section 4.8 of the SmpC attempts to differentiate whether the table entries arise from the E/C/F/TAF or RPV studies or the post-marketing experience.

Patient exposure

The assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which 2,396 patients received emtricitabine+tenofovir alafenamide given with elvitegravir+cobicistat as a fixed-dose combination tablet, pooled data from 686 patients in the controlled studies TMC278-C209 and TMC278-C215 in antiretroviral treatment-naïve HIV-1 infected adults, who received rilpivirine 25 mg once

daily in combination with other antiretroviral medicinal products, and on post-marketing experience with emtricitabine/rilpivirine/tenofovir disoproxil fumarate.

In Phase 1 studies, a total of 197 healthy subjects received at least 1 dose of the FTC/RPV/TAF FDC.

Adverse events

Table 17. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Adverse Events Related to Study Drug Reported in ≥ 1% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term	E/C/F/TAF (N=866)	STB (N=867)
Number of Subjects Experiencing Any Study-Drug-Related Adverse Event	342 (39.5%)	364 (42.0%)
Gastrointestinal disorders	185 (21.4%)	224 (25.8%)
Nausea	90 (10.4%)	113 (13.0%)
Diarrhoea	62 (7.2%)	74 (8.5%)
Flatulence	19 (2.2%)	25 (2.9%)
Vomiting	16 (1.8%)	27 (3.1%)
Abdominal distension	13 (1.5%)	9 (1.0%)
Abdominal pain	11 (1.3%)	11 (1.3%)
Abdominal pain upper	9 (1.0%)	11 (1.3%)
General disorders and administration site conditions	61 (7.0%)	46 (5.3%)
Fatigue	43 (5.0%)	35 (4.0%)
Metabolism and nutrition disorders	26 (3.0%)	17 (2.0%)
Decreased appetite	12 (1.4%)	9 (1.0%)
Musculoskeletal and connective tissue disorders	29 (3.3%)	39 (4.5%)
Osteopenia	8 (0.9%)	17 (2.0%)
Nervous system disorders	97 (11.2%)	82 (9.5%)
Headache	52 (6.0%)	47 (5.4%)
Dizziness	26 (3.0%)	19 (2.2%)
Somnolence	9 (1.0%)	10 (1.2%)
Psychiatric disorders	47 (5.4%)	58 (6.7%)
Abnormal dreams	13 (1.5%)	26 (3.0%)
Insomnia	17 (2.0%)	14 (1.6%)
Renal and urinary disorders	10 (1.2%)	20 (2.3%)
Proteinuria	7 (0.8%)	10 (1.2%)
Skin and subcutaneous tissue disorders	46 (5.3%)	42 (4.8%)
Rash	13 (1.5%)	11 (1.3%)

Table 18. RPV Studies C209 and C215: Treatment-Related Adverse Events Reported of at least grade 2 in severity in ≥ 1% of Subjects in the RPV or Control Group (Regardless of Severity) (Phase 3 Week 96 Pooled Analysis)

System Organ Class Preferred term, n (%)	C209		C215		Pooled	
	RPV N = 346	Control N = 344	RPV N = 340	Control N = 338	RPV N = 686	Control N = 682
Any treatment-related[a] AE of at least Grade 2	**61 (17.6)**	**115 (33.4)**	**55 (16.2)**	**111 (32.8)**	**116 (16.9)**	**226 (33.1)**
Psychiatric Disorders	**18 (5.2)**	**38 (11.0)**	**23 (6.8)**	**27 (8.0)**	**41 (6.0)**	**65 (9.5)**
Insomnia	5 (1.4)	10 (2.9)	8 (2.4)	7 (2.1)	13 (1.9)	17 (2.5)
Depression	6 (1.7)	6 (1.7)	5 (1.5)	6 (1.8)	11 (1.6)	12 (1.8)
Abnormal dreams	4 (1.2)	12 (3.5)	4 (1.2)	4 (1.2)	8 (1.2)	16 (2.3)
Anxiety	2 (0.6)	6 (1.7)	1 (0.3)	2 (0.6)	3 (0.4)	8 (1.2)
Nightmare	2 (0.6)	7 (2.0)	0	3 (0.9)	2 (0.3)	10 (1.5)
Nervous System Disorders	**16 (4.6)**	**35 (10.2)**	**7 (2.1)**	**34 (10.1)**	**23 (3.4)**	**69 (10.1)**
Headache	6 (1.7)	6 (1.7)	5 (1.5)	9 (2.7)	11 (1.6)	15 (2.2)
Dizziness	4 (1.2)	23 (6.7)	0	21 (6.2)	4 (0.6)	44 (6.5)
Somnolence	2 (0.6)	5 (1.5)	2 (0.6)	4 (1.2)	4 (0.6)	9 (1.3)
Gastrointestinal Disorders	**9 (2.6)**	**15 (4.4)**	**12 (3.5)**	**18 (5.3)**	**21 (3.1)**	**33 (4.8)**
Diarrhea	4 (1.2)	5 (1.5)	3 (0.9)	4 (1.2)	7 (1.0)	9 (1.3)
Nausea	4 (1.2)	8 (2.3)	1 (0.3)	9 (2.7)	5 (0.7)	17 (2.5)
Vomiting	0	3 (0.9)	2 (0.6)	7 (2.1)	2 (0.3)	10 (1.5)
Investigations	**8 (2.3)**	**14 (4.1)**	**11 (3.2)**	**15 (4.4)**	**19 (2.8)**	**29 (4.3)**
AST increased	2 (0.6)	2 (0.6)	5 (1.5)	2 (0.6)	7 (1.0)	4 (0.6)
Blood triglycerides increased	0	5 (1.5)	0	2 (0.6)	0	7 (1.0)
General Disorders and Administration Site Conditions	**5 (1.4)**	**21 (6.1)**	**8 (2.4)**	**5 (1.5)**	**13 (1.9)**	**26 (3.8)**
Metabolism and Nutrition Disorders	**8 (2.3)**	**8 (2.3)**	**4 (1.2)**	**12 (3.6)**	**12 (1.7)**	**20 (2.9)**
Hyperlipidemia	1 (0.3)	4 (1.2)	1 (0.3)	3 (0.9)	2 (0.3)	7 (1.0)
Skin and Subcutaneous Tissue Disorders	**7 (2.0)**	**28 (8.1)**	**4 (1.2)**	**32 (9.5)**	**11 (1.6)**	**60 (8.8)**
Rash	3 (0.9)	15 (4.4)	1 (0.3)	21 (6.2)	4 (0.6)	36 (5.3)
Rash maculo-papular	0	3 (0.9)	0	6 (1.8)	0	9 (1.3)
Ear and Labyrinth Disorders	**0**	**4 (1.2)**	**1 (0.3)**	**4 (1.2)**	**1 (0.1)**	**8 (1.2)**

There are no unblinded safety data in HIV-infected patients using F/R/TAF.

New safety data using F/R/TAF in healthy subjects

The three new Phase 1 studies provide the only safety data but these are of very limited relevance to the intended clinical use.

GS-US-366-1159

AEs were reported in 6 subjects (6.3%) following FTC/RPV/TAF, 10 (10.5%) following RPV and 8 (8.3%) following E/C/F/TAF. The most frequently reported AEs were constipation (9 [9.4%]), nausea and headache (6 [6.3%] each). Constipation was reported for 2 (2.1%) following FTC/RPV/TAF, 6 (6.3%) following RPV and

2 (2.1%) following E/C/F/TAF. Nausea was reported in one, one and 4 after each treatment while headache was reported for 3, 1 and 2 per treatment. AEs considered related to study drug by the investigator were reported in none, one and four subjects after respective treatments.

GS-US-366-1651

AEs were reported in 8/60 (13.3%) after dosing under fasted conditions, 1/30 (3.3%) after dosing with moderate-fat food and 4/30 subjects (13.3%) following dosing with high-calorie, high-fat food. No AE was reported in > 1 subject. One subject had AEs that were considered by the investigator as related to study drug, which included Grade 1 AEs of nausea, vomiting and dizziness that occurred after dosing on the day of administration of FTC/RPV/TAF under fed conditions (high-calorie, high-fat food). All these events resolved on the same day without treatment.

GS-US-366-1689

AEs were reported in 15 subjects (35.7%), including 7 (16.7%) following LDV/SOF, 6 (14.3%) following F/R/TAF and 8 (19.0%) following combined treatment. AEs reported in 2 or more subjects were:

- LDV/SOF: nausea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects)
- FTC/RPV/TAF: constipation (9.5%, 4 subjects)
- LDV/SOF+FTC/RPV/TAF: constipation (4.8%, 2 subjects) and headache (4.8%, 2 subjects).

All AEs were Grade 1 or 2. Five subjects (11.9%) had AEs that were considered treatment related but none occurred with F/R/TAF alone (2 with LDV/SOF and 3 with combined treatment). One subject completed 11 days F/R/TAF and then started combined treatment. On Day 12 (Day 1 of LDV/SOF+F/R/TAF) she had Grade 2 non-serious colitis and eventually discontinued on Day 28. The AE of colitis was considered related to study drug by the investigator.

There have been no deaths or SAEs in the three Phase 1 studies.

In GS-US-366-1689 with 11-day treatment periods laboratory abnormalities were reported for 17 subjects (40.5%) following LDV/SOF, 20 (47.6%) following F/R/TAF and 20 (47.6%) following combination treatment. The most common laboratory abnormalities are shown in the table below.

Three subjects had Grade 3 or 4 laboratory abnormalities. Grade 3 laboratory abnormalities included increased LDL (observed with each treatment; see above), positive occult blood in urine (following F/R/TAF; single occasion and probably menstrual) and increased AST (following F/R/TAF). One Grade 4 laboratory abnormality of increased creatine kinase following F/R/TAF was reported. This subject had a baseline AST of 23 U/L that increased on Day 26 to 217 U/L (Grade 3). Creatine kinase was also assessed for this subject only and found to be 9081 U/L (Grade 4). No corresponding AEs were reported, as the elevations were consistent with physical exercise. Both laboratory values returned to within the reference range by the end of study (Day 34).

Laboratory findings

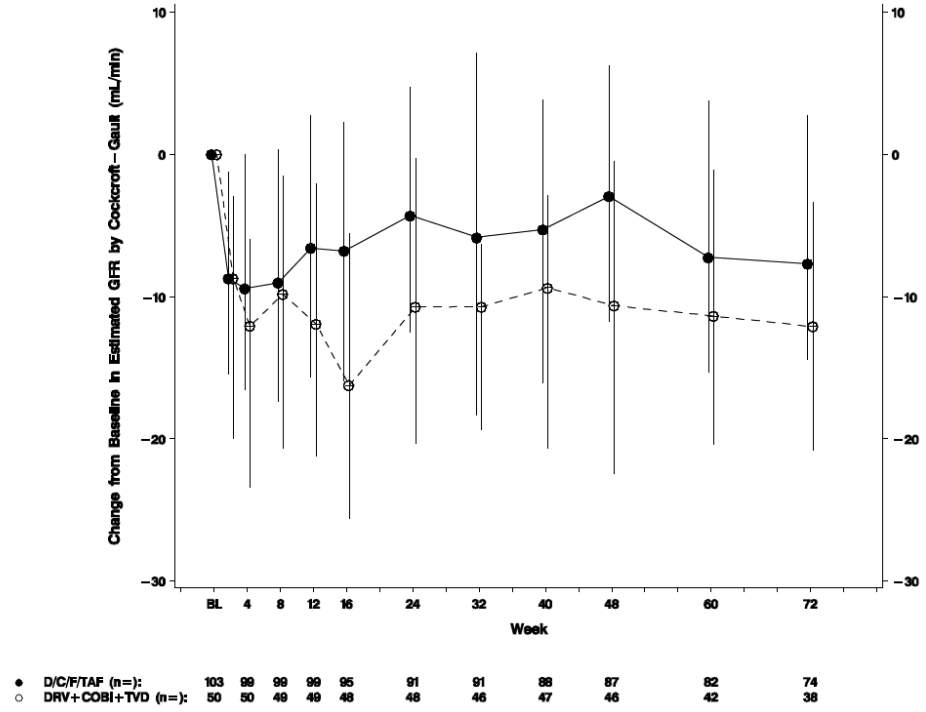
Renal laboratory parameters for emtricitabine+tenofovir alafenamide-containing regimens

In GS-US-299-0102 increases from baseline in mean values for serum creatinine occurred in both groups but were smaller at weeks 24 and 48 in the D/C/F/TAF group. Note that the actual changes were small in both

groups (e.g. increases from baseline at Week 48 were D/C/F/TAF 0.06 mg/dL vs. DRV+COBI+TVD 0.09 mg/dL [p = 0.053]).

Decreases from baseline in median eGFRCG occurred in both groups but were smaller in the D/C/F/TAF group. For example, at Week 48 the median changes from baseline were D/C/F/TAF -2.9 mL/min vs. DRV+COBI+TVD -10.6 mL/min (p = 0.017). The changes from baseline in eGFRCKD-EPI, creatinine and eGFRCKD-EPI, cysC all followed the observations for eGFRCG.

Figure 5. GS-US-299-0102: Median (Q1, Q3) of Change from Baseline in Estimated GFR by Cockcroft-Gault (mL/min) by Visit (Safety Analysis Set)



Proteinuria was reported for 32.4% in the D/C/F/TAF group and 34.0% in the DRV+COBI+TVD group. Most proteinuria by dipstick was Grade 1 or 2; one in the DRV+COBI+TVD group had Grade 3. There were numerical but not statistically significant differences between treatment groups in median percentage change from baseline in UPCR or UACR (UPCR: D/C/F/TAF -8.22% vs. DRV+COBI+TVD -27.52%; UACR -13.1% vs. -22.6%).

The median percent increase from baseline at Week 48 in RBP to creatinine ratio was D/C/F/TAF 9% vs. DRV+COBI+TVD 54% (p = 0.003) whereas the median percent change from baseline at Week 48 in beta-2-microglobulin to creatinine ratio was -42.0% vs. 2.3% (p = 0.002), respectively.

There were no clinically relevant changes from baseline in median values for the other renal biomarkers in either group (FEPO4 and FEUA using serum creatinine adjusted or unadjusted values) and no statistically significant differences between groups.

Renal laboratory parameters for rilpivirine-containing regimens

The pooled data from the Phase 3 TMC278-C209 and TMC278-C215 studies of treatment-naïve patients demonstrate that serum creatinine increased and estimated glomerular filtration rate (eGFR) decreased over 96 weeks of treatment with rilpivirine. Over 96 weeks of treatment with rilpivirine mean changes of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) for creatinine and -13.3 mL/min/1.73 m^2 (range: -63.7 mL/min/1.73 m^2 to 40.1 mL/min/1.73 m^2) for eGFR were observed.

Lipid laboratory parameters for emtricitabine+tenofovir alafenamide-containing regimens

In studies in treatment-naïve patients, increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, and triglycerides at Week 96. The median increase from baseline for these parameters was greater in patients receiving emtricitabine+tenofovir alafenamide compared with patients receiving emtricitabine+tenofovir disoproxil fumarate, both given with elvitegravir+cobicistat as a fixed-dose combination tablet ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL- and HDL-cholesterol, and triglycerides). Median (Q1, Q3) change from baseline at Week 96 in total cholesterol to HDL-cholesterol ratio was 0.1 (-0.3, 0.7) in patients receiving emtricitabine+tenofovir alafenamide and 0.0 (-0.4, 0.5) in patients receiving emtricitabine+tenofovir disoproxil fumarate ($p < 0.001$ for the difference between treatment groups).

Lipid laboratory parameters for rilpivirine-containing regimens

At 96 weeks in the pooled Phase 3 C209 and C215 studies of treatment-naïve patients, in the rilpivirine+emtricitabine/tenofovir disoproxil fumarate arm the mean change from baseline in total cholesterol (fasted) was 2 mg/dL, in HDL-cholesterol (fasted) 4 mg/dL, in LDL-cholesterol (fasted) -1 mg/dL, and in triglycerides (fasted) -14 mg/dL. In the efavirenz+emtricitabine/tenofovir disoproxil fumarate arm the mean change from baseline in total cholesterol (fasted) was 26 mg/dL, in HDL-cholesterol (fasted) 11 mg/dL, in LDL-cholesterol (fasted) 14 mg/dL, and in triglycerides (fasted) 6 mg/dL.

Cortisol

In the pooled Phase 3 TMC278-C209 and TMC278-C215 studies of treatment-naïve patients, at Week 96, there was an overall mean change from baseline in basal cortisol of -19.1 (-30.85; -7.37) nmol/L in the rilpivirine arm and of -0.6 (-13.29; 12.17) nmol/L in the efavirenz arm. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine arm (+18.4 ± 8.36 nmol/L) than in the efavirenz arm (+54.1 ± 7.24 nmol/L). Mean values for the rilpivirine arm for both basal and ACTH-stimulated cortisol at Week 96 were within the normal range. These changes in adrenal safety parameters were not clinically relevant.

Discontinuation due to adverse events

Across all studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study.

2.6.1. Discussion on clinical safety

There are no safety data in patients specific to F/R/TAF. The safety data from the ongoing switch studies (either from Atripla or from Eviplera) will be useful. Meanwhile the safety data from the three new studies in healthy subjects are of very limited relevance. Nevertheless they do not raise any new concerns.

The data in adolescents were not generated with F/R/TAF but they do provide some support for use from the age of 12 years and 35 kg body weight. There were no important differences in the safety profiles in adolescents compared to adults. These studies are described under the heading paediatric population in section 4.8 of the SmPC.

Regarding the specific issue of bone effects for TAF in the adolescents, the overall mean and median changes from baseline in spine and TBLH BMD at Weeks 24 and 48 were positive in Study GS-US-292-0106. At Week 24, 3/47 subjects (6.4%) had a ≥ 4% decrease in spine BMD but none had a ≥ 4% decrease in TBLH BMD. Also, 5/47 showed a worsening (change from > -2 to ≤ -2) from baseline in their spine or TBLH height-age BMD Z-scores at Weeks 24 and/or 48. However, the interplay between these and other factors is complex in a population that is mostly actively growing and it is not possible to identify any specific factors that definitely pre-disposed these patients to develop decreases in BMD. Moreover, it is not possible to discern from 48 weeks uncontrolled safety data whether long term exposure to relatively low plasma TFV levels could ultimately lead to similar effects on bone as observed with TDF. This possibility has been raised during assessment of the prior TAF dossiers and is reflected in the RMPs. More data from GS-US-292-0106 will become available since there is an extension period.

In the E/C/F/TAF Phase 2/3 studies there were direct comparisons of safety with STB in previously untreated patients and assessments of safety after switching from TDF to TAF within regimens. The AE profile of E/C/F/TAF was mostly very similar to that of STB. Overall the data suggested benefits in terms of renal and bone effects for TAF vs. TDF, which was apparent in prospective comparisons in ART-naïve patients as well as post-switching.

Detailed assessment of renal function in patients with eGFRCG 30-69 mL/min treated with E/C/F/TAF supports no adjustment of the FTC dose when CrCL is < 50 mL/min. Thus far there have not been any cases of PRT or Fanconi's syndrome with TAF. Use of RPV is not restricted by renal function and therefore the proposal to use F/R/TAF from CrCL values 30 mL/min upwards is acceptable but the SmPC also notes that RPV does have a modest effect on serum creatinine, resulting in decreased eGFR.

Current data, including updates provided during the review of E/C/F/TAF, do not suggest that the nonclinical findings translate into a concern regarding the ocular safety of TAF. There was one adolescent with uveitis considered to be drug-related by the investigator. At present it seems reasonable to keep this issue under close review with appropriate reflection in the RMP.

In previously ART-naïve patients E/C/F/TAF was associated with higher rates of abnormal fasting lipids, including Grade 3 and 4 abnormalities, than STB. The differences between TAF and TDF-containing regimens are thought to mainly reflect the known lipid-lowering effect of TFV and the loss of this effect due to the much lower plasma levels of TFV in those given E/C/F/TAF vs. STB. Also, based on the finding that median changes from baseline decreased in renally impaired patients in 0112 who switched to E/C/F/TAF from a non-TDF-containing regimen the applicant suggests that the effect on lipids was not due to TAF *per se*.

Furthermore, the lipid changes after initiation of E/C/F/TAF are in line with those observed with several other ART regimens that do not contain TDF. In the Phase 3 RPV studies in the ART-naïve there was a minimal change in fasting lipids vs. EFV-containing regimens with the same NRT backbones. On this basis the effects

on lipids during treatment with F/R/TAF seems unlikely to be very different from the effects observed with E/C/F/TAF.

There was no excess of Grade 3 or 4 hyperuricaemia with E/C/F/TAF in the ART-naïve and only a slightly higher rate of hyperuricaemia. Mean and median uric acid levels were effectively unchanged from baseline to Week 48 in the E/C/F/TAF group with a small decrease in the STB group. AEs that could be due to hyperuricaemia were not observed. However, the applicant should address the potential concern regarding co-administration of any TAF-containing regimen with xanthine oxidase inhibitors.

The safety profiles of RPV in Phase 3 studies and of Eviplera in the two switch studies have been extensively reviewed previously and have been taken into account in the SmPC for F/R/TAF.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The known safety profile has been reflected in the SmPC for F/R/TAF. Another beneficial effect is that the renal safety profile of TAF appears to be better than that of TDF in patients previously naïve to ART and in those who switched from TDF to TAF. There are also post-marketing data available for Eviplera that have been taken into account.

2.7. Risk Management Plan

Safety concerns

Table 19. Summary of Safety Concerns

	Safety Concerns for Odefsey	**Attributable Component of Odefsey**
Important Identified Risks	Post-treatment hepatic flares in HIV/HBV coinfected patients	FTC, TAF
	Development of drug resistance	RPV
	Depression	RPV
	Severe skin reactions	RPV-containing FDC products
Important Potential Risks	Renal toxicity	TAF
	Bone events due to potential proximal renal tubulopathy/loss of BMD	TAF
	Ocular effects (posterior uveitis)	TAF
	Overdose (including overdose through accidental concurrent use of Odefsey with RPV and TDF-containing products)	Odefsey (as a STR), RPV, TAF
	Off-label use in patients with a baseline viral load > 100,000 HIV-1 RNA copies/mL	Odefsey (as a STR), RPV
	QT interval prolongation	RPV
	Hepatotoxicity	RPV
	Blood cortisol decreased	RPV

Missing Information	Long-term safety information in adults and adolescents	Odefsey (as a STR),
	Safety in children aged 4 weeks to < 12 years	RPV, TAF
	Safety in elderly patients	FTC, RPV, TAF
	Safety in pregnancy and lactation	FTC, RPV, TAF
	Safety in patients with severe hepatic impairment (CPT score C)	RPV, TAF
	Safety in patients with HCV coinfection	TAF
	Safety in patients with moderate to severe renal impairment	FTC, RPV, TAF
	Development of drug resistance in long term use	Odefsey (as a STR)
	Drug-drug interactions	TAF

Pharmacovigilance plan

Table 20. Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan (Categories 1-3)

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Interventional studies (Category 3)				
Study GS-US-366-1160 A Phase 3b, Randomized, Double-Blind Study to Evaluate Switching from a Regimen Consisting of EFV/FTC/TDF FDC to FTC/RPV/TAF FDC in Virologically-Suppressed, HIV-1 Infected Subjects	A switch study to evaluate Odefsey in HIV-1 positive subjects who are virologically-suppressed on EFV/FTC/TDF	*Missing information:* Long-term safety information in adults and adolescents Development of drug resistance in long term use	Started	Week 48 report: Q4 2016 Week 96 report: Q4 2017
Study GS-US-366-1216 A Phase 3b, Randomized, Double-Blind Switch Study to Evaluate the Safety and Efficacy of FTC/RPV/TAF FDC in HIV-1 Positive Subjects who are Virologically Suppressed on FTC/RPV/TDF	A switch study to evaluate Odefsey in HIV-1 positive subjects who are virologically-suppressed on FTC/RPV/TDF	*Missing information*: Long-term safety information in adults and adolescents Development of drug resistance in long term use	Started	Week 48 report: Q4 2016 Week 96 report: Q4 2017
Non-interventional studies (Category 3)				
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to ARVs, including Odefsey, during pregnancy	*Missing information*: Safety in pregnancy	Started	Interim reports to be included in Odefsey PSURs (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Nonclinical studies (Category 3)				
In vitro study on the potential for significant effects on plasma TFV concentrations upon coadministration of TAF and xanthine oxidase inhibitors	To provide information on the potential for a drug-drug interaction between TAF and xanthine oxidase inhibitors	*Missing information*: Drug-drug interactions	Planned	Final report: Q4 2016

Risk minimisation measures

Table 21. Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important identified risk(s)		
Post-treatment hepatic flares in HIV/HBV coinfected patients	Section 4.4 of the SmPC informs about the risk of exacerbation of hepatitis in HIV-1/HBV coinfected patients following discontinuation of Odefsey.	None
Development of drug resistance	Section 4.1 of the SmPC includes the statement that Odefsey is indicated in treatment of adults and adolescents with HIV-1 without known mutations associated with resistance to the NNRTI class, TFV or FTC. Sections 4.4 and 5.1 of the SmPC recommend that genotypic resistance testing should guide the use of Odefsey.	None
Depression	Section 4.8 of the SmPC describes depression as an ADR to RPV.	None
Severe skin reactions	Section 4.8 of the SmPC describes severe skin reactions with systemic symptoms as an ADR identified during post marketing surveillance of Eviplera.	None
Important potential risk(s)		
Renal toxicity	Section 4.4 of the SmPC informs that a potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with TAF cannot be excluded.	None
Bone events due to potential proximal renal tubulopathy/loss of BMD	None	None
Ocular effects (posterior uveitis)	None	None
Overdose (including overdose through accidental concurrent use of Odefsey with RPV- and TDF-containing products)	Section 4.2 of the SmPC recommends that the dose is one tablet, once daily, and warnings in Sections 4.4 and 4.5 of the SmPC that Odefsey should not be administered concomitantly with other medicinal products containing RPV, TAF or TDF. Section 4.9 of the SmPC provides guidance on patient	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	monitoring and treatment in the event of overdose.	
Off-label use in patients with a baseline viral load > 100,000 HIV-1 RNA copies/mL	Section 4.1 of the SmPC clearly indicates the use of Odefsey in adult and adolescent patients with a viral load ≤ 100,000 HIV-1 RNA copies/mL.	None
QT interval prolongation	Sections 4.4 and 4.5 of the SmPC warn that RPV has been associated with prolongation of QTc interval at supratherapuetic doses and should be used with caution in combination with medicinal products with a known risk of Torsade de Pointes. Section 4.9 of the SmPC recommends monitoring of ECG (QT interval) in the event of overdose.	None
Hepatotoxicity	Section 4.8 of the SmPC describes increased transaminases (AST and/or ALT) and increased bilirubin as ADRs to RPV and notes that patients coinfected with HBV and/or HCV are at increased risk of transaminase elevations with RPV.	None
Blood cortisol decreased	Section 4.8 of the SmPC describes changes in basal and ACTH-stimulated cortisol associated with RPV at Week 96 in pooled C209 and C215 studies. It is noted that the changes in adrenal safety parameters are not considered clinically relevant and that there were no clinical signs or symptoms suggestive of adrenal or gonadal dysfunction in adults.	None
Missing information		
Long-term safety information in adults and adolescents	None	None
Safety in children aged 4 weeks to < 12 years	Section 4.2 of the SmPC states that the safety and efficacy of Odefsey in children younger than 12 years of age or weighing < 35 kg have not yet been established and that no data are available.	None
Safety in elderly patients	Section 4.2 of the SmPC notes that no dose adjustment of Odefsey is required in elderly patients.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Safety in pregnancy and lactation	Section 4.6 of the SmPC provides information on pregnancy in humans for the FTC component and in animals for all components of Odefsey, and notes that Odefsey should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Section 4.6 of the SmPC provides information on excretion of FTC in human milk, that it is unknown whether RPV or TAF is excreted in human milk, and informs that Odefsey should not be used during breastfeeding.	None
Safety in severe hepatic impairment (CPT score C)	Section 4.2 of the SmPC informs that Odefsey is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C). Section 5.2 of the SmPC states that the effect of severe hepatic impairment on the pharmacokinetics of RPV or TAF have not been studied, and that the impact of liver impairment on the pharmacokinetics of FTC should be limited.	None
Safety in patients with HCV coinfection	Section 4.4 of the SmPC states that the safety and efficacy of Odefsey have not been established in patients coinfected with HIV-1 and HCV.	None
Safety in patients with moderate to severe renal impairment	Section 4.2 of the SmPC provides a statement that Odefsey should not be used in patients with estimated CrCl < 30 mL/min as there are no data available regarding the use of Odefsey in this population.	None
Development of drug resistance in long term use	None	None
Drug-drug interactions	Section 4.5 of the SmPC provides information on interactions that have not been studied, potential effects on drug levels, and recommendations concerning coadministration with Odefsey.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Odefsey (emtricitabine / rilpivirine / tenofovir alafenamide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

TAF was selected for development specifically because it had potential to be active with much lower TFV plasma levels and hence improved safety vs. TDF. Thus, selection of the TAF dose could not be based on matching plasma profiles of TFV achieved with TAF vs. those observed with TDF. The TAF dose in F/R/TAF provides plasma TAF levels comparable with those obtained when 10 mg TAF is given with a strong P-gp inhibitor as part of E/C/F/TAF.

E/C/F/TAF, containing 10 mg TAF in the presence of a strong P-gp inhibitor (COBI), demonstrated a consistently high level of efficacy in previously ART-naïve patients in two Phase 3 studies. In the two Phase 3 studies with E/C/F/TAF 10 mg vs. STB in ART-naïve patients fewer patients in the E/C/F/TAF group had a > 3% decrease from baseline in hip or spine BMD, noting nonetheless that such decreases did still occur in the 48 weeks after starting treatment with E/C/F/TAF. The FRAX analysis also suggested a benefit for E/C/F/TAF over STB as did bone biomarkers. On switching from TDF to TAF in another study with E/C/F/TAF 10 mg it was also apparent that TAF had markedly less effects on BMD.

Another beneficial effect is that the renal safety profile of TAF appears to be better than that of TDF in patients previously naïve to ART and in those who switched from TDF to TAF. Additionally, detailed assessments of renal function in the E/C/F/TAF study in patients with baseline eGFRCG in the range 30-69 mL/min support a conclusion that F/TAF has an acceptable renal safety profile in patients in the 30-50 mL/min range. The data also support use of FTC without dose adjustment in this group and RPV is approved for use in mild and moderate renal insufficiency.

F/R/TAF provides plasma levels of RPV bioequivalent to those achieved on dosing RPV alone under similar dosing conditions (i.e. after a standard moderate fat meal). Therefore the contribution of RPV to the efficacy of F/R/TAF could be presumed to be similar to that exerted when it is combined with FTC/TDF, including administration as the FDC Eviplera. In Phase 3 studies with RPV in combination with FTC/TDF or with other NRTIs, the viral suppression rates have been lower than observed with E/C/F/TAF, especially in the subset with the highest baseline viral loads, with emergence of NNRTI RAMs in a substantial proportion of virological failures. However, the F/R/TAF SmPC recommends dosing with food and restricts use to patients with viral loads < 100,000 c/mL.

Uncertainty in the knowledge about the beneficial effects

GS-US-292-103 showed that although plasma TAF was very slightly lower on dosing with Genvoya compared with F/TAF 25 mg, the plasma TFV AUC was lower after dosing with F/TAF 25 mg vs. Genvoya. This finding, which remains mechanistically unexplained, suggested an effect of COBI on the compartmental disposition of TFV.

- The finding raised a question regarding the basis for extrapolation of efficacy from Genvoya to F/TAF regardless of the third agent co-administered and whether or not the regimen included P-gp inhibitors COBI or RTV.
- It also raised a question regarding the CNS levels of TFV-DP that may be achieved with F/TAF, and, hence, the efficacy of various TAF-containing regimens against HIV within the CNS.

The applicant responded to these concerns during the procedure and the questions were referred to the Virology SAG. When considering these issues the following observations have some relevance.

To ascribe the difference in TFV plasma levels that was observed when TAF was administered with or without COBI to a differential effect on the whole body distribution of TFV would require that systemic concentrations of COBI are sufficient to exert effects on relevant transporters outside of the gut.

In vitro, COBI inhibits the transporters P-gp, BCRP, MATE1, MRP-2, OATP1B1 and OATP1B3. Its effect on plasma exposures to substrates of P-gp and/or BCRP via inhibition at the gut level is clear. However, in the context of explaining effects on plasma TFV levels after oral administration of TAF, it should be noted that TFV is not a substrate for P-gp, MRP2 or BCRP and its renal elimination should not be affected by COBI based on the calculated $C_{max,u}/IC_{50}$ ratios. Regarding the potential for systemic effects on other transporters it is clear that COBI reaches sufficient concentrations to inhibit MATE1 in the kidney, with consequent effects on serum creatinine. However, it is not expected to reach sufficient concentrations to inhibit P-gp at the BBB and inhibition of BCRP and MRP4 at the BBB does not seem to have marked effects on their substrates. Overall, existing knowledge regarding COBI and its effects on transporters, as well as the substrate profile of TFV, do not explain the modest difference in TFV plasma levels observed when TAF was given with and without COBI to healthy subjects. There is no clear basis for concluding that the difference truly reflects different whole

body distribution of TFV when TAF is administered with or without COBI or that dosing with and without COBI will affect brain parenchyma levels of the active moiety TFV-DP.

TFV is not the active moiety but is the moiety associated with adverse renal and bone effects. Since TFV plasma levels were slightly lower for F/TAF 25 mg vs. TAF 10 mg given with COBI there is no reason to expect a worse safety profile for F/TAF when used without COBI compared to Genvoya. In addition, the safety data from GS-US-311-1089, in which subjects either switched to TAF or remained on TDF, each with FTC and a wide range of third agents (including PI/r combinations), indicated that the safety profile for TAF-treated patients vs. TDF-treated patients was consistent with observations made in the Phase 3 Genvoya studies that compared Genvoya with Stribild.

In summary, although there remains a theoretical possibility that the presence of a P-gp inhibitor as part of an overall TAF-containing ART regimen could affect entry of TAF into the brain and, thus, TFV-DP levels, the overall picture at present suggests that this is a remote possibility. CSF levels of TFV or TAF cannot be regarded as highly predictive of TFV-DP in the brain. Brain penetration in nonclinical studies may poorly predict the human situation. There is at least a theoretical possibility that use of TAF rather than TDF could improve on levels of TFV-DP achieved in the CNS replicating sites.

The general experience with the more highly effective ART regimens that have become available especially in the last decade support a conclusion that effective and sustained virologic suppression in plasma is associated with CSF virologic suppression or, at least, only asymptomatic and usually temporary detection of HIV-1 RNA in CSF. There no reason to think that rates of plasma virologic failure or CSF virologic failure are more likely to occur with regimens containing TAF vs. otherwise identical regimens containing TDF. Thus, F/R/TAF should exert similar activity to Eviplera when used in accordance with identical restrictions and warnings and there is no good reason to expect that the risk of escape HIV-1 replication in the brain is any greater with the former vs. the latter.

The SAG concurred with the conclusion that F/TAF should pose no difference vs. Truvada in control over HIV replication in plasma and in the CNS when each is given with the same third agent, including RPV.

There are concerns regarding the adequacy of 25 mg TAF in the presence of a strong inducer of P-gp. Since co-administration of F/R/TAF is contraindicated with strong inducers of CYP3A because of the effect on RPV, and since inducers of CYP3A and P-gp overlap, use of F/R/TAF is effectively contraindicated with potent P-gp inducers. Use of F/R/TAF with strong inhibitors of P-gp is not recommended since no dose reduction is possible with this FDC.

For E/C/F/TAF and for RPV there are currently few data available in adolescents. The available data for E/C/F/TAF suggest high efficacy in this age group. RPV appears slightly less effective in adolescents than adults and the same issues relating to baseline viral load and emergence of resistance apply as for adults. However, adherence to F/R/TAF when presented as a FDC may be better. The safety data with E/C/F/TAF thus far do suggest that TAF can be used in growing adolescents and that the restriction placed on use of TDF need not apply. However, longer exposures and larger numbers of treated patients are needed to confirm the current findings.

Risks

Unfavourable effects

In comparative studies in ART-naïve patients the AE profile of E/C/F/TAF was mostly very similar to that of STB. E/C/F/TAF was associated with higher rates of abnormal fasting lipids, including Grade 3 and 4 abnormalities, than TDF-containing comparative regimens. Similarly, higher rates of abnormal fasting lipids were observed in those who switched to E/C/F/TAF vs. those who maintained a TDF-containing regimen. The difference between TAF and TDF-containing regimens likely reflects the known lipid-lowering effect of TFV and the much lower plasma levels of TFV in those given E/C/F/TAF. Nevertheless, the effect of TAF-containing regimens resembles that of other commonly used ART regimens without TDF and the benefits of TAF vs. TDF in terms of renal and bone effects appear to outweigh any concerns there may be regarding the lipid profile.

The known safety profile has been reflected in the SmPC for F/R/TAF. There are also post-marketing data available for Eviplera that have been taken into account.

Uncertainty in the knowledge about the unfavourable effects

Thus far there have not been any cases of PRT or Fanconi's syndrome in patients treated with TAF. More extensive and longer-term data are needed to confirm the observation. In addition, although data thus far support a conclusion that TAF is much less likely than TDF to exert negative effects on BMD or on renal function it remains to be seen whether very long term exposure to low TFV plasma levels could have an effect. This matter can really only be addressed in routine use.

Taking into account the metabolic pathway, it was noted that Grade 3 or 4 hyperuricaemia occurred in 2 E/C/F/TAF and no non-switch patients in GS-US-292-0109. Also, any grade hyperuricaemia occurred in 13.2% vs. 5.0% although no AEs were related to abnormal uric acid. Thus far there does not appear to be a link between the hyperuricaemia and gout or other AEs that could be due to hyperuricaemia (including renal stones). However, this matter needs to be kept under review as a potential risk. The possible effect of co-administering xanthine oxidase inhibitors on the final metabolic fate of TAF also needs to be addressed.

Current data do not suggest that the nonclinical findings translate into a concern regarding the ocular safety of TAF. There was one adolescent with uveitis considered to be drug-related by the investigator. At present it seems reasonable to keep this issue under close review as reflected in the RMP.

Balance

Importance of favourable and unfavourable effects

E/C/F/TAF has been shown to achieve high virologic suppression rates in the ART-naïve and to support maintenance of suppression after switching from successful regimens. The safety profile for the most part is similar or improved vs. that of STB, especially notable for the renal and bone effects. The fact that lipid abnormalities are more likely to occur with TAF then TDF does not impact on the overall conclusions on safety provided that the rates observed are shown to be in line with those that occur with other commonly used regimens.

RPV co-administered with FTC/TDF and taken with food exerts acceptable antiviral efficacy in patients with no known RAMs of relevance and with baseline viral loads < 100,000 c/mL. At a dose of 25 mg taken once daily with food RPV has been shown to have an acceptable safety profile when administered in conjunction with FTC/TDF. If anything, the safety profile for F/R/TAF can be expected to be more benign than that of Eviplera.

While the application is based on bridging to the Genvoya and Edurant studies the potential issues regarding bridging were thoroughly explored during the procedure. In conclusion, there were no remaining major issues precluding acceptance of the bridging strategy of this application.

Benefit-risk balance

The fixed dose combination F/TAF/R offers an alternative option to Eviplera with which similar efficacy can be expected. The improved renal safety profile allows the administration in patients with estimated creatinine clearance > 30 ml/min and no dose adjustments are required. However the potential risk of nephrotoxicity from chronic exposure cannot be excluded and deserves to be monitored. Based on the evaluation of quality, efficacy and safety data the benefit-risk balance is favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Odefsey 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 (see sections 4.2, 4.4 and 5.1), is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

New Active Substance Status

Based on the review of data, the CHMP considers that the active substance tenofovir alafenamide (TAF) contained in the medicinal product Odefsey is a derivative of tenofovir disoproxil (both prodrugs of tenofovir). The active substance tenofovir alafenamide is contained in the marketing authorisation Genvoya which was authorised in the Union on 19/11/2015. Tenofovir alafenamide is therefore not a new active substance in itself, as it is a constituent of a medicinal product previously authorised within the Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0107/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.