Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Emtricitabine/Tenofovir alafenamide (as fumarate)

Proprietary Product Name: Descovy

Sponsor: Gilead Sciences Pty Ltd

First round evaluation: 30 October 2015
Second round valuation: 6 March 2016

TGA Health Safety Regulation

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List of common abbreviations

Abbreviation	Meaning
3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
aGFR	actual glomerular filtration rate
AIDS	acquired immunodeficiency syndrome
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
BHIVA	British HIV Association
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
Cat A	cathepsin A
CD4	cluster determinant 4
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COBI, C	cobicistat (Tybost®)

Abbreviation	Meaning
CSR	clinical study report
C-telopeptide	type I collagen C-telopeptide
CYP	cytochrome P450 enzyme
Cys C	cystatin C
ddI	didanosine
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
dNTP	2' deoxynucleoside triphosphate
DRV, D	darunavir
DTG	dolutegravir
DXA	dual-energy x-ray absorptiometry
EASC	European AIDS Clinical Society
EC50	concentration of a compound inhibiting virus replication by 50%
EOP2	End of Phase II
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya)
EFV	efavirenz
eGFR	estimated glomerular filtration rate
eGFRCG	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
ESRD	end-stage renal disease
EU	European Union
EVG, E	elvitegravir (Vitekta®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination

Abbreviation	Meaning
FTC, F	emtricitabine (Emtriva®)
FTC-DP	emtricitabine diphosphate
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
GS-7340	tenofovir alafenamide fumarate
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV, HIV-1, HIV-2	human immunodeficiency virus, type 1, type 2
IC95	concentration that results in xx% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IN	integrase
IND	Investigational New Drug
INSTI	integrase strand-transfer inhibitor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
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

Abbreviation	Meaning
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
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PP	Per Protocol
PRT	proximal renal tubulopathy
PSP	Pediatric Study Plan
PTH	parathyroid hormone
PVF	Pure virologic failure
Q1, Q3	first quartile, third quartile
-R	resistant
RBP	retinol binding protein
RNA	ribonucleic acid
rNTP	ribonucleoside triphosphate
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event

Abbreviation	Meaning
SAP	statistical analysis plan
SD	standard deviation
SI	selectivity index (ratio of CC50 to IC50)
SOC	system organ class
STB	elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (coformulated; Stribild®)
STR	single-tablet regimen
TAF	tenofovir alafenamide
TAM	thymidine analog mutation
TBLH	total body less head
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TFV-MP	tenofovir monophosphate (previously referred to as PMPAp)
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada)
UACR	urine albumin to creatinine ratio
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
vs	versus

1. Introduction

This is a submission for a new fixed dose combination of emtricitabine and tenofovir alafenamide fumarate under the tradename Descovy.

Descovy is a fixed dose combination tablet containing emtricitabine (FTC or F) which is a nucleoside reverse transcriptase inhibitor (NRTI) and tenofovir alafenamide fumarate (TAF) which is a nucleotide reverse transcriptase inhibitor.

The proposed indication is for Descovy to be used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of Descovy.

2. Clinical rationale

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

The success of potent and well-tolerated antiretroviral therapy (ART) means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS–associated co-morbidities. Clinical attention has become more focused on the optimisation of tolerability, long-term safety, and adherence to potent ART regimens. There remains a significant medical need for new, effective therapies that take into consideration the non-HIV co-morbidities, demographics of the aging HIV-infected population, antiretroviral (ARV) resistance, and regimen simplification. Chronic kidney disease is important, since observational studies have demonstrated a relationship between kidney disease and progression to AIDS and death. Moreover, HIV-associated nephropathy present in up to 30% of patients is a common cause of end-stage renal disease (ESRD) requiring dialysis and potential transplantation. ART with proven efficacy and safety in the both elderly and young patients is important; however there are limited data and treatment options are available in both populations. The elderly have increased risks for co-morbidities, including those related to renal function and bone mineralisation. There are specific and complex challenges for the treatment of adolescents, especially related to adherence, and who also represent the population that will require ART for the longest time.

Given the duration for which a newly diagnosed person with HIV-1 may take an ART regimen throughout his or her lifetime, the F/TAF (Descovy) tablet, when administered with other antiretroviral agents, may provide the potential for the longevity of treatment that optimises tolerability, long-term safety, and durable efficacy. For HIV-infected patients, Descovy may have advantages over the existing marketed product of Truvada; specifically less proteinuria, less need for renal monitoring, and less impact on bone mineralisation relative to F/TDF treatment. The relatively low dose of TAF (10 mg vs TDF 300 mg) that is used in the boosted F/TAF also allows for co-formulation and co-administration with multiple other third ARV agents. This will allow HIV-infected, virologically suppressed patients to convert from a TDF-based regimen with possible renal and bone safety advantages.

Comment: The rationale for developing HIV-1 therapies that have long-term effectiveness while minimising non-HIV related morbidities is an essential goal.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission is divided into two components:

1. The two bioequivalence studies describing the bioequivalence of F/TAF as stand-alone FDC when compared with the Genvoya FDC, which contains F/TAF and for which there are substantial Phase III efficacy and safety data. The bioequivalence data are for the FDC F/TAF 200 mg/10 mg and F/TAF 200 mg/25 mg as studies GS-US-311-1472 and GS-US-311-1473. The additional study, not included in the Genvoya dossier, is the GS-US-311-1089, which is a preliminary PK report of TFV-DP in PBMCs in a cohort of patients who are enrolled in a pivotal Phase III clinical efficacy and safety study of Descovy versus Truvada and various third agents, both boosted and unboosted. This study has not been reported in full as it appears not to have been completed and analysed at the time of this submission.
2. The sponsor has also included, in this submission, the total dossier for their Genvoya application in order to support their supposition that, as there is bioequivalence between F/TAF as an FDC and F/TAF as a component of Genvoya, the Phase III clinical trial data for Genvoya should be considered in the assessment of this Descovy application. In total, the sponsor has submitted 27 study dossiers of clinical trial data, in addition to clinical discussion papers. Many of these studies overlap in terms of their objectives and therefore cannot be clearly categorised as efficacy, safety or pharmacokinetics/pharmacodynamics. The evaluator has focussed on the most relevant and pivotal studies for review as many of the studies submitted have identical designs, methodologies and analytical frameworks and geographic locations.

The following clinical information was included with this submission:

- 15 Phase I and Phase II studies of clinical pharmacology, including 10 that provided pharmacokinetic data and 5 that provided pharmacodynamic data. For further detailed analysis of these studies please refer to assessment for Genvoya.
- 2 pivotal efficacy/safety studies GS-US-292-0104 and GS-US-292-0111. Both studies are randomised; double-blind trials conducted in HIV-1 infected adults and provide a direct comparison of E/C/F/TAF (Genvoya) with E/C/F/TDF (Stribild), the currently approved and marketed FDC.
- Additional studies include GS-US-292-0109; a Phase III, open-label study to evaluate the potential renal and/or bone mineralisation benefits of switching from a TDF-based regimen to the Genvoya in virologically-suppressed HIV-1 positive subjects; GS-US-292-0112; an open-label study of Genvoya in patients with mild to moderate renal impairment and GS-US-292-0106; an open-label study of Genvoya in HIV-infected treatment naive adolescents.
- Data on the bioequivalence of Descovy with a range of third antiretroviral agents are submitted in GS-US-120-0118.

3.2. Paediatric data

The submission included paediatric data as related to clinical studies on Genvoya, not specifically on Descovy. The Genvoya data are provided on HIV-infected treatment naive adolescents 12 years old or greater (GS-US-292-0106). There are no bioequivalence or clinical data for Descovy in adolescents. This is especially relevant in relation to the recommended use of Descovy 200 mg/10 mg administered in combination with anti-retroviral therapies boosted by Ritonavir and those in the 200 mg/25 mg dosage not boosted with either cobicistat or ritonavir.

3.3. Good clinical practice

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

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

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

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

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary Drug
PK in healthy adults	General PK - Single dose	GS-US-292-0108	E/C/F/TAF
	- Multi-dose	GS-US-292-0103	E/C/F/TAF
		GS-US-292-0101	TAF
	Bioequivalence† - Single dose	GS-US-311-1472 and GS-US-311-1473 GS-US-311-1089	F/TAF
	Food effect	GS-US-292-0110	E/C/F/TAF
PK in special populations	Target HIV infected -Multi-dose	GS-US-292-0112	TAF
	Hepatic impairment	GS-US-120-0114	TAF
	Renal impairment	GS-US-120-0108	E/C/F/TAF

PK topic	Subtopic	Study ID	Primary Drug
	Adolescents (12-18 years of age) §	GS-US-292-0106	E/C/F/TAF
	Elderly		
	Japanese Healthy subjects	GS-US-292-0108	E/C/F/TAF
PK interactions of Genvoya	Sertraline	GS-US-292-1316	E/C/F/TAF
	Sofosbuvir	GS-US-342-1167	E/C/F/TAF
	Efavirenz and Darunavir	GS-US-311-0101	TAF+COBI
	Rilpivirine	GS-US-120-0117	TAF
	ATV+RTV/DRV+RTV/LPR/r	GS-US-120-0118	TAF
	Methadone and Buprenorphine/Naloxone	GS-US-216-0125	EVG/COBI

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration. *Studies where the primary drug is E/C/F/TAF were submitted as part of the Genvoya assessment dossier.*

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated. Most pharmacokinetic studies of F/TAF were conducted as part in the Genvoya submission where Descovy was a component of the Genvoya FDC with EVG and COBI. This results in some difficulties in determining the pharmacokinetics of Descovy as a standalone FDC.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

Sites and mechanisms of absorption

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

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

Comment: The sponsor presents data on TAF boosting with ritonavir (GS-US-120-0118) suggesting that ritonavir has equivalent TAF boosting capacity as cobicistat. However, while the main action of ritonavir is to inhibit the liver enzyme system CYP 450 3A4, and thus increase the serum exposure to protease inhibitors that are metabolised via the Cytochrome P450 3A4 pathway and current data are available to show that ritonavir also acts to inhibit P-gp it is not clear it ritonavir acts to exactly the same extent as does cobicistat. As ritonavir is administered in different doses (100 mg to 200 mg) a dose ranging study of ritonavir and cobicistat may elucidate this issue.

4.2.1.2. Bioavailability

Absolute bioavailability

TAF

Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (approximately 40%), based on animal data. TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine. Inhibition of P-gp by a boosting agent (for example, COBI or RTV) reduces P-gp–mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. Cumulative results from Studies GS-US-311-1473, GS-US-292-0103, and GS-US-292-0101, indicated that TAF exposure following a 10-mg dose (either as a single agent co-administered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg either as a single agent or as a component of F/TAF.

The effect of food on TAF absorption was evaluated in 2 Phase I studies:

1. when given as part of F/TAF (200/25 mg; GS-US-311-1386) and
2. when given as part of E/C/F/TAF (GS-US-292-0110). Food has an effect on TAF absorption; however, the observed differences were not considered, by the sponsor, to be clinically relevant given the wide range of safe and efficacious TAF exposure established. However, no bioavailability studies were conducted with boosting agents in the fasting state.

Compared with administration under fasting conditions, administration of a single dose of TAF following a high-fat meal resulted in a decreased C_{max} (15% when administered as F/TAF [200/25 mg] and 37% when administered as E/C/F/TAF) and an increased AUC_{last} (77% when administered as F/TAF [200/25 mg] and 17% when administered as E/C/F/TAF).

FTC

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

the systemic circulation, resulting in a high absolute bioavailability value (93% as shown in Study FTC-110).

The effect of food on the absorption of FTC was evaluated when given as part of F/TAF (200/25 mg; GS-US-311-1386). The findings from this study were consistent with those from a previous study (FTC-111), which supports the current recommendation that FTC can be administered without regard to food.

Urinary excretion data provide evidence that FTC is extensively absorbed after single or repeated oral doses administered in either the capsule or solution formulations. Urinary recovery of unchanged FTC averaged 47% to 74% in these studies following oral administration of 200 mg FTC as a single dose or at steady-state following once-daily administration. Total recovery of unchanged FTC and its metabolites in urine, as determined in a [^{14C}]FTC mass balance study, averaged 85.8% of the administered oral dose, providing evidence of extensive oral absorption. The remainder of the [^{14C}]FTC dose recovered in faeces (13.7%) exclusively as unchanged FTC, primarily over the 48- to 96-hour post-dose period.

At the FTC therapeutic dose (200 mg once daily given as the capsule formulation), the steady-state peak plasma FTC concentration averaged approximately 2 µg/mL. FTC disposition follows linear, first-order kinetics, with steady-state plasma FTC concentration-time profiles predictable based on single-dose data. The steady-state plasma AUC over the 24 hour dosing interval following 200 mg once-daily dose averaged 10 µg•h/mL, which is the same as the AUC_{inf} value following a single-dose administration. The steady-state condition was generally achieved following 4 consecutive daily doses of FTC (3 days). The T_{max}, $t_{1/2}$ estimates, and urinary excretion data were similar between the single-dose and steady-state conditions, that is indicating linear kinetics. In general, C_{max} value (approximately 2 µg/mL) did not show substantial increase following multiple-dose administration, reflecting a small accumulation index in the absorption phase. The steady-state trough plasma FTC concentration following a 200 mg once daily dose averaged approximately 0.075 µg/mL, which is approximately 5 fold higher than the mean in vitro concentration that resulted in 90% inhibition (IC_{90}) value (0.014 µg/mL) for inhibition of HIV-1 replication. In Study FTC-101, plasma concentrations of FTC (C_{max}, AUC, and C_{min}) increased in a dose-proportional manner following both single- and multiple-dose administration over the dose range of 25 to 200 mg given once or twice daily.

Bioavailability relative to an oral solution or micronized suspension

Not applicable as Descovy is not available as a suspension.

Bioequivalence of clinical trial and market formulations

No major changes, other than those associated with process scale-up, film-coating colour, and tablet debossing were made to the tablet manufacturing process after the completion of Phase I clinical trials. The F/TAF 200/10 mg and F/TAF 200/25 mg formulations for which bioequivalence to E/C/F/TAF tablets was investigated are identical to the commercial F/TAF tablet formulations. The F/TAF tablet formulation was initially evaluated in Phase I clinical trials, with FTC dosage strength maintained at 200 mg. Phase I clinical trial results and acceptable chemical stability of TAF resulted in selection of a 10 mg TAF strength for use by patients boosted with cobicistat. This dosage was then extrapolated to use with the boosting agent, Ritonavir on the evidence that ritonavir is derived from a similar biological structure as cobicistat.

A higher strength of 25 mg TAF was also developed for use in patients who were taking drug regimens not boosted with cobicistat.

Bioequivalence of different dosage forms and strengths

There are no dosage forms or strengths of the FDC (F/TAF) that are not addressed in this application. The two dosage of the FDC 200/10 and 200/25 are addressed.

Bioequivalence to relevant registered products

In this section there are two studies submitted by the sponsor and presented as the pivotal bioequivalence studies supporting this registration application. The studies are in healthy adults and are presented to demonstrate bioequivalence of the FDC Descovy (200 mg/10 mg) + EVG + COBI with the FDC Genvoya E/C/F/TAF in Study GS-US-311-1472. Although Genvoya is not registered at this time, this is the only section identified in the report that applies to this study. The second study submitted is GS-US-311-1473 which compares the bioequivalence of Descovy (200 mg/25 mg) administered as the FDC or as the FDC Genvoya E/C/F/TAF. These studies will now be presented in detail as they are the pivotal submission studies.

GS-US-311-1472

Study Title

A Phase I, Randomised, Open-Label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide fumarate between F/TAF (200/10 mg) and E/C/F/TAF (150/150/200/10 mg) Fixed-Dose Combination Tablets.

This was a single centre Phase I study conducted between 8 July 2014 (First Subject Screened) and 3 September 2014 (Last Subject Observation). The methodology and results have not been published nor peer reviewed, except by the sponsor, as this study was conducted by a Clinical Research Organisation (CRO). Study treatments were administered orally under fed conditions (moderate calorie/moderate fat meal) following an overnight fast. A total of 116 healthy male and female subjects were planned for enrolment to obtain 104 evaluable subjects (target of 52 per sequence group), with an approximate even distribution of males and females.

Objectives

The primary objective of this study was as follows:

- To evaluate the bioequivalence of emtricitabine (FTC; F) and tenofovir alafenamide (TAF) administered as F/TAF (200/10 mg) fixed-dose combination (FDC) tablet simultaneously with elvitegravir (EVG) and cobicistat (COBI) or as elvitegravir (EVG; E)/COBI (C)/FTC/TAF (E/C/F/TAF) (150/150/200/10 mg) FDC tablet

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of single oral doses of EVG, COBI, FTC, and TAF administered as FDC tablets (E/C/F/TAF and F/TAF) or single agents (EVG and COBI).

Methodology

This was a randomised, open-label, single-dose, 2-way, crossover study to determine the bioequivalence of FTC and TAF, administered as F/TAF FDC tablet simultaneously with EVG and COBI or as E/C/F/TAF FDC tablet. Following screening and Day −1 procedures, subjects were randomised to 1 of 2 treatment sequences (AB or BA) and received a single dose of 1 of the following treatments (A or B) on Days 1 and 7:

- *Treatment A*: Single dose of F/TAF (200/10 mg) FDC tablet administered simultaneously with EVG 150 mg and COBI 150 mg tablets orally, under fed conditions
- *Treatment B:* Single dose of E/C/F/TAF (150/150/200/10 mg) FDC tablet administered orally, under fed conditions

Subjects were admitted to the study clinic on Day −1 and remained confined to the clinic until Day 13. Subjects received follow-up a phone call on Day 21 ± 2 days (14 [± 2] days after the last dose of study drug.

Figure 1. GS-US-311-1472 Overview of Phase I Trial Structure

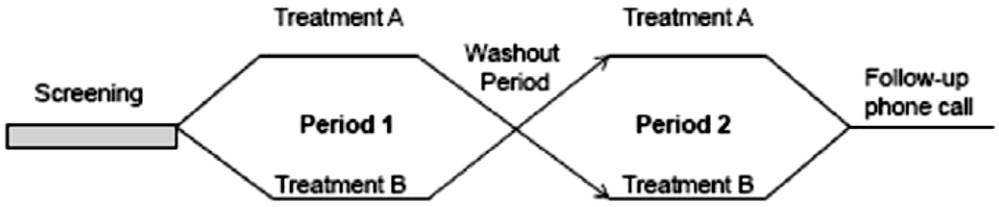
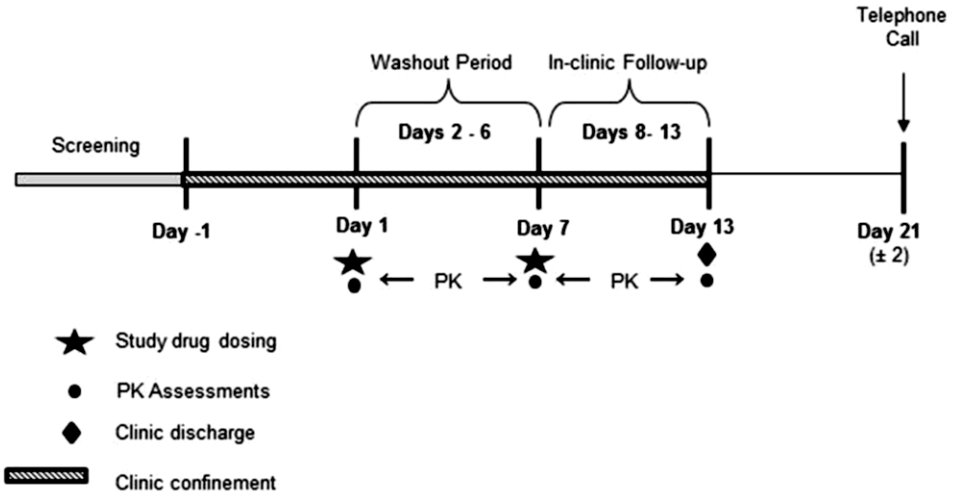


Figure 2: GS-US-311-1472 Timeframe of Assessments.



Number of Subjects (Planned and Analysed)

Planned: 116 subjects (58 subjects in each treatment sequence [AB and BA], for a target of approximately 52 evaluable subjects per sequence)

Randomised

100 subjects (50 in sequence AB; 50 in sequence BA)

Analysed: 100 subjects (Safety Analysis Set, and TAF, FTC, EVG, and COBI Pharmacokinetic [PK] Analysis Sets). Ninety-nine subjects received F/TAF administered simultaneously with EVG and COBI, and all 100 subjects received E/C/F/TAF.

Analysis of Pharmacokinetics

The following plasma PK parameters were calculated for all subjects with evaluable PK profiles: C_{max}, T_{max}, λz, C_{last}, T_{last}, $t_{1/2}$, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, Vz/F, and CL/F. Pharmacokinetic parameters were estimated using standard of non-compartmental methods (Phoenix WinNonlin® software). The linear up/log down trapezoidal rule was used in conjunction with the appropriate non-compartmental model, with input values for dose, time of dose, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible. Individual subject concentration data for each analyte (that is, FTC, TAF, EVG, and COBI) and individual subject PK parameter data was listed and summarised using descriptive statistics by treatment. Summary statistics (numbers of subjects, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) are presented for both individual subject concentration data and individual subject PK parameters by treatment. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values were presented for individual subject PK parameter data.

Individual concentration data listings and summaries included all subjects with reported concentration data. The sample size for each time point was based on the number of subjects with non-missing concentration data at that time point. The number of subjects with

concentration BLQ was presented for each time point. For summary statistics, BLQ values were treated as zero at pre-dose and one-half of LLOQ for post-dose time points, where LLOQ was corrected for the dilution factor (that is reported dilution/dilution factor). Individual PK parameter data listings and summaries included all subjects for whom PK parameter(s) could be derived. The sample size for each PK parameter was based on the number of subjects with non-missing data for that PK parameter.

A parametric analysis of variance using a mixed-effects model appropriate for a crossover design was fitted to the natural logarithmic transformation of the PK parameters (AUC_{inf}, Auklet, and C_{max}) using the PK analysis set. Two-sided 90% CIs were constructed for the ratios of GLSMs of each PK parameter (that is, AUC_{inf}, AUC_{last}, and C_{max}) for TAF and FTC. The statistical model included treatment, sequence, and period as fixed effects and subject within sequence as a random effect. The test-to-reference ratio and associated 90% CI were calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which was consistent with the two 1-sided tests approach. Bioequivalence of the F/TAF FDC to the FTC and TAF components in E/C/F/TAF FDC was concluded if the 90% CI of the GLSM ratio of the PK parameters for each analyte between 2 formulations was within the boundaries of 80% to 125%. Sensitivity analyses were conducted for the key PK analyses since several subjects experienced incomplete blood draws. These incomplete draws resulted in sample collection that did not allow the maximum concentration of the drug in the blood (C_{max}) or sufficient characterisation of absorption phase to be estimated accurately.

The sensitivity analyses included all data including those subjects and periods in which incomplete draws occurred. This analysis was denoted as secondary in the TFLs. The sensitivity analyses consisted of the PK parameter summary table and the statistical comparisons table of test versus reference treatments.

Pharmacokinetic Results

Table 2: Statistical comparisons of plasma TAF and FTC PK parameters AUC_{last}, AUC_{inf}, and C_{max} (F/TAF 200/10 mg +EVG 150 mg +COBI 150 mg vs E/C/F/TAF 150/150/200/10 mg)

TAF		Test		Reference	GLSM Ratio (Test/ Reference) (%)	
F/TAF (200/10 mg) +E+C (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	97	336.6 (33.9)	99	340.2 (33.8)	97.96	94.69,101.34
AUC_{inf} (h•ng/mL)	97	351.8 (31.0)	99	354.1 (32.9)	98.34	94.81,101.99
C_{max} (ng/mL)	97	301.6 (48.8)	99	310.3 (48.7)	96.86	89.36,104.99
FTC		**Test Mean (%CV)**		**Reference Mean**	**GLSM Ratio (Test/ Reference) (%)**	
F/TAF (200/10 mg) +E+C (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	97	10159.2 (17.2)	99	10086.8 (15.9)	99.84	98.41,101.29
AUC_{inf}	97	10535.1 (27.0)	99	10294.4	100.67	98.24,103.16

FTC		Test Mean (%CV)		Reference Mean	GLSM Ratio (Test/ Reference) (%)	
(h•ng/mL)				(15.8)		
C_{max} (ng/mL)	97	1660.8 (20.6)	99	1662.6 (19.1)	99.57	96.78,102.44

The Geometric Least Squares Mean (GLSM) ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria for bioequivalence. The median T_{max} for TAF was 1.50 hours following F/TAF +EVG +COBI and 1.00 hours following E/C/F/TAF. The median T_{max} for FTC was 2.02 hours following F/TAF +EVG +COBI and 2.00 hours following E/C/F/TAF.

Safety

Safety was comparable between the 2 study drugs in this study. No deaths, SAEs, or Grade 4 AEs were reported. One AE leading to premature study drug discontinuation of macular rash was reported following administration of E/C/F/TAF; this event was Grade 2 and considered related to study drug by the investigator. With the exception one Grade 3 AE of arthralgia (considered not related to study drug), all other AEs were Grade 1 or 2 in severity.

Adverse events reported in > 1 subject during any study treatment included headache, nausea, diarrhoea, pruritus, papular rash, feeling hot, anxiety, dyspepsia, vomiting, abdominal distension, erythema, musculoskeletal chest pain, excoriation, palpitations, dizziness, vessel puncture site pain, and insomnia.

No Grade 4 and 6 Grade 3 laboratory abnormalities were observed during this study. All Grade 3 abnormalities were occult blood on urinalysis in female subjects (4 of 6 subjects had confirmed menses). All other laboratory abnormalities observed were Grade 1 or 2.

There were no clinically relevant changes from baseline in renal laboratory parameters (serum creatinine, eGFRCG [creatinine clearance], or serum phosphate) in any treatment group. Additionally, there were no clinically relevant changes from baseline in uric acid levels, the primary metabolite of TAF.

No clinically significant changes in vital sign measurements were observed during this study. No pregnancies occurred during this study.

GS-US-311-1473

Title of Study: A Phase I, Randomized, Open-Label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between F/TAF (200/25 mg) and E/C/F/TAF (150/150/200/10 mg) Fixed-Dose Combination Tablets. The important aspect of this study is that it addresses the bioequivalence of the TAF 25 mg dose form which is recommended for administration for HIV-1 infection when a booster (COBI or RTV) is not concurrently taken.

This was a single site study conducted between 30 June and 25 August, 2014. It was a Phase I open label study conducted with a planned 116 healthy adult subjects who were HIV-1 antibody negative.

Objectives

The primary objective of this study was as follows:

- To evaluate the bioequivalence of FTC and TAF administered as F/TAF (200/25 mg) or as E/C/F/TAF

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of a single oral dose of FTC and TAF administered as F/TAF (200/25 mg) and a single oral dose of EVG, COBI, FTC, and TAF administered as E/C/F/TAF

Study design

This was a randomised, open-label, single-dose, 2-way, crossover study to determine the BE of FTC and TAF, administered as F/TAF (200/25 mg) or as E/C/F/TAF. Following screening and Day −1 procedures, subjects were randomised to 1 of 2 treatment sequences (AB or BA) and received a single dose of 1 of the following treatments (A or B) on Days 1 and 7:

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

Subjects were admitted to the study clinic on Day −1 and remained confined to the clinic until Day 13. Subjects received a follow-up phone call on Day 21 ± 2 days (14 [±2] days after the last dose of study drug).

Pharmacokinetic results

Table 3: Statistical comparisons of plasma TAF and FTC PK parameters AUC_{last}, AUC_{inf}, and C_{max} (F/TAF 200/25 mg vs E/C/F/TAF 150/150/200/10 mg)

TAF PK Parameter	N	Test Mean (%CV)	N	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h*ng/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32	96.48, 104.31
AUC_{inf} (h*ng/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54	94.61, 102.62
C_{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63	95.46, 112.49
FTC PK Parameter	**N**	**Test Mean (%CV)**	**N**	**Reference Mean (%CV)**	**GLSM Ratio (Test/Reference) (%)**	**90% CI (%)**
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h*ng/mL)	116	9423.9 (19.3)	116	10475.3 (19.7)	90.01	88.88, 91.16
AUC_{inf} (h*ng/mL)	116	9654.6 (19.3)	116	10706.6 (19.6)	90.20	89.06, 91.35
C_{max} (ng/mL)	116	1577.4 (26.8)	116	1601.7 (19.6)	97.26	94.57, 100.03

The Geometric Least Squares Mean (GLSM) ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria specified for bioequivalence. The median T_{max} for TAF was the same (1.50 hours), while the median T_{max} for FTC was 2.00 hours following administration of F/TAF (200/25 mg) compared with 3.00 hours following administration of E/C/F/TAF. These results indicate that the bioequivalence of F/TAF 200 mg/25 mg is equivalent to the E/C/F/TAF 150/150/200/25 mg.

Safety results

Safety was comparable between the 2 study drugs in this study. No deaths, AEs leading to premature study drug discontinuation, or Grade 4 AEs were reported. One serious AE (SAE) of peritoneal haemorrhage was reported following F/TAF administration; this event was Grade 3 and considered not related to study drug by the investigator. With the exception of the Grade 3 AE of peritoneal haemorrhage, all other AEs were Grade 1 or 2 in severity.

Adverse events reported in > 1 subject during any study treatment included nausea, headache, constipation, vomiting, diarrhoea, dizziness, tension headache, and toothache. One Grade 4 and 2 Grade 3 laboratory abnormalities were observed during this study. One subject had a Grade 4 laboratory abnormality of increased lipase (with a Grade 2 amylase elevation on the same day)

but no AE was reported for the subject. Two female subjects had Grade 3 occult blood in urine, one of whom had confirmed menses at the time. All other laboratory abnormalities observed were Grade 1 or 2.

There were no clinically relevant changes from baseline in renal laboratory parameters (serum creatinine, eGFRCG, or serum phosphate) in any treatment group. Additionally, there were no clinically relevant changes from baseline in uric acid levels, the primary metabolite of TAF.

No clinically significant changes in vital sign measurements were observed during this study. No pregnancies occurred during this study.

4.2.1.3. Influence of food

This aspect was investigated in Study GS-US-311-1386. This study was a Phase I, randomised, open-label study to determine the effect of food on the pharmacokinetics of tenofovir alafenamide when administered as Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination tablet in healthy volunteers.

The primary objectives of this study were as follows:

1. To evaluate the effect of food on the PK of TAF when administered as F/TAF
2. To evaluate the effect of food on the PK of FTC when administered as F/TAF

The secondary objective of this study was as follows:

1. To evaluate the safety and tolerability of F/TAF administered under fed and fasted conditions

This was a randomised, open-label, single-dose, 2-treatment, 2-period, crossover, food-effect study. Following screening and Day −1 assessments, eligible subjects were randomised (1:1) to 1 of 2 treatment sequences (AB or BA) and received the following study drug treatments (first treatment on Day 1 and second treatment on Day 8).

- *Treatment A (fasted)*: Single dose of F/TAF (200/25 mg), administered orally under fasted conditions in the morning
- *Treatment B (fed):* Single dose of F/TAF (200/25 mg), administered orally under fed conditions in the morning

Subjects were admitted to the study centre on Day -1 and remained confined to the clinic until the morning of Day 14. Subjects received a follow-up telephone call on Day 22 ± 2 days.

A total of 40 subjects were randomised, and all received at least 1 dose of study drug. Of these, 38 subjects (95.0%) received both doses of study drug, and 2 discontinued after receiving F/TAF under fasted conditions (Treatment A) only; the reasons for discontinuation of study drug (and study) were AE and pregnancy, respectively. One of the 38 subjects who completed study drug discontinued the study early due to withdrawal of consent; therefore, 37 subjects (92.5%) completed the study.

The majority of subjects in the Safety Analysis Set were male (60.0%, 24 subjects). The median age was 28 years (range: 20 to 45). The majority of subjects were White (72.5%) and were not Hispanic or Latino (97.5%). At baseline, the median (Q1, Q3) BMI was 26.5 (24.1, 27.8) kg/m^2, and the median (Q1, Q3) eGFRCG was 121.8 (108.5, 132.5) mL/min.

TAF and FTC plasma PK parameters AUC_{inf}, AUC_{last}, and C_{max}, and the statistical comparisons of these parameters following the administration of F/TAF under fasted conditions and fed conditions (high-calorie, high-fat meal): When administered under fed conditions, the mean (%CV) C_{max} value was 207.2 (63.2) ng/mL (with an SD of 131.03) and mean (%CV) AUC_{last} value was 254.5 (42.6) ng•h/mL (with an SD of 108.40).

TAF AUC_{inf} and AUC_{last} increased by 75% and 77%, respectively, when administered under fed conditions compared with fasted conditions. TAF C_{max} decreased by 15% when administered under fed conditions compared with fasted conditions and was accompanied by a delay in median T_{max} (increase from 0.50 hours under fasted conditions to 1.00 hour under fed conditions). FTC AUC_{inf} and AUC_{last} decreased by 9% and FTC C_{max} decreased by 27%, when administered under fed conditions compared with fasted conditions, and there was a delay in median T_{max} (increase from 1.00 hour under fasted conditions to 2.00 hours under fed conditions).

Comment: This apparent increase in the AUC of TAF under fed conditions is comparable to the increase in AUC when TAF 10 mg is boosted. It is relevant to note that with a TAF dose of 10 mg under fed conditions the AUC is almost equivalent to the 25 mg unboosted dose. It is also relevant to note that all subsequent PK studies of TAF have been undertaken under fed conditions, thus maximising AUC, whereas the recommendation for administration states that food intake is not relevant to dosing. Studies of bioavailability have not been presented of the TAF 10 mg dose under fed and fasted conditions, except where the 10 mg dose is a component of the Genvoya FDC, and therefore boosted with cobicistat.

Safety results

No deaths were reported during this study. One subject had a confirmed pregnancy after she had received a dose of F/TAF administered under fasted conditions, and study drug was discontinued. The subject subsequently had a spontaneous abortion approximately 2 weeks after dosing. This was an SAE and considered by the investigator to be related to study drug. One subject discontinued study drug due to an AE of neutropenia. After administration of F/TAF under fasted conditions on Day 1, neutrophil levels decreased on Day 3 to Grade 1, falling further on Days 4 and 5 to Grade 3, followed by Grade 2 on Days 6 through 8, and then resolving to within the normal range on Day 9. The investigator considered the AE to be related to study drug.

The percentage of subjects with any AE was 30.0% (12 of 40 subjects) following F/TAF administered under fasted conditions and 26.3% (10 of 38 subjects) following F/TAF administered under fed conditions. AEs that were considered by the investigator as related to study drug were reported in 20.0% (8 subjects) and 18.4% (7 subjects), respectively. The most common AEs were nausea and headache (each reported in 7.5% [3 subjects] following F/TAF administered under fasted conditions and 5.3% [2 subjects] following F/TAF administered under fed conditions), and chills (5.3% [2 subjects] following F/TAF administered under fed conditions only).

The majority of AEs were Grade 1 (mild). Two subjects had a Grade 3 (severe) AE (neutropenia and spontaneous abortion), both following F/TAF administered under fasted conditions and considered by the investigator as related to study drug.

There were no clinically relevant changes in clinical laboratory parameters, vital signs, or body weight during the study.

Conclusions

The overall conclusions of this study are as follows:

- Overall TAF exposure (AUC_{inf}) increased by 75% when F/TAF (200/25 mg) was administered under fed conditions compared with fasted conditions. The wide range of TAF exposure associated with potent antiviral activity established in Study GS-US-120-0104 and with safety and efficacy in the E/C/F/TAF clinical program (predicted individual steady-state mean [95% CI, %CV] AUC 206.4 ng•h/mL [55.6 to 526.1 ng•h/mL, 71.8%]) indicates that the TAF PK differences upon F/TAF administration with or without food may not be clinically relevant.

- Overall FTC exposure (AUC_{inf}) decreased by 9% when F/TAF (200/25 mg) was administered under fed conditions compared with fasted conditions. These findings are consistent with those from a previous study (FTC-111), which supports the current recommendation that FTC can be administered without regard to food.
- Single doses of F/TAF, administered under fed and fasted conditions were generally well tolerated in this study.
- Overall, according to the sponsor, the differences in TAF or FTC exposures upon administration with food are not expected to result in clinically relevant differences in efficacy or safety; therefore, F/TAF can be administered without regard to food. Clinical data provided are only for the TAF 25 mg dosage. Data for the 10 mg dosage are incorporated into the Genvoya submission and involve boosting with COBI. No data on the food effect of boosting with ritonavir are available.

Table 4: F/TAF Study GS-US-311-1386: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Study Treatments (PK Analysis Sets)

	Mean (%CV) by Treatment		
	F/TAF Fed (Test) (N = 38)	F/TAF Fasted (Reference) (N = 40)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{inf} (ng•h/mL)	266.8 (42.0)[a]	147.0 (42.5)	175.38 (163.93, 187.63)
AUC_{last} (ng•h/mL)	254.5 (42.6)	145.8 (42.9)	176.57 (166.19, 187.60)
C_{max} (ng/mL)	207.2 (63.2)	230.1 (36.2)	84.53 (74.92, 95.37)
FTC PK Parameter			
AUC_{inf} (ng•h/mL)	9181.9 (15.6)	10,122.6 (15.5)	91.11 (88.84, 93.44)
AUC_{last} (ng•h/mL)	8964.4 (15.6)	9876.4 (15.6)	91.22 (88.90, 93.60)
C_{max} (ng/mL)	1551.2 (22.6)	2097.8 (19.1)	73.50 (69.26, 78.00)

a n = 33; TAF AUC_{inf} could not be calculated in 5 subjects.

4.2.1.4. Dose proportionality

The main dose proportionality study, a thorough study conducted with TAF was in relation to a QT/QTc study in 48 healthy subjects, tenofovir alafenamide at the therapeutic dose or at a supra-therapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

4.2.1.5. Bioavailability during multiple-dosing

The PK profile of TAF has been evaluated in 21 Phase I studies, 2 Phase II studies, 1 Phase II/III study, and 4 Phase III studies. The TAF PK profile has been characterised following single doses and at steady-state in healthy and HIV-infected individuals at doses ranging from 8 to 125 mg. Overall, TAF behaved dose proportionally and in a linear manner across the range of doses studied. The TAF PK profile is characterised by rapid absorption, with a median plasma T_{max} of approximately 0.50 hours, and rapid elimination, with a median plasma $t_{1/2}$ of approximately 0.40 hours and BLQ plasma concentrations by approximately 5 hours postdose (Study GS-US-120-0104). Due to the short plasma $t_{1/2}$, TAF does not accumulate in plasma.

Pharmacokinetics of FTC after single- and multiple-dose administration in healthy subjects

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

prior to reaching the systemic circulation, resulting in a high absolute bioavailability value (93% as shown in Study FTC- 110). At the therapeutic dose (200 mg once daily given as the capsule formulation), the steady-state peak plasma FTC concentration averaged approximately 2 µg/mL FTC disposition follows linear, first-order kinetics, with steady-state plasma FTC concentration-time profiles predictable based on single-dose data. The steady-state plasma AUC over the 24 hour dosing interval following 200 mg once daily averaged 10 µg•h/mL, which was comparable with the $AUC_{0\text{-}inf}$ value following a single-dose administration and was consistent with the PK principle.

4.2.1.6. Effect of administration timing

There appears to be no specific effect of timing on administration of TAF. When taken in the FDC with food, timing of dosing does not have any clinical recommendation.

4.2.2. Distribution

1.1.1.1.1. Volume of distribution

The distribution of TAF into compartments other than plasma (for example, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated in humans.

4.2.2.1. Plasma protein binding

The protein binding of TAF was moderate in human plasma with the per cent unbound value of 20% based on multiple human ex vivo studies with the mean per cent unbound TAF ranged 14% to 23% (GS-US-120-0108 and GS-US-120-0114). In a human ADME study, following administration of an oral 25 mg dose of [^{14C}] TAF in healthy subjects, the whole blood-to-plasma concentration ratio of [^{14}C]-radioactivity increased from 0.6 at 0.25 hours post dose to 2.4 at 216 hours post-dose, suggesting a relatively slower clearance of [^{14}C]-radioactivity from blood cells relative to the plasma [^{14}C]-radioactivity time-course (GS-US-120-0109).

1.1.1.1.2. Tissue distribution

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

The distribution of TAF into compartments, other than plasma, has not been clinically evaluated in humans. TAF is rapidly incorporated into PBMCs, spending very little time in plasma. As TAF is metabolised to tenofovir by Cat A, the level in plasma is very low, compared with TDF. Following oral administration of [^{14}C] TAF to mouse and dog, [^{14}C] TAF-derived radioactivity was widely distributed to most of the tissues in all species. Consistent with high hepatic extraction, high levels of radioactivity were observed in the liver; high radioactivity was also measured in the kidney. Low levels of radioactivity were observed in brain and testis in mouse. No melanin binding was observed in rats. Distribution trends in the pigmented uveal tract of the eye and pigmented skin suggested that [^{14}C] TAF-related radioactivity was not selectively associated with melanin-containing tissues in the pigmented mouse. Distribution studies in dogs showed 5.7 to 15 fold higher $_{[14C]}$-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [^{14}C] -TAF relative to [^{14}C] -TDF. Following single intravenous administration of [^{14}C] TFV in male rats, the highest concentrations of radioactivity were found in the kidney, liver, urine, and large intestine and trace amounts were observed in bone or bone marrow

4.2.3. Metabolism

4.2.3.1. Sites of metabolism and mechanisms / enzyme systems involved

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. Intracellular metabolic activation of TAF in PBMCs or HIV-target cells including lymphocytes involves conversion to TFV by cathepsin A (Cat A). In contrast to PBMCs, TAF is primarily hydrolysed by carboxylesterase-1 in primary hepatocytes. Of the HIV PIs (DRV, ATV, LPV, and RTV), the boosting agent COBI, and HCV PIs (telaprevir, boceprevir, TMC-435, BI-201355, MK-5172, GS-9256, and GS-9451), the HCV PIs telaprevir and boceprevir, which are known to inhibit Cat A, were the only ones that changed the antiretroviral effect of TAF in primary CD4+ T lymphocytes (reduced 23 fold and 3-fold, respectively). These data support the co-administration of the tested therapeutic PIs, with the exception of telaprevir or boceprevir, in combination with TAF, without negatively affecting its clinical pharmacology and intracellular conversion to TFV. Emtricitabine and TFV are analogues of 2 different nucleosides, cytosine and adenosine, respectively, and do not share a common intracellular metabolism pathway. In experiments where both FTC and TFV were incubated together at concentrations higher than achieved in the plasma (10 μM), the intracellular phosphorylation of FTC and TFV to their active intracellular anabolites was not affected.

4.2.3.2. Non-renal clearance

As above, less than 1% of TAF is excreted via renal clearance. The majority is metabolised to TFV where it is excreted via the kidneys.

4.2.3.3. Metabolites identified in humans

Active metabolites

The metabolite profiles were determined in human plasma, urine, and faeces following administration of a single oral dose of [^{14}C] TAF (GS-US-120-0109). Tenofovir alafenamide is also 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. TAF is eliminated following metabolism to its major metabolite TFV. TAF and TFV have a median plasma $t_{1/2}$ of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

4.2.3.4. Pharmacokinetics of metabolites

The pharmacologically active metabolite, TFV-DP, has a $t_{1/2}$ of 150-180 hours within PBMCs. The pharmacokinetics of TAF were measured in peripheral blood mononuclear cells (PBMCs) in a pivotal Phase III clinical study (GS-US-311-1089). As this study may be submitted in the future as providing the clinical and safety evidence to support the use of F/TAF, this study will be described in some detail in this section:

GS-US-311-1089 is an ongoing Phase III, randomised, double-blind, switch study to evaluate the efficacy of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF as determined by the proportion of subjects with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48. This interim pharmacokinetics (PK) report describes the assessment of intracellular TFV-DP concentrations in peripheral blood mononuclear cells (PBMCs) in subjects receiving F/TAF or FTC/TDF, in the presence of various third agents, boosted (by RTV) and unboosted.

This discussion will focus on the PK results in PBMCs rather than detailing all study methodologies and assessments as they do not have relevance for the limited report submitted in this dossier.

Study objectives

The primary objective of Study GS-US-311-1089 is:

- To evaluate the efficacy of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF as determined by the proportion of subjects with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48

The secondary objectives of Study GS-US-311-1089 are:

- To evaluate the bone safety of two regimens as determined by the percentage change from baseline in hip and spine BMD at Week 48
- To evaluate the efficacy, safety and tolerability of two regimens through Week 48 and Week 96
- To evaluate the PK of TAF and TFV

Treatment groups

Approximately 660 subjects were planned to be enrolled. All eligible subjects were randomised in a 1:1 ratio to 1 of the following 2 treatment arms:

- *Treatment Arm 1:* F/TAF + Placebo-to-match FTC/TDF; 3rd agent remains the same (planned N = 330)
- *Treatment Arm 2*: FTC/TDF + Placebo-to-match F/TAF; 3rd agent remains the same (planned N = 330)

Key eligibility criteria

HIV-1 positive subjects who met the following criteria:

- Currently receiving an antiretroviral (ARV) regimen containing FTC/TDF in combination with one 3rd agent for ≥ 6 consecutive months prior to screening.
- Plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay) and not experienced 2 consecutive HIV-1 RNA above detectable levels after achieving a confirmed (2 consecutive) HIV-1 RNA below detectable levels on the current regimen in the past year. Plasma HIV-1 RNA should be < 50 copies/mL at the screening visit.
- Estimated glomerular filtration rate ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance.

Schedule of assessments

After screening, eligible subjects were randomised to Treatment Arm 1 or 2 and treated for 96 weeks. Following the screening and Day 1 visits, subjects return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 96.

Trough blood samples were collected at Week 4 (20 to 24 hours post dose) to determine the intracellular TFV-DP concentrations in PBMCs.

The PBMC PK analysis set included all subjects who were enrolled in the study, have received at least 1 dose of study medication, and have non-missing intracellular TFV-DP concentration data (pg/million cells). The PBMC PK analysis set was used for pharmacokinetics analyses of TFV-DP.

For analysis of intracellular TFV-DP concentration data, subjects were grouped according to the treatment they actually received.

Data presentation

Intracellular TFV-DP concentration data were summarised using descriptive statistics by treatment (F/TAF versus FTC/TDF). Additionally, intracellular TFV-DP concentration data were summarised using descriptive statistics by treatment (F/TAF versus FTC/TDF) and randomisation stratum of the 3rd agents (ritonavir-boosted protease inhibitors versus others). Nine summary statistics (sample size, mean, SD, the coefficient of variation [CV (%)], minimum, median, maximum, Q1, and Q3) were presented for PBMC concentration data.

The geometric mean, 95% confidence interval (CI) of geometric mean, and the mean and SD of the natural-log transformed values were presented.

Intracellular TFV-DP concentration data were also summarised by the individual third agent (that is, ATV/r [ritonavir-boosted atazanavir], DRV/r [ritonavir-boosted darunavir], LPV/r [ritonavir-boosted lopinavir], dolutegravir [DTG], efavirenz [EFV], maraviroc [MVC], nevirapine [NVP], Raltegravir [RAL], and Rilpivirine [RPV]), and for F/TAF and FTC/TDF groups, separately, using descriptive statistics.

As Study GS-US-311-1089 is an ongoing randomised, double-blind, active-controlled study, the individual treatment assignments remained blinded to the Gilead study team members during the analysis of the intracellular TFV-DP concentration data. The Gilead lead study statistician prepared the statistical analysis plan for the intracellular TFV-DP data analysis. An external statistician, who was granted access to the real treatment codes and who was not directly involved in the current trial, conducted the statistical analyses of PBMC data. The internal study team members reviewed analysis results, while remaining blinded to individual subject treatment assignments.

Disposition of study subjects

At the time of this interim analysis (January 2015), a total of 668 subjects had been randomised, 665 subjects had been enrolled (that is, subjects who had returned to the clinic and completed Day 1 visit assessment), and 663 subjects had been treated with at least 1 dose of study drug.

Analysis sets

A total of 663 subjects were included in the Safety Analysis Set, which was composed of 333 subjects in the F/TAF treatment arm and 330 subjects in the FTC/TDF treatment arm. Of these subjects, 579 subjects were included in the PBMC PK Analysis Set, including 308 subjects in the F/TAF treatment arm and 271 subjects in the FTC/TDF treatment arm. One subject ([information redacted]), whose third agent was RAL, was excluded from the PBMC PK analysis set as the subject was incorrectly enrolled into the stratum of F/TAF 10 mg and received the randomised study drug.

Pharmacokinetic evaluation

The ongoing Study GS-US-311-1089 allows for a direct comparison of intracellular concentrations of the active phosphorylated metabolite TFV-DP between F/TAF and FTC/TDF in combination with various third agents, boosted (by RTV) and unboosted. Intracellular TFV-DP concentrations for subjects who received F/TAF or FTC/TDF, irrespective of third agents, and the TFV-DP comparison across TAF- versus TDF-based regimens, are presented in the table below.

F/TAF administration resulted in intracellular TFV-DP concentrations that were greater than 4 fold higher relative to FTC/TDF (14.2 versus 3.4 pg/10^6 cell). It should be noted that the proportion of subjects who were taking boosted (RTV) and unboosted third agents were similar in each of the FTC/TDF and F/TAF arms, resulting in a concentration differential that was independent of boosting in this comparison.

Table 5: 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)	

Comparison of TFV-DP concentrations by individual third agents (unboosted) indicated that there was a range of values that may be influenced by the small numbers of subjects in several of the third agent treatment subgroups for example, EFV n=8; MVC n=1 and RPV n=3. This last group of RPV as a third agent had a 95% CI of 0.1 to 2271.4 pg/10^6 cell, which indicates there may have been a problem with the methodology. This has not been discussed in the report provided by the sponsor.

Table 6: GS-US-311-1089: Summary of Intracellular PBMC TFV-DP Concentrations for Subjects Who Received F/TAF 200/25 mg by Unboosted 3rd ARV Agent (PBMC PK Analysis Set)

	Geometric Mean (95% CI) by Unboosted 3rd ARV Agent						
	+ DTG (n = 24)	+ EFV (n = 8)	+ MVC (n = 1)	+ NVP (n = 67)	+ RAL (n = 56)	+ RPV (n = 3)	Total (n = 159)
Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	17.2 (10.0, 29.6)	6.4 (2.6, 15.6)	26.8 (NA)	18.3 (14.0, 24.0)	19.6 (14.3, 26.7)	16.1 (0.1, 2271.4)	17.6 (14.7, 21.2)

Table 7: GS-US-311-1089: Summary of Intracellular PBMC TFV-DP Concentrations for Subjects Who Received F/TAF 200/10 mg by RTV-Boosted 3rd ARV Agent (PBMC PK Analysis Set)

	Geometric Mean (95% CI) RTV-Boosted 3rd ARV Agent			
	+ ATV+RTV (n = 50)	+ DRV+RTV (n = 82)	+ LPV/r (n = 17)	Total (n = 149)
Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	15.6 (12.3, 19.8)	9.7 (8.0, 11.7)	8.7 (5.4, 14.1)	11.2 (9.7, 13.0)

Comment: The results of F/TAF with the boosted third agents indicate the intracellular concentration of TFV-DP is around 2-3 times the concentration seen with FTC/TDF, rather than the four fold difference noted by the sponsor in the Genvoya studies. It is also noted that the concentration seems to be independent of the level of boosting agent used as the PBMC concentration is marginally lower with 200 mg of RTV (LPV/r) compared with boosting with RTV 100 mg (ATV+RTV and DRV+RTV). As the 95% CIs are so wide for many of the results, it would be useful to also have the median values. It appears the exposure of TAF does not have a proportional relationship with the intracellular TFV-DP concentration and may be interpreted as not totally dependent of boosting with RTV at the dose of 10 mg and that taking the 10 mg dose with food may have the same PBMC intracellular effect.

4.2.3.5. Consequences of genetic polymorphism

Not applicable.

4.2.4. Excretion

4.2.4.1. Routes and mechanisms of excretion

As TAF is almost entirely converted to TFV intracellularly, there is almost no excretion of the ingested product. TFV is excreted via the kidneys.

4.2.4.2. Mass balance studies

Mass balance was determined in Study GS-US-120-0109. The primary objective of this study was to determine the mass balance of TAF following administration of a single, oral dose of radiolabeled carbon-14 [^{14}C] TAF.

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

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

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

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

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

4.2.4.3. Renal clearance

Both TFV and FTC are excreted via renal clearance. TAF and TFV have a median plasma $t_{1/2}$ of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

4.2.5. Pharmacokinetics in the target population

HIV disease status did not have an effect on TAF exposure in healthy and HIV-infected subjects, and was not a statistically or clinically relevant covariate based on population PK analyses. A

statistically significant effect of HIV disease status on TFV PK parameters was observed; however, the range of TFV exposures across healthy and HIV-infected was comparable and the observed relationship between disease status and TFV exposure is therefore unlikely to be clinically relevant. One of the pivotal PK studies to determine the pharmacokinetics in the target population is GS-US-120-0104. This is a Phase I, randomised, partially-blinded, active and placebo-controlled study of the safety, pharmacokinetics, and antiviral activity of GS-7340 (TAF) monotherapy in subjects with HIV-1.

Subjects were randomised in a 2:2:2:1:2 ratio to one of the following 5 treatment groups:

- Treatment Group 1: TAF 8-mg tablet
- Treatment Group 2: TAF 25-mg tablet
- Treatment Group 3: TAF 40-mg tablet
- Treatment Group 4: TDF 300-mg tablet
- Treatment Group 5: Placebo-to-match TAF tablet

Treatments 1, 2, 3 and 5 (TAF and matched placebo) were blinded, while Treatment 4 (TDF) was open label.

4.2.5.1. Study population

A total of 36 subjects were planned to be enrolled in this study. A total of 40 eligible subjects were randomised into the study. Two subjects were randomised and never dosed (1 subject each in the TAF 40-mg treatment group and placebo-to-match TAF treatment group). Nine subjects received TAF 8 mg, 8 subjects received TAF 25 mg, 8 subjects received TAF 40 mg, 6 subjects received open-label TDF 300 mg, and 7 subjects received placebo-to-match TAF. A total of 37 subjects completed the study; 1 subject was lost to follow-up.

Of the 38 randomised and treated subjects, 37 (97.4%) were male, 20 (52.6%) were White, and 14 (36.8%) were Black. The mean age was 38 years (range: 20 to 57 years), the mean BMI was 26.8 kg/m^2 (range: 19.9 to 37.3 kg/m^2), and the mean eGFRCG was 118.2 mL/min (range: 64.2 to 173.9 mL/min).

4.2.5.2. Results

Following administration of TAF 8 mg, 25 mg, or 40 mg, TAF was rapidly absorbed with detectable levels at the first sampling time point (0.25 hours) and a median T_{max} of approximately 0.50 hours. TAF $t_{1/2}$ was approximately 0.40 hours and plasma concentrations were below the limit of quantitation (BLQ) by approximately 5 hours post-dose. Pharmacokinetic exposure parameters of TAF were similar within each dose group following single- and multiple-dose administration, as expected given the short plasma $t_{1/2}$ of TAF. Following administration of TAF 8 mg, 25 mg, 40 mg, or TDF 300 mg (TFV equivalent dose of 4.8 mg, 15.1 mg, 24.1 mg, and 135.6 mg, respectively), the highest TFV plasma concentrations were observed when given as TDF. TFV plasma levels were greater within each dose group following multiple dosing, relative to single dose administration, indicating accumulation, and in general, single-dose exposure (AUC_{inf}) was comparable with steady-state exposure (AUC_{tau}).

Table 8: Pharmacokinetic parameters of TAF (GS-US_292-0104)

TAF PK Parameter	TAF Multiple-Dose PK Day 10		
	TAF 8 mg (n = 9)	TAF 25 mg (n = 8)	TAF 40 mg (n = 8)
AUC_{last} (ng•h/mL), Mean (%CV)	54.7 (92.6)	115.2 (33.4)	308.9 (33.6)
AUC_{last} (ng•h/mL), Median (Q1, Q3)	27.5 (20.3, 103.3)	109.1 (101.4, 132.9)	344.2 (213.4, 383.4)
C_{max} (ng/mL), Mean (%CV)	85.8 (116.3)	223.6 (58.8)	629.5 (57.0)
C_{max} (ng/mL), Median (Q1, Q3)	41.5 (24.9, 80.2)	177.2 (131.0, 318.3)	606.4 (299.6, 948.4)
T_{max} (h), Median (Q1, Q3)	0.50 (0.50, 0.50)	0.50 (0.50, 0.75)	0.50 (0.38, 0.50)
$t_{1/2}$ (h), Median (Q1, Q3)	0.38 (0.26, 0.50)[a]	0.39 (0.34, 0.54)	0.42 (0.32, 0.49)

Q1 = first quartile; Q3 = third quartile
a n = 8
Notes: AUC_{last} is presented for multiple-dose PK because TAF concentrations are below the limit of quantitation (BLQ) by approximately 5 hours postdose and utilizing AUC_{last} instead of AUC_{inf} or AUC_{tau}, respectively, provides a more appropriate measure of exposure assessment. To account for the variability in the data, the mean and median AUC_{last} and C_{max} are presented.

TFV exposure following administration of TDF 300 mg was consistent with historical data and substantially higher than when given as TAF. At steady state, following multiple-dose administration of TAF 8 mg, 25 mg, or 40 mg, the mean TFV AUC_{tau} values were 97%, 86%, and 79% lower, respectively, while mean TFV C_{max} values were 98%, 94%, and 89% lower, respectively, as compared with the mean TFV AUC_{tau} and C_{max} observed when dosed as TDF 300 mg. Peripheral blood mononuclear cell TFV-DP AUC_{tau} was similar when given as TAF 8 mg or TDF 300 mg. Following multiple-dose administration of TAF 25 mg and 40 mg, mean TFV-DP AUC_{tau} values were approximately 7 fold and approximately 25 fold higher, relative to TDF 300 mg.

Table 9: Pharmacokinetic parameters of TFV-DP (GS-US_292-0104)

TFV-DP PK Parameter	TFV-DP Multiple-Dose PK Day 10			
	TAF 8 mg (n = 6)	TAF 25 mg (n = 4)	TAF 40 mg (n = 7)	TDF 300 mg (n = 4)
AUC_{tau} (µM•h), Mean (%CV)	3.50 (77.6)	21.38 (76.8)	74.47 (92.7)	2.98 (118.4)
AUC_{tau} (µM•h), Median (Q1, Q3)	2.50 (1.60, 5.80)	15.80 (9.60, 33.15)	53.40 (28.30, 104.70)	1.60 (1.00, 4.95)

Q1 = first quartile; Q3 = third quartile
Note: To account for the variability in the data, the mean and median AUC_{tau} are presented.

4.2.6. Pharmacokinetics in other special populations

4.2.6.1. Pharmacokinetics in subjects with impaired hepatic function

In subjects with mild hepatic impairment, the plasma exposure parameters of TAF were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 7.52%, 8.17%, and 10.99% lower, respectively) relative to matched control subjects with normal hepatic function (GS-US-120-0114). The upper bounds of the 90% CIs were below the protocol-defined clinically significant increase of 100% in TAF AUC_{inf}, AUC_{last}, or C_{max} for subjects with mild hepatic impairment compared with normal

matched control subjects, and the observed decreases are not considered to be clinically relevant.

In subjects with moderate hepatic impairment, the plasma exposure parameters of TAF were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 12.69%, 15.06%, and 18.70% higher, respectively) relative to matched control subjects with normal hepatic function. The upper bounds of the 90% CIs were below the protocol-defined clinically significant increase of 100% in TAF AUC_{inf}, AUC_{last}, or C_{max} for subjects with moderate hepatic impairment compared with normal matched control subjects, and the observed increases are not considered to be clinically relevant. No clinically relevant differences in TAF or TFV PK were observed in subjects with mild to moderate hepatic impairment; therefore, no TAF dose adjustment is required in patients with mild to moderate hepatic impairment.

The effect of severe hepatic impairment on the PK of TAF has not been studied.

4.2.6.2. Pharmacokinetics in subjects with impaired renal function

No clinically relevant differences in TAF exposure was observed between healthy subjects and subjects with severe renal impairment, defined as having a calculated creatinine clearance [CLcr] of 15 ≤ CLcr ≤ 29 mL/min at screening [severe renal impairment group] (GS-US-120-0108) Calculated CLcr was determined using the Cockcroft-Gault formula (eGFRCG). Following screening procedures and baseline assessments (Day 0), eligible subjects in each of the 2 groups (severe renal impairment and control) received a single dose of TAF 25 mg (1 x 25-mg tablet) administered orally on Day 1. Enrolment of subjects in the control group began after the corresponding matched subject in the severe renal impairment group had completed PK assessments.

Subjects with severe renal impairment had a 1.9 fold higher TAF systemic exposure as assessed by AUC_{inf} relative to subjects with normal renal function. This difference was not considered clinically relevant, as it is less than a 2 fold difference. Subjects with severe renal impairment had a 6.05 fold mean increase in systemic TFV exposure as assessed by AUC_{inf} relative to subjects with normal renal function. The TFV exposure encountered in subjects with severe renal impairment in this study after a single dose of TAF 25 mg was within or below the range of TFV plasma exposures measured in other studies after administration of TDF 300 mg in subjects and patients with normal renal function.

TAF plasma protein binding measured at 1 and 4 hours was similar between subjects with severe renal impairment and subjects with normal renal function (mean per cent unbound was approximately 20% at 1 hour and approximately 14% at 4 hours in both groups). TFV plasma protein binding measured at 2 and 24 hours was also similar between subjects with severe renal Plasma TFV exposure in subjects with mild-to-moderate renal impairment were within or below the range of TFV plasma exposure after administration of TDF 300 mg in both healthy, HIV-uninfected subjects and in HIV-infected patients with normal renal function. Additionally, population PK analyses of TAF and TFV from pooled Phase I, II and III study populations showed that baseline eGFR was not a statistically or clinically relevant covariate influencing TAF PK.

Table 10: Pharmacokinetic parameters for TAF and TFV after a single dose of TAF 25 mg on subjects with severe renal impairment or normal renal function

Mean (%CV)	Severe Renal Impairment (n = 14)	Normal Renal Function (n = 13)
TAF		
AUC_{inf} (ng•h/mL)	513.2 (47.3)	267.3 (49.2)
AUC_{last} (ng•h/mL)	510.6 (47.4)	265.9 (49.5)
C_{max} (ng/mL)	363.7 (65.7)	198.8 (62.1)
$t_{1/2}$ (h)	0.75 (51.8)	0.53 (22.8)
CL/F (mL/h)	61,717.8 (56.8)	117,633.1 (53.9)
CL_r (mL/min)	4.2 (77.6)	35.8 (51.7)
Percent of dose recovered in urine (%)	0.47 (95.6)	2.00 (34.6)
A_e (ng)	117,230.4 (95.6)	500,408.6 (34.6)
TFV		
AUC_{inf} (ng•h/mL)	2073.8 (47.1)	342.6 (27.2)
AUC_{last} (ng•h/mL)	1694.9 (43.1)	298.0 (26.1)
C_{max} (ng/mL)	26.4 (32.4)	9.5 (36.5)
$t_{1/2}$ (h)	56.53 (19.6)	51.28 (12.2)
CL/F (mL/h)	8531.4 (36.4)	47,013.8 (26.3)
CL_r (mL/min)	51.4 (40.1)	209.4 (24.6)
Percent of dose recovered in urine (%)	30.12 (24.6)	24.17 (23.3)
A_e (ng)	4,548,490 (24.6)	3,650,168 (23.3)

Table 11: Statistical comparison of TAF and TFV PK parameters in subjects with severe renal impairment or normal renal function

GLSM Ratio % (90% CI) Severe Renal Impairment (Test) vs Normal Renal Function (Reference)		
PK Parameter	**TAF**	**TFV**
AUC_{inf} (ng•h/mL)	191.89 (137.81, 267.18)	573.76 (457.21, 720.01)
AUC_{last} (ng•h/mL)	192.26 (137.81, 268.21)	545.91 (442.82, 672.99)
C_{max} (ng/mL)	179.43 (123.73, 260.20)	279.31 (231.48, 337.02)

N =14 for the renal impairment group and N = 13 for the matched control group

4.2.6.3. Pharmacokinetics according to age

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

Comment: Exposures of FTC and TAF achieved in 24 paediatric patients aged 12 to < 18 years were similar to exposures achieved in treatment-naïve adults. These studies were all conducted in subjects administered TAF and compared with Genvoya. There are no studies reported in adolescent subjects administered

other anti-retroviral drugs and the booster ritonavir. Therefore, the recommendation that Descovy can be given with other anti-retrovirals (other than Genvoya) and boosted with ritonavir is not supported by clinical evidence.

4.2.7. Pharmacokinetics in other special population / according to other population characteristic

Population PK analyses indicated no statistically significant or clinically relevant influence on TAF exposure based on body size measures (body weight, body surface area, or body mass index [BMI]), age (range 12 to 82 years), sex, race, eGFRCG, and population (healthy subjects versus treatment-naive HIV subjects versus treatment-experienced HIV subjects). A modest, statistically significant effect of race (Black versus non-Black) and sex on TFV PK parameters was observed. However, the range of TFV exposure across race and across males and females was comparable and, as such, these observed relationships are not considered to be clinically relevant. No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for FTC or TAF.

4.2.8. Pharmacokinetic interactions

4.2.8.1. Pharmacokinetic interactions demonstrated in human studies

The potential for TAF and TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities. The inhibitory activity of TAF with human liver microsomal CYP isozymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed at concentrations up to 25 µM. The inhibition constant (IC_{50}) values calculated for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were greater than 25 µM. TAF weakly inhibited CYP3A-mediated oxidation of midazolam or testosterone with IC_{50} values of 7.6 and 7.4 µM, respectively. TFV at 100 µM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 was assessed at TAF concentration at 50 µM (AD-120-2040). There was no evidence for time- or cofactor-dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control. Although TAF is a weak inhibitor of CYP3A, at clinically relevant concentrations, TAF is unlikely to affect hepatic CYP3A activity. While CYP3A activity may be affected in the intestine, where high levels of TAF can be achieved, the exposure to TAF in intestine should be transient and the potential for significant drug interaction is unlikely. In addition, since E/C/F/TAF contains COBI, a specific CYP3A inhibitor, the effect caused by TAF, if any, is expected to be minimal. Moreover, any induction potential by TAF is countered by co-administration with COBI.

TAF is transported by P-gp and metabolised by esterases expressed in the intestine. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly affect P-gp activity may lead to changes in TAF availability. However, upon co-administration with COBI in E/C/F/TAF, near maximal inhibition of P-gp by COBI is achieved, leading to increased availability of TAF with resulting exposure comparable with TAF 25 mg single agent. As such, TAF exposure following administration of E/C/F/TAF is not expected to be further increased when used in combination with another P-gp inhibitor. This is supported by a clinical study with E/C/F/TAF and investigation agent GS-5816, a P-gp inhibitor, which showed no clinical relevant changes in TAF or TFV upon co-administration of E/C/F/TAF with GS-5816, relative to E/C/F/TAF alone (GS-US-342-1167). Because TAF was found to be a substrate for hepatic transporters organic anion transporting polypeptide (OATP) B1 and OATP1B3, exposure to TAF may be affected by inhibitors of OATP1B1 and OATP1B3 or by genetic polymorphisms affecting their transport activities. The effects of differences in OATP1B1 and OATP1B3 activity are, however, not expected to be clinically relevant given the high passive permeability of TAF.

Co-administration of TAF single agent with a modest CYP inducer, such as EFV, resulted in slightly lower TAF exposure (14%-22%) and a commensurate lowering of TFV exposure (GS-US-311-0101). As such, administration of E/C/F/TAF with a modest CYP3A inducer may result in lower TAF exposure. However, the magnitude of change in TAF and TFV would be expected to be less following E/C/F/TAF due to the presence of the potent CYP3A inhibitor COBI.

4.2.8.2. TAF and CYP3A Inhibitor Ritonavir (Study GS-US-120-0118)

One of the pivotal aspects of this submission the recommendation that Descovy can be administered with a booster, which means that the dosage of the TAF component of Descovy can be reduced from 25 mg to 10 mg. The pharmacokinetics of this recommendation are supported in relation to the use of cobicistat (150 mg) with extensive evidence provided in the Genvoya dossier. The studies submitted to support the use of the booster, ritonavir, will be presented in this section in some detail as currently, ritonavir is possibly the most widely used boosting agent for protease inhibitors in the management of HIV-1 infection.

This study is a pharmacokinetic study evaluating the drug interaction potential of tenofovir alafenamide with a boosted protease inhibitor or unboosted integrase inhibitor in healthy subjects.

Objectives

The primary objectives of this study were as follows:

- To evaluate the effect of commonly boosted PIs ATV+RTV; DRV+RTV; LPV/r, or the INSTI DTG on the PK of TAF
- To evaluate the PK of ATV, DRV, LPV, and DTG alone and in combination with FTC and TAF

The secondary objectives of this study were as follows:

- To evaluate the safety of administration of FTC and TAF plus ATV+RTV, DRV+RTV, LPV/r, and DTG
- To evaluate PK of TFV following the co-administration of FTC and TAF plus ATV+RTV, DRV+RTV, LPV/r, and DTG, relative to the administration of FTC and TAF alone.

Study design

This was an open-label study of the PK drug interaction potential of TAF with the RTV-boosted PIs ATV+RTV, DRV+RTV, and LPV/r, or the integrase inhibitor Dolutegravir, in 40 healthy adult subjects. Subjects received a single dose of TAF 10 mg + FTC 200 mg, followed by 13 days of daily dosing of ATV+RTV, DRV+RTV, LPV/r, or DTG, followed by an additional single dose of TAF 10 mg + FTC 200 mg administered in the presence of steady-state RTV-boosted PI or unboosted DTG. Serial PK samples were collected to evaluate the relevant PK parameters for TAF and TFV or ATV, DRV, LPV, and DTG, administered alone or in combination. Subjects were enrolled in 1 of 4 treatment cohorts. The study was planned to enrol 40 subjects (10 subjects per cohort) to obtain 32 evaluable subjects (8 subjects per cohort). The following study treatments were administered:

- *Treatment A* = Treatment F: FTC 200 mg + TAF 10 mg once, administered in the morning with food
- *Treatment B:* ATV 300 mg + RTV 100 mg once daily, administered in morning with food
- *Treatment C*: DRV 800 mg + RTV 100 mg once daily, administered in morning with food
- *Treatment D*: 4 × LPV/r 200/50 mg once daily, administered in morning with food
- *Treatment E:* DTG 50 mg once daily, administered in the morning with food

Subjects were confined at the study centre from Day −1 until completion of PK and safety assessments on Day 16.

Table 12: Distribution of Allocated Treatment groups GS-US-120-0118

Cohort	Day 1	Days 2–14	Day 15
	Reference 1	Reference 2	Test
1	A	B	A + B
2	A	C	A + C
3	A	D	A + D
4	F	E	F + E

Study population

Forty subjects were enrolled in the study to receive study drug (10 subjects in each of the 4 cohorts). Thirty-nine of the 40 subjects completed the study. One subject assigned to Cohort 4 (FTC+TAF, DTG, and FTC+TAF+DTG treatment) withdrew consent prior to study completion. The median age in Cohorts 1, 2, 3, and 4 was 32, 35, 34, and 36 years, respectively (overall range: 23 to 45 years). Of the 40 subjects enrolled, 27 were males and 13 were female. The majority of subjects were white (30 of 40 subjects) and of Hispanic/Latino ethnicity (34 of 40 subjects).

Pharmacokinetic results

Co-administration of ATV+RTV or LPV/r with FTC+TAF increased TAF exposures approximately 91% and 47%, respectively, versus FTC+TAF alone (Table 13). Following dosing with DRV+RTV or DTG, the TAF exposure was unchanged. See table below:

Table 13: TAF Study GS-US-120-0118: Statistical Comparisons of TAF PK Parameter Estimates between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	164.8 (18.1)	91.6 (39.9)	188.92 (155.37, 229.71)
AUC_{last} (ng•h/mL)	162.6 (18.8)	89.5 (40.8)	191.06 (155.08, 235.40)
C_{max} (ng/mL)	146.5 (46.9)	76.8 (29.4)	176.72 (128.19, 243.63)
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	80.5 (30.4)	80.0 (41.8)	104.34 (84.14, 129.39)
AUC_{last} (ng•h/mL)	78.6 (30.9)	77.4 (43.6)	106.27 (83.59, 135.10)
C_{max} (ng/mL)	102.3 (46.5)	73.4 (49.4)	141.80 (96.11, 209.22)
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	122.5 (42.7)	82.7 (34.0)	144.75 (114.15, 183.55)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
AUC_{last} (ng•h/mL)	120.8 (43.9)	80.0 (34.1)	146.73 (116.60, 184.65)
C_{max} (ng/mL)	157.5 (39.4)	68.7 (28.7)	218.97 (171.88, 278.97)
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	105.1 (31.7)	100.9 (51.2)	116.62 (93.49, 145.48)
AUC_{last} (ng•h/mL)	103.0 (30.6)	98.5 (53.3)	119.02 (95.83, 147.82)
C_{max} (ng/mL)	83.4 (30.6)	79.9 (60.6)	123.64 (87.79,174.13)

Table 14: TAF Study GS-US-120-0118: Statistical Comparisons of TFV PK Parameter Estimates between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	285.9 (22.1)	113.7 (36.0)	261.59 (213.95, 319.84)
AUC_{last} (ng•h/mL)	102.1 (18.0)	41.7 (22.4)	247.77 (216.82, 283.14)
C_{max} (ng/mL)	8.8 (20.9)	4.3 (30.7)	212.35 (185.83, 242.65)
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	258.9 (21.5)	137.2 (49.2)	204.61 (153.78, 272.25)
AUC_{last} (ng•h/mL)	103.8 (12.7)	43.5 (24.2)	242.74 (207.17, 284.41)
C_{max} (ng/mL)	9.2 (21.2)	3.9 (34.1)	241.54 (198.10, 294.51)
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	409.8 (22.0)	98.2 (23.6)	416.36 (349.56, 495.93)
AUC_{last} (ng•h/mL)	129.0 (12.5)	40.3 (16.2)	322.01 (298.02, 347.93)
C_{max} (ng/mL)	12.7 (25.6)	3.4 (21.1)	374.52 (319.28, 439.30)
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	114.9	94.2	124.94 (106.46, 146.62)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
	(16.9)	(27.6)	
AUC_{last} (ng•h/mL)	43.0 (19.8)	41.7 (20.0)	104.25 (98.74, 110.08)
C_{max} (ng/mL)	3.8 (23.1)	3.7 (44.3)	109.91 (96.39, 125.32)

Co-administration of TAF 10 mg + FTC 200 mg had no effect on the PK of RTV-boosted PIs or DTG. See table below:

Table 15: TAF Study GS-US-120-0118: Statistical Comparisons of ATV, DRV, LPV, and DTG PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

ATV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs ATV+RTV (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	64,035.2 (47.0)	64,692.1 (46.3)	98.73 (96.35, 101.18)
Ctau (ng/mL)	1636.9 (91.7)	1619.0 (91.3)	100.08 (96.04, 104.29)
C_{max} (ng/mL)	5730.2 (17.3)	5946.9 (21.7)	97.55 (88.98, 106.94)
DRV PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs DRV+RTV (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	97,486.1 (23.9)	97,646.2 (27.1)	100.63 (95.70, 105.81)
Ctau (ng/mL)	2598.0 (45.9)	2374.1 (47.6)	112.83 (95.20, 133.73)
C_{max} (ng/mL)	8472.5 (16.6)	8567.7 (18.7)	99.09 (90.85, 108.08)
LPV PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs LPV/r (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	179,207 (30.1)	176,925 (24.3)	100.41 (92.38, 109.15)
Ctau (ng/mL)	2004.9 (88.2)	1954.4 (73.1)	97.58 (85.00, 112.02)
C_{max} (ng/mL)	14,662.6 (19.2)	14,592.3 (17.4)	100.29 (95.05, 105.83)

DTG PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs DTG (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	77,932.9 (19.3)	74,127.5 (16.0)	102.31 (97.09, 107.81)
C_{tau} (ng/mL)	2063.8 (30.3)	1949.3 (25.1)	104.88 (97.17, 113.19)
C_{max} (ng/mL)	5894.9 (6.7)	5148.0 (17.6)	115.29 (104.48, 127.22)

Comment: This study provides no clear explanation as to why the TAF exposure does not increase with the DRV+RTV dose, but increases with the LPV/r and the ATV + RTV doses. It would be expected that RTV would independently increase TAF exposure, irrespective of the co-administered protease inhibitor (in this case darunavir). This suggests a problem with either the experimental design or the analytic methodology. As this is the pivotal study used by the sponsor to make the recommendation for the use of the 10 mg dose of TAF with a booster, other than COBI, it is important to determine why this apparent discrepancy was reported and was either apparently not discussed or possibly not understood by the reviewer.

Safety results

No SAEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE.

The percentage of subjects with at least 1 AE was: FTC+TAF (4 of 40 subjects), ATV+RTV (10 of 10 subjects), FTC+TAF+ATV+RTV (1 of 10 subjects), DRV+RTV (2 of 10 subjects), LPV/r (9 of 10 subjects), DTG (3 of 10 subjects), and FTC+TAF+DTG (1 of 9 subjects). No AEs were reported during the following treatments: FTC+TAF+DRV+RTV and FTC+TAF+LPV/r. Adverse events reported in at least 2 subjects for each treatment included ocular icterus (10 of 10 subjects [100%] with ATV+RTV treatment), diarrhea (5 of 10 subjects [50%] with LPV/r treatment), dry mouth (5 of 10 subjects [50%] with LPV/r treatment), dysgeusia (3 of 10 subjects [30%] with LPV/r treatment), and headache (2 of 10 subjects [20%] with DTG treatment).

All AEs were reported as Grade 1 (mild) or Grade 2 (moderate). No Grade 3 or 4 events were reported.

Adverse events considered by the investigator to be possibly related to study drug: 1 of 10 subjects (2.5%) with FTC+TAF treatment (flatulence, n = 1; nausea, n = 1), 10 of 10 subjects (100%) with ATV+RTV treatment (ocular icterus, n = 10; jaundice, n = 1), and 5 of 10 subjects (50%) with LPV/r treatment (diarrhea, n = 5; vomiting, n = 1).

Increases from baseline in median values for total bilirubin were observed during ATV+RTV treatment (median increases of 3.8 mg/dL on Day 8 and 2.9 mg/dL on Day 14). No other clinically relevant changes from baseline in median values were observed for any hematology or chemistry parameter, and median values for all other parameters were within normal range before and after dosing.

Comment: The observation that 100% of the healthy subjects developed jaundiced sclera (ocular icterus) during this brief intervention has not been addressed by the sponsor as to whether this make be caused only by the Atazanavir or by the interaction between the TAF/FTC and the ATV+RTV.

Table 16: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
Atazanavir/cobicistat	↑ tenofovir alafenamide	TAF exposure is expected to increase when atazanavir/cobicistat is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.
Atazanavir/ritonavir[c]	↑ tenofovir alafenamide	TAF exposure is increased when atazanavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.
Darunavir/cobicistat[c]	— tenofovir alafenamide ↑ tenofovir tenofovir	Tenofovir exposure is increased when darunavir /cobicistat is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.
Darunavir/ritonavir[c]	— tenofovir alafenamide ↑ tenofovir tenofovir	Tenofovir exposure is increased when darunavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.
Lopinavir/ritonavir[c]	↑ tenofovir alafenamide	TAF exposure is increased when lopinavir/ritonavir is used in combination with DESCOVY. The recommended dose of DESCOVY is 200/10 mg once daily.
Tipranavir/ritonavir	↓ tenofovir alafenamide	Tenofovir alafenamide exposure may decrease when tipranavir/ritonavir is used in combination with DESCOVY. There are no data available to make dosing recommendations. Co-administration with DESCOVY is not recommended.
Other Protease Inhibitors	Effect is unknown	There are no data available to make dosing recommendations for coadministration with other protease inhibitors.
Other Agents		
Anticonvulsants:		
carbamazepine oxcarbazepine	↓ tenofovir alafenamide	Co-administration of carbamazepine, oxcarbazepine,

Concomitant Drug Class: Drug Name	Effect[b]	Clinical Comment
phenobarbital phenytoin		phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease TAF plasma concentrations which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.
Antifungals		
itraconazole ketoconazole	↑ tenofovir alafenamide	Co-administration of itraconazole or ketoconazole, both of which are P-gp inhibitors, may increase plasma concentrations of TAF. No dose adjustment is required.
Antimycobacterial:		
rifabutin rifampin rifapentine	↓ tenofovir alafenamide	Co-administration of rifampin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeuticeffect and development of resistance. Co-administration of DESCOVY with rifabutin, rifampin, or rifapentine isnot recommended.
Herbal Products:		
St. John's wort (Hypericum perforatum)	↓ tenofovir alafenamide	Co-administration of St. John's wort, a P-gp inducer, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of DESCOVY with St. John's wort isnot recommended.

a: This table is not all inclusive. b= increase, ↓ = decrease, ↔ = no effect c: Indicates that a drug-drug interaction study was not conducted.

1.1.1.2. Clinical implications of in vitro findings

Table 17: Dose Recommendations for F/TAF with Potential Concomitant Antiretroviral Drugs

ARV Drug	Recommended F/TAF Dose (mg)	TAF-Equivalent Dose[a] (mg)
EFV	200/25	12[b]
RPV		24
DTG[c]		17[b]/30
RAL		—[d]
MVC		—[d]
NVP		—[d]
ATV+COBI	200/10	—[e]
ATV+RTV		19
DRV+COBI		11
DRV+RTV		11
LPV/r		15

a TAF-Equivalent Dose calculated based on percentage change in TAF AUC with/without coadministered drug (assuming that both drugs are administered concurrently). Expected exposure in fed state unless otherwise noted.
b Expected exposure in fasted state.
c Because DTG may be administered without regard to food, expected exposures are provided for both the fed and fasted states.
d No DDI study performed. Dosing recommendation based on the nonclinical profiles of TAF and the specified ARV.
e No DDI study performed. Dosing recommendation extrapolated based on nonclinical information and the DDI study between TAF and ATV+RTV.

Comment: The recommended dosing is made in the fed state. Data from previous studies indicates that, at least with the 25 mg, unboosted dose of TAF, administration with a meal increases the exposure by around 75%. Therefore, the recommended dosing should also take into account administration in the fasted state. The recommended dose with DTG is an example of the differential between fed and fasted states as in the fed state TAF dose equivalent is 30 mg, and in the fasted state the TAF dose equivalent is 17 mg. This indicates that the fed state almost doubles the dose equivalent.

Table 18: Drug Interactions: Changes in Pharmacokinetic Parameters for TAF in the Presence of the Co-administered Drug [a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 + 100 ritonavir once daily	10 once daily	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150 daily	8 once daily	12	2.83 (2.20,3.65)	2.65 (2.29,3.07)	NC
Darunavir	800 + 150 cobicistat once daily	25 once daily	11	0.93 (0.72,	0.98 (0.80,	NC

Co-administered Drug	Dose of Co-administered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]; No effect = 1.00		
				C_{max}	AUC	C_{min}
				1.21)[d]	1.19)[d]	
Darunavir	800 + 100 ritonavir once daily	10 once daily	10	1.42 (0.96, 2.09)[e]	1.06 (0.84, 1.35)[e]	NC
Dolutegravir	50 once daily	10 once daily	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600 once daily	40 once daily[c]	11	0.78 (0.58,1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800/200 ritonavir once daily	10 once daily	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25 once daily	25 once daily	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 once daily	10 once daily	19	1.00 (0.86,1.16)	0.96 (0.89,1.03)	NC

NC = Not Calculated. a. All interaction studies conducted in healthy volunteers. b. All No Effect Boundaries are 70% -143% unless otherwise specified. c. Study conducted with DESCOVY (FTC/TAF). d. Mean ratio of tenofovir PK parameters (90% CI) was 3.16 (3.00, 3.33) for C_{max}, 3.24 (3.02, 3.47) for AUC, and 3.21 (2.90, 3.54) for C_{min}. e. Mean ratio of tenofovir PK parameters (90% CI) was 2.42 (1.98, 2.95) for C_{max}, 2.43 (2.07, 2.84) for AUC_{last}. f. Study conducted with Genvoya.

There appears to be no apparent interaction between TAF and the commonly administered anti-retroviral agents, such that the PK values of these agents remain unchanged in the presence of TAF. See table below:

Table 19: Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of TAF[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 +100 ritonavir once daily	10 once daily	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Cobicistat	150 once daily	8 once daily	14	1.06 (1.00, 1.12)	1.09 (1.03, 1.15)	1.11 (0.98, 1.25)
Darunavir	800 + 150 cobicistat once daily	25 once daily[c]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 + 100 ritonavir once daily	10 once daily	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 once daily	10 once daily	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800/200 ritonavir once daily	10 once daily	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[d]	2.5 once daily, orally	25 once daily	18	1.02 (0.92, 1.13)	1.12 (1.03, 1.22)	NC
	1 once daily IV			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25 once daily	25 once daily	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 single dose	10 once daily[e]	19	1.14 (0.94, 1.38)	1.09 (0.90,1.32)	NC

NC = Not Calculated. a. All interaction studies conducted in healthy volunteers. b. All No Effect Boundaries are 70% -143% unless otherwise specified. c. Study conducted with DESCOVY (FTC/TAF). d. A sensitive CYP3A4 substrate. e. Study conducted with Genvoya.

4.3. Evaluator's overall conclusions on pharmacokinetics

The drug for which the sponsor seeks approval is tenofovir alafenamide fumarate (TAF). This compound is intended as a replacement component for tenofovir disoproxil fumarate (TDF) in

the fixed dose combination which is currently approved as Truvada. The other component of Truvada and of the proposed drug Descovy is FTC. FTC has been extensively assessed and approved both individually and in combination. The formulations and dosages in the applicant STR will remain the same as in the Genvoya combination. TAF is a prodrug of tenofovir which is metabolised intracellularly by Cathepsin A (CatA) to tenofovir diphosphate, the form that has anti-viral activity. The reason the sponsor is applying to replace TDF with TAF is that TDF has higher and more prolonged plasma circulating levels of tenofovir which is associated with an increased risk of renal and bone toxicity. The PK studies submitted by the sponsor indicate that TAF at a dose of 10 mg in the STR (boosted by COBI or RTV) or 25 mg (unboosted) have a circulating level of tenofovir that is 90% less than the current dose of TDF 300 mg, which is the approved dose component of Truvada. The sponsor has submitted an extensive number of studies to support this application which indicate that the pharmacokinetics of TAF are not affected by race, mild to moderate hepatic failure, renal failure or age (for teenagers more than 12 years of age). Specifically, the clinical trial with Japanese subjects GS-US-292-0108 demonstrated no PK effect of Japanese origins. PK studies conducted as a part of the pivotal efficacy/safety clinical trial, GS-US-292-0104 and GS-US-0111 show that the AUC_{tau} of E/C/F/TAF was 91% lower than tenofovir exposure compared with E/C/F/TDF and the PBMC AUC_{tau} was 4.1 times higher with administration of E/C/F/TAF compared with E/C/F/TDF.

The Study GS-US-311-1386 indicated that under fed conditions the overall TAF exposure increased by 75%, when compared with fasted conditions. While this increase may not be relevant in relation to the safety margin for dosing, it may be relevant for the role of boosting the 10 mg dose when substituted for the 25 mg dose. As it appears the 10 mg dose when increased by 75% following ingestion with food may be equal to the exposure when administered as with a booster. The difference is not made clear by the sponsor and requires some clarification. The observation that one subject had a spontaneous abortion after stopping the TAF dose, and this was related to the study drug was not addressed by the sponsor. This observation may require further clarification, especially in relation to the issue of increased exposure following ingestion with food. The study looking at boosters with TAF shows that DRV+Rtv does not increase TAF exposure while the other combination does increase TAF exposure. The study with boosters should be repeated in fasted state rather than fed state as it is not possible to determine the role of booster vs fed state.

In Study GS-US-311-1089 the results of F/TAF with the boosted third agents indicate the intracellular concentration of TFV-DP is around 2-3 times the concentration seen with FTC/TDF, rather than the four fold difference noted by the sponsor in the Genvoya studies. It is also noted that the concentration seems to be independent of the level of boosting agent used as the PBMC concentration is marginally lower with 200 mg of RTV (LPV/r) compared with boosting with RTV 100 mg (ATV+RTV and DRV+RTV). As the 95% CIs are so wide for many of the results, it would be useful to also have the median values. It appears the exposure of TAF does not have a proportional relationship with the intracellular TFV-DP concentration and may be interpreted as not totally dependent of boosting with RTV at the dose of 10 mg and that taking the 10 mg dose with food may have the same PBMC intracellular effect.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 20 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 20: Submitted pharmacodynamic studies, primarily from Genvoya dossier Not 0specifically for Descovy as taking with third agents, other than EVG/COBI

PD Topic	Subtopic	Study ID	Primary Drug
Primary Pharmacology	Effect on antiviral activity	GS-US-120-1101	TAF
	Effect on Antiviral activity of escalating doses	GS-US-120-0104	TAF
Secondary Pharmacology	Effect on QTcF	GS-US-120-0107	TAF
Population PD and PK-PD analyses	Healthy subjects	GS-US-292-0103 GS-US-292-0108 GS-US-292-0110	
	Target population ‡§	GS-US-292-0102 GS-US-292-0106 GS-US-292-0104 GS-US-292-0109 GS-US-292-0111 GS-US_292-0112	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

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

5.2. Summary of pharmacodynamics

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

5.2.1. Mechanism of action

Tenofovir alafenamide fumarate (TAF) is a second generation oral prodrug of tenofovir that compared to TDF, delivers increased intracellular levels of tenofovir diphosphate (TFV-DP) allowing for a reduction in circulating tenofovir exposure. TAF is expected to provide enhanced delivery of tenofovir to peripheral blood mononuclear cells (PBMCs), resulting in higher intracellular levels of the active phosphorylated moiety tenofovir-diphosphate, more effective suppression of residual viral replication in a wider range of reservoir and anatomic sanctuaries of HIV, and lower systemic circulating levels of tenofovir, resulting in a better overall profile. TAF displayed mean anti-HIV activity (EC50) of 0.008 µM, 0.0031 µM, and 0.014 µM in MT-2 cells, PBMCs and macrophages, respectively. In contrast, tenofovir DF displayed corresponding values of 0.050 µM, 0.015 µM, and 0.055 µM, and tenofovir 4.8 µM, 1.9 µM, and 1.4 µM, respectively. The CC50 for GS-7340 (83 µM) and TDF (95 µM) were comparable. These indicate

that the in vitro activity of TAF against HIV-1 in MT-2 cells is 600 fold greater than tenofovir and 6 fold greater than TDF. Unlike TDF, TAF is stable in plasma, but is rapidly converted to tenofovir inside peripheral blood mononuclear cells (PBMCs) and MT-2 cells. TAF is metabolised to TFV, a nucleotide analogue (that is, a nucleoside monophosphate analogue) which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, TFV diphosphate (TFV-DP). The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) and nucleotide diphosphate kinase, which are highly active and ubiquitous. AK exists as multiple isozymes (AK1 to AK4), with the phosphorylation of TFV mediated most efficiently by AK2. The intracellular metabolism of TAF and TFV (each 10 μM) in intact MT-2 cells indicated that after a two hour incubation, only 2% of TAF remained intact and the formation of TFV-DP continued to increase for up to 24 hours. At 24 hours, the intracellular concentration of TFV-DP was approximately 2.6 mM after incubation with 10 μM TAF, as compared to approximately 1.2 μM after incubation with 10 μM TFV. The intracellular levels of TFV-DP are consistent with the 600 fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Metabolism of TAF was studied in different human blood lymphocyte subpopulations, CD4+ and CD8+ T-cells, NK cells, B-cells and macrophages/monocytes. Following incubation with GS-7340, all lymphocyte subpopulations demonstrate significant uptake of radioactivity ranging from 3.0 nmol/mln for monocytes to 1.7 nmol/mln for B-cells. Concentration of the active metabolite TFV-DP was substantial in all cell populations, ranging from 0.29 nmol/mln for NK-cells to 0.81 nmol/mln for CD8+-lymphocytes.

GS-7340 is metabolised inside host cells to the active metabolite TFV-DP. The Ki of TFV-DP for reverse transcription (RNA-directed DNA synthesis) is 0.02 μM, more than 200 fold lower than its Ki for human DNA polymerase α, and more than 3000 fold lower than its Ki values for human DNA polymerases β and γ.

5.3. Pharmacodynamic effects

5.3.1. Primary pharmacodynamic effects

TAF is a phosphonoamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation by cathepsin A, TAF is more efficient than TDF in loading TFV into peripheral blood mononuclear cells (PBMCs) (including lymphocytes, macrophages, and other HIV target cells). Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV-DP. TFV-DP inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

TFV has activity that is specific to HIV-1 and HIV-2 and hepatitis B virus (HBV). In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells. TFV-DP is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in vitro.

The bioavailability of TAF when administered alone is estimated to be ≤ 40%, based on dog and human hepatic extraction data. TAF is transported by P-glycoprotein (P-gp) and metabolised by esterases expressed in the intestine. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases, so drugs that strongly inhibit P-gp activity increase TAF availability. Upon co-administration of TAF with COBI single agent, near maximal inhibition of P-gp by COBI is achieved, leading to increased availability of TAF (Study GS-US-311-0101). For the E/C/F/TAF FDC tablet that contains TAF 10 mg, TAF bioavailability is increased approximately 2.3-fold, consistent with the exposure that occurs with the TAF 25 mg single agent (Study GS-US-292-0103). Following the administration of the E/C/F/TAF FDC tablet, the exposures of EVG, COBI, and FTC were equivalent to those observed following administration of EVG, COBI, or FTC single

agents at the same dosages and consistent with those observed historically following administration of STB (Study GS-US-292-0103).

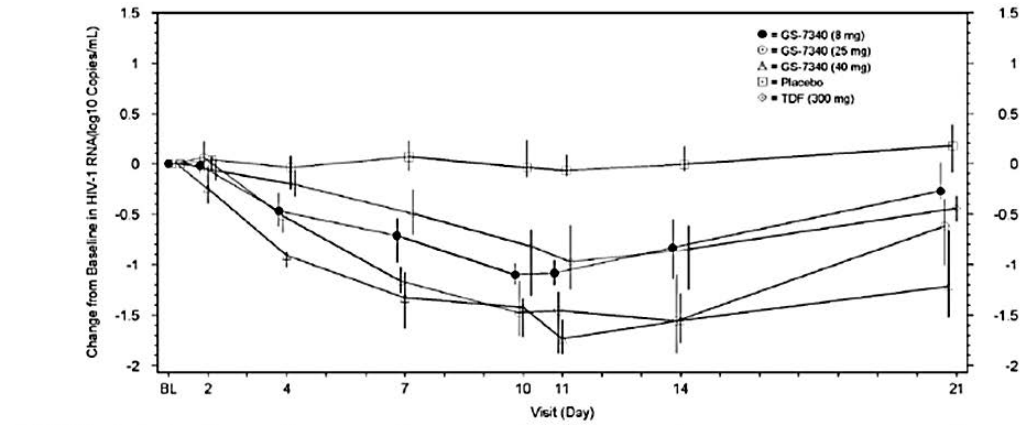
5.3.2. Secondary pharmacodynamic effects

HIV disease status did not have an effect on TAF exposure in healthy and HIV-infected subjects, and was not a statistically or clinically relevant covariate based on population PK analyses. A statistically significant effect of HIV disease status on TFV PK parameters was observed; however, the range of TFV exposures across healthy and HIV-infected was comparable and the observed relationship between disease status and TFV exposure is therefore unlikely to be clinically relevant.

5.3.3. Relationship between drug concentration and pharmacodynamic effects

In the proof-of-concept Study GS-US-120-0104, following once-daily administration of single-agent TAF 8, 25, 40 mg, or TDF 300 mg, the median (Q1, Q3) $DAVG_{11}$ values (the primary efficacy endpoint) were −0.76 (−0.86, −0.57), −0.94 (−1.12, −0.76), −1.08 (−1.35, −0.97), and −0.48 (−0.57, −0.34) log10 copies/mL, respectively. The median DAVG11 (log10 copies/mL) in the TAF 25-mg and 40-mg treatment groups showed significantly greater decreases compared with the TDF 300-mg treatment group (−0.94 and −1.08 versus −0.48, p = 0.017 and p = 0.006, respectively) with a statistically significant difference also observed between the TAF 8-mg and 40-mg treatment groups (−0.76 versus −1.08, p = 0.003). Median (Q1, Q3) change from baseline to Day 11 in HIV-1 RNA values were −1.08 (−1.20, −0.96), −1.46 (−1.88, −1.28), −1.73 (−1.88, −1.55) and −0.97 (−1.24, −0.62) log10 copies/mL for TAF 8, 25, 40 mg, and TDF 300 mg, respectively. The decreases in median viral load for both TAF 25 mg and TAF 40 mg were statistically significantly greater than that observed for TAF 8 mg (p = 0.030 and 0.002, respectively).

Figure 3: GS-US-120-0104: Median (Q1, Q3) of changes from Baseline in HIV-1 RNA (log10 copies/mL) by visit (Full analysis set)



Note: Baseline HIV-1 RNA is defined to be the geometric mean of the last 2 available nonmissing HIV-1 RNA values before the first dose.

Moreover, TAF PK/PD analyses evaluating TAF exposure versus response in the 2 pivotal Phase III studies (GS-US-292-0104, GS-US-292-0111) using results from the FDA snapshot algorithm showed uniformly high virologic success across the quartile categories of TAF AUC_{tau} with no trends in exposure-response relationship observed, confirming the dose selection of TAF 10 mg for the E/C/F/TAF FDC that provides equivalent exposure as TAF 25 mg single agent.

Two short-term studies (FTC-101 and FTC-102) were conducted to determine the dose-response relationship and to define a dosage regimen for FTC in Phase III studies. Study FTC-

101 was an open-label, sequential, dose-ranging trial evaluating the in vivo antiviral activity of FTC in HIV-infected subjects given 14 days of monotherapy at 25 mg twice daily, 100 mg once daily, 100 mg twice daily, 200 mg once daily, and 200 mg twice daily. A total of 41 subjects (N = 8 or 9 per dose group) naive to 3TC and abacavir (ABC) were enrolled. At screening, CD4 cell count ranged from 198 to 1071 cells/mm^3 and plasma HIV-1 RNA ranged from 3.9 to 5.9 log10 copies/mL. Plasma HIV-1 RNA was measured at baseline and frequently over the 14 days of treatment. Pharmacokinetics of FTC in plasma and FTC-TP in PBMCs were also evaluated.

Potent ARV suppression occurred in all dosage cohorts, with a strong trend toward greater activity at the higher doses. Viral suppression in the 200-mg once-daily group was as good as in the 200-mg twice-daily group. The 200-mg once-daily dose group showed a median change in plasma HIV-1 RNA from baseline at Day 15 of 1.9 log10 as compared with 1.3, 1.5, 1.7, and 1.9 log10 for the 25-mg twice-daily, 100-mg once-daily, 100-mg twice-daily, and 200-mg twice-daily dose groups, respectively. The onset of anti-HIV activity occurred within 48 hours of initiating FTC dosing, with the most rapid viral load decline occurring between Days 3 and 8. Results of statistical analyses of HIV-1 RNA average area under the curve minus baseline (AAUCMB), change from baseline at Day 15 (last day on study treatment), and maximum change from baseline consistently supported the dose-response relationship and the maximal antiviral effect at the 200-mg once-daily and 200-mg twice-daily doses.

5.3.4. Genetic-, gender- and age-related differences in pharmacodynamic response

There appears to be no specific genetic, gender and age-related differences in pharmacodynamic effects. However, there have been no studies submitted on the FDC (FTC/TAF) specifically in adolescents. The data on adolescents is extrapolated directly from the Genvoya submission.

5.3.5. Pharmacodynamic interactions

The Pharmacokinetic and pharmacodynamic interactions presented in the submission are taken directly from the Genvoya submission where TAF is compared with Stribild. The sponsor uses the bioequivalence data for the 10 mg and 25 mg dosages of TAF to bridge the data between the FDC (FTC/TAF) and Genvoya.

5.4. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic data presented in this section has been assessed from the Genvoya dossier as there are no specific pharmacodynamic studies related to Descovy. Study GS-US-311-1089 has data on the concentration of TFV-DP in PBMCs in the presence Descovy and a range of third agents, both boosted with RTV and unboosted. These pharmacokinetic data provide some indirect evidence that the pharmacodynamics of Descovy will be similar to those of Truvada, but this is not specifically addressed in the submission. It is possible that when the GS-US-311-1089 study is analysed there will be specific pharmacodynamic data to draw conclusions on Descovy.

6. Dosage selection for the pivotal studies

The pivotal studies submitted by the sponsor are two Phase I bioequivalence studies in healthy subjects. The studies have been presented in detail under Pharmacokinetics.

7. Clinical efficacy

No clinical efficacy studies using the FDC FTC/TAF have been submitted to directly support this application. The sponsor has provided two pivotal bioequivalence studies GS-US-311-1472 and GS-US-311-1473. These Phase I studies in healthy adults do not address any issues of clinical

efficacy. By demonstrating bioequivalence the sponsor is then using the Genvoya data on clinical efficacy to support the inference that Descovy as a standalone FDC will have the same clinical efficacy as Genvoya when combined with COBI and EVG (as in Genvoya) or with other boosted or unboosted anti-retroviral combinations.

The six clinical studies (GS-US-292-0102 (Phase II); GS-US-292-0104 (Phase III; naive); GS-US-292-0111 (Phase III; naive); GS-US-292-0109 (Phase III; virologically suppressed; switch study)

GS-US-292-0106 (single arm; adolescents); GS-US-292-0112 (renal impairment) submitted to support the application were conducted with the Genvoya FDC and not with the Descovy FDC. While this may indirectly support the clinical efficacy of Descovy, the studies do not address the issues of Descovy administered in any form other than as an FDC in combination with COBI and EVG. The clinical efficacy of this combination was assessed in the Genvoya submission by the TGA.

This dossier contains exactly the same efficacy studies that were submitted for Genvoya. No other clinical efficacy Phase III studies are included in the dossier. Study GS-US-311-1089 is a Phase III clinical efficacy and safety study which would possibly provide data to support the application. A preliminary pharmacokinetic sub-study of this clinical trial is assessed in detail in this report but it is limited to the concentration of TFV-DP in PBMCs.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

No specific studies were submitted to address safety issues in the target population.

The pivotal bioequivalence Studies **GS-US-311-1472 and GS-US-311-1473** were conducted in healthy adults and the food affect study was also conducted in healthy adults. These were the only studies where safety was directly observed, as a secondary outcome, in a population administered Descovy.

GS-US-120-0118 is the other study where safety was observed was an open label study in healthy adults administered Descovy and a range of other anti-retroviral drugs, both boosted and non-boosted to measure pharmacokinetics.

The studies on clinical safety have been assessed in detail in the Genvoya submission by TGA. There were 6 pivotal safety efficacy studies assessed in the Genvoya dossier and these are the same studies submitted in this dossier. These studies include the FDC E/C/F/TAF as Genvoya and compare the safety and efficacy to Stribild, previous approved by TGA. There are no Phase III clinical studies in the target population of HIV-1 infected patients, either adults or adolescents, in this dossier that consider the safety of the FDC, Descovy.

Data are provided on safety parameters for TAF and FTC as separate components but not in the form which is the subject of this application.

8.2. Post-marketing experience

There is no post-marketing experience with Descovy.

8.3. Safety related to drug-drug interactions and other interactions

Study GS-US-311-1386 investigated the food effect of administration of Descovy under fed and fasting conditions. Details of the study design are given in section. This study was conducted in health adults. There was a single case report of a female subject who was found to be pregnant soon after administration of the first dose of Descovy under fasted conditions. Two weeks after withdrawal from the study she presented to the emergency room of a hospital and had a spontaneous abortion, which the study investigator determined was due to administration of Descovy. Description of the narrative was provided in the dossier:

8.3.1. Gilead (sponsor's) assessment

The protocol requires the use of highly effective contraceptive methods. In this case, the patient reported use of condoms, spermicide, and a diaphragm. Pregnancy was attributed to contraceptive failure. The patient received one dose of study drug, and any role this may have played in the event is difficult to determine given that the incidence of first trimester spontaneous abortion in the general population is 8-20%.

Comment: It is unclear, from this report, the possible biological relationship between administration of Descovy and spontaneous abortion. However, given the menstrual history of having the last menstrual period on May 1, and the possibility the pregnancy could have occurred in May, the fact that it was not diagnosed until July seems questionable, Also, the history of a negative β HCG on June 24 and a positive β HCG on July 1, appears questionable, given the level of β HCG detected. However, as no data are available, even though this is an SAE, there can be no conclusions drawn from this report.

8.4. Ocular Icterus with Atazanavir plus Ritonavir

Study was an open label Phase 1 trial designed to determine the pharmacokinetics of TAF and TFV in **:** FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10). The study GS-US-120-0118 was conducted in 40 health adults. Details of the study design, patient population and methodology of determining the pharmacokinetics are described in detail in *Pharmacokinetics*. The safety profile of interactions of FTC+TAF+ATZ+RTV was described as a secondary outcome. The most prevalence AE reported in this study was ocular icterus (yellowing of the sclera), which is an indication of jaundice caused by raised bilirubin. This occurred in all 10 subjects (100%). Ocular icterus is a known effect of atazanavir and usually occurs in around 5% of patients. Moreover, raised bilirubin, which was reported as a Grade 3 or 4 AE in 9/10 subjects (90%) is also a known side effect of atazanavir and occurs in around 5-10% of patients. Therefore the increased rate of report of icterus and raised bilirubin may have been exacerbated by the concurrent administration of FTC/TAF. However, there is no biological explanation given by the sponsor for this observation in the study report.

8.5. Evaluator's overall conclusions on clinical safety

The safety data for this submission contains no data for the specific FDC of Descovy that is directly the subject of the application by the sponsor. There are data on the combination of the components of Descovy (FTC and TAF) as they are combined with EVG and COBI in Genvoya, but there are no safety data for the subject of the application which is to use Descovy in combination with a boosted or unboosted range of second anti-retroviral agents such as ATV, DRV or LPV. The limited safety data presented as secondary outcomes in the Phase I studies of fed and fasting conditions in healthy adults and in the pharmacokinetic studies with other anti-retroviral agents in healthy adult subjects do not meet the criteria of having appropriately designed Phase III clinical study in the target population. The sponsor will need to submit a Phase III study before clinical safety can be assessed for Descovy. The limited safety data

presented as secondary outcomes in the GS-US-120-0118 study give some assurance that with a single dose of FTC and TAF as separate agents with selected secondary agents, there are limited safety concerns, except with the ATV+RTV combination where there appears to be suggestion that the FTC+TAF may exacerbate the bilirubin increase usually attributed to the ATV. This cannot be confirmed in this short-term Phase I study, considering the limited exposure to both FTC-TAF and to ATV+RTV and given this study was conducted in healthy subjects. The case of a spontaneous abortion in the GS-US-311-1386 appears to have been a coincidental finding, but given the investigator attributed the cause of the spontaneous abortion to the FTC+TAF study drug it needs to be considered as a safety issue. No information is provided by the sponsor to elucidate this issue, even though it was classified as a study drug related SAE.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Descovy in the proposed usage are:

- The benefit of Descovy is the same as the benefit of Truvada which is an FDC comprising a nucleotide and a nucleoside reverse transcriptase inhibitor. However, the actual benefits of Descovy cannot be assessed until a Phase III clinical trial has been conducted and the results assessed.
- Descovy will be available in two dose formulations to be administered with and without booster. The described advantage of Descovy as a once-daily tablet that can be taken with or without food is a potential advantage.
- The apparent benefit of the TAF component of Descovy, when administered to HIV-1 infected patients may be to reduce the risk of renal impairment and reduction in bone mineral density. However, this benefit has only been shown with the Genvoya FDC, not when used with other anti-retroviral drugs. The apparent benefits of Descovy have been shown with the TAF 10 mg dose when boosted with Cobicistat 150 mg. No data have been submitted on the clinical benefit of TAF 25 mg when administered with FTC and other non-boosted anti-retroviral agents.

9.2. First round assessment of risks

The risks of Descovy in the proposed usage are:

- It is not possible to determine the risks of Descovy in the absence of a Phase III clinical trial in the target population. It appears a study GS-US-311-1089 may provide some data to clarify this issue when it is analysed and the results presented by the sponsor.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Descovy, given the proposed usage, is favourable, when administered as the FDC, Genvoya. There are not sufficient data to determine the benefit-risk balance in the proposed usage, except where Descovy will be used in combination with EVG and COBI either separately or as the FDC Genvoya. This combination is under consideration by the TGA.

9.4. First round recommendation regarding authorisation

The first round recommendation is that Descovy should not be approved for its proposed usage. The recommendation is that Descovy can be approved for HIV-1 infection when administered in the FTC/TAF 200 mg/10 mg formulation in combination with Cobicistat and Elvitegravir, including adolescents 12-18 years of age. As there are no Phase III data on the clinical efficacy and safety of Descovy in adults and adolescents (12-18 years of age), when administered with other anti-retrovirals or boosted with ritonavir, this indication should not be approved until Phase III clinical trial data are available in the target population.

10. Clinical questions

10.1. Pharmacokinetics

The administration of FTC/TAF 200 mg/10 mg with DRV + RTV indicated there was no change in the exposure to TAF in healthy adults. The rationale for administration of the 10 mg dose formula of TAF is that its serum exposure will be increased when administered with a booster such as COBI or RTV and the mechanism for this increased serum exposure is that the booster will increase exposure and therefore increase the intra-cellular TFV level. However, the booster increased the TAF level by 91% with ATV + RTV and 47% with LPV/rtv, but not at all with the DRV + RTV or the Dolutegravir alone. This can see in the table below.

Table 21: TAF Study GS-US-120-0118: Statistical Comparisons of TAF PK Parameter Estimates between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	164.8 (18.1)	91.6 (39.9)	188.92 (155.37, 229.71)
AUC_{last} (ng•h/mL)	162.6 (18.8)	89.5 (40.8)	191.06 (155.08, 235.40)
C_{max} (ng/mL)	146.5 (46.9)	76.8 (29.4)	176.72 (128.19, 243.63)
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	80.5 (30.4)	80.0 (41.8)	104.34 (84.14, 129.39)
AUC_{last} (ng•h/mL)	78.6 (30.9)	77.4 (43.6)	106.27 (83.59, 135.10)
C_{max} (ng/mL)	102.3 (46.5)	73.4 (49.4)	141.80 (96.11, 209.22)
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	122.5 (42.7)	82.7 (34.0)	144.75 (114.15, 183.55)
AUC_{last} (ng•h/mL)	120.8 (43.9)	80.0 (34.1)	146.73 (116.60, 184.65)
C_{max} (ng/mL)	157.5 (39.4)	68.7 (28.7)	218.97 (171.88, 278.97)
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
AUC_{inf} (ng•h/mL)	105.1 (31.7)	100.9 (51.2)	116.62 (93.49, 145.48)
AUC_{last} (ng•h/mL)	103.0 (30.6)	98.5 (53.3)	119.02 (95.83, 147.82)
C_{max} (ng/mL)	83.4 (30.6)	79.9 (60.6)	123.64 (87.79, 174.13)

Therefore, there appears to be a completely inconsistent pattern of boosting with Ritonavir. The PK studies have been conducted in healthy adults, not in the target population who may have factors associated with bowel absorption of TAF in the presence of ritonavir. Can the sponsor explain the inconsistencies of boosting by ritonavir and why all studies have been conducted in fed populations when it is noted that TAF exposure increases by around 80% in the fed state as compared with the fasted state. Furthermore, there are no PK studies in the adolescent population for which the sponsor is seeking approval, especially given the possibility of dose adjustment requirements in young adolescent populations.

Regarding Study GS-US-311-1089 the results of F/TAF with the boosted third agents indicate the intracellular concentration of TFV-DP is around 2-3 times the concentration seen with FTC/TDF, rather than the four fold difference noted by the sponsor in the Genvoya studies. It is also noted that the concentration seems to be independent of the level of boosting agent used as the PBMC concentration is marginally lower with 200 mg of RTV (LPV/r) compared with boosting with RTV 100 mg (ATV+RTV and DRV+RTV). As the 95% CIs are so wide for many of the results, it would be useful to also have the median values. It appears the exposure of TAF does not have a proportional relationship with the intracellular TFV-DP concentration and may be interpreted as not totally dependent of boosting with RTV at the dose of 10 mg and that taking the 10 mg dose with food may have the same PBMC intracellular effect.

10.1.1. Pharmacodynamics

The Study GS-US-311-1386 conducted in healthy adult subjects investigated the effect of fed and fasted conditions on the exposure to TAF and FTC. This study demonstrated that the exposure of TAF 25 mg in a fed condition was increased by 75%. This is about the same level of increased exposure that was observed with boosted TAF. It is therefore unclear as to why the dose of TAF of 10 mg is recommended for unboosted, when it would seem biologically plausible that a 10 mg dose with a meal would result in similar exposure to TAF as would be gained by administration of a 25 mg dose. This discrepancy should be explained by the sponsor. The sponsor is requested to explain why all studies have been conducted in fed populations, rather than assessing the effect of food on the pharmacodynamics as it appears the increased exposure of TAF in the fed state, as compared with the fasted state as this may be an important factor in determining the intracellular concentration of TAF.

10.1.2. Efficacy

The efficacy of Descovy has not been shown in this submission, other than as a component of Genvoya. The efficacy of Descovy should be reported in the results of a Phase III clinical trial. It is necessary for the sponsor to provide evidence of efficacy of Descovy in combination with anti-retrovirals, other than EVG and boosted with other than COBI.

10.1.3. Safety

- The safety of Descovy is implied in this submission, but requires controlled Phase III clinical trial scrutiny to document safety in the target population.
- The association between TAF 25 mg and spontaneous abortion should be clarified.

- The association between administration of Descovy, in combination with ATV+RTV and increase bilirubin, beyond the expected level, should be clarified.

10.1.4. PI and CMI

The current product information assumes the results of a Phase III trial which has not yet been conducted, but extends the data beyond the evidence. The available evidence for prescribing Descovy is the same as for Genvoya and should not include boosting with ritonavir, on the basis of the Phase I bioequivalence study in healthy adults. Recommendations relating to administration of Descovy in the target population need to be supported by Phase III studies conducted with the target population.

11. Second round evaluation of clinical data submitted in response to questions

The following are responses by the sponsor to questions raised in this assessment report:

11.1.1. Pharmacokinetics

There appears to be a completely inconsistent pattern of boosting with Ritonavir. The PK studies have been conducted in healthy adults, not in the target population who may have factors associated with bowel absorption of TAF in the presence of ritonavir. Can the sponsor explain the inconsistencies of boosting by ritonavir and why all studies have been conducted in fed populations when it is noted that TAF exposure increases by around 80% in the fed state as compared with the fasted state.

11.1.1.1. Response by sponsor

While the exact mechanism of the different boosting effect and resulting TAF exposures is unknown, it is likely due to the different pharmacological properties of co-administered third agents. Similarly, the same magnitude of boosting effect was observed when ATV and DRV were administered with COBI, indicating the differential effect is due to the third agent and not due to the pharmaco-enhancer (see table below).

Table 22: Summary of changes in TAF exposure with concomitant drugs boosted with RTV and COBI

	TAF AUC_{last} (ng•h/mL) GLSMs by Treatment			
Concomitant Drug	Test: TAF + Concomitant Drug	Reference: TAF	GLSM Ratio (90% CI) Test/Reference (%)	Study
DRV + COBI*	221.95	227.30	97.64 (80.38, 118.62)	GS-US-311-0101
DRV+RTV	74.76	70.35	106.27 (83.59, 135.10)	GS-US-120-0118
ATV + COBI	182.21	104.08	175.06 (154.81, 197.96)	GS-US-311-1388
ATV+RTV	160.28	83.89	191.06 (155.08, 235.40)	GS-US-120-0118
LPV/r	111.07	75.70	146.73 (116.60, 184.65)	GS-US-120-0118

GLSM = geometric least square mean
* F/TAF 25 mg was used in this study, all other studies used F/TAF 10 mg.

This phenomenon has been observed with another P-gp substrate prodrug tenofovir disoproxil fumarate (TDF), where variable systemic levels of TFV were observed when TDF was used with different protease inhibitors with ritonavir. Indeed, in vitro assessment showed that protease inhibitors, including ATV, DRV, RTV and LPV, can both inhibit and induce P-gp, and differential

net effect of inhibition and induction of intestinal P-gp could explain the variable boosting effect of ritonavir on TAF In the case of darunavir (DRV) + ritonavir (RTV), similar exposures of TAF following multiple-dose co-administration of FTC+TAF with DRV+RTV vs FTC+TAF alone was likely due to a mixed inhibitory/inductive effect on P-gp influencing TAF absorption, as higher TAF exposure was observed following a single dose of DRV+RTV, but the effect abated following multiple dosing due to a time-dependent induction effect of DRV+RTV. This finding is also consistent with results following multiple-dose co-administration of FTC+TAF with DRV+COBI from Study GS-US-311-0101. Based on DRV being an in vitro inducer of P-gp and RTV being an inhibitor and time-dependent inducer of P-gp, the combination of DRV and RTV is likely to increase P gp–mediated TAF cycling across the brush border membrane of the intestine, thereby allowing for increased conversion of TAF to TFV pre-systemically.

Using population PK modelling, data from HIV-infected subjects (pivotal E/C/F/TAF Phase III Studies GS-US-292-0104 and GS-US-292-0111) were compared with those from healthy subjects (E/C/F/TAF Studies GS-US-292-0103, GS-US-292-0108, and GS-US-292-0110) following multiple-dose administration of E/C/F/TAF. Based on population PK analyses, HIV disease status did not have an effect on TAF exposure and was not a statistically significant or clinically relevant covariate (TAF Population PK Report). Therefore the drug interaction studies conducted in healthy volunteers are applicable to the target population.

11.1.1.2. Evaluator's conclusion

The sponsor has provided a detailed response, including considerable new data that wasn't part of the first round submission. The sponsor notes that the variation in exposure of TAF following boosting by Ritonavir is most likely due to the third agent used with the TAF/FTC and that this was noted to be the same with the TDF/FTC combination and also when Cobicistat was used as the boosting agent. Data submitted by the sponsor in support of this observation includes the exposure of TAF is consistent across both boosting agent when used with different protease inhibitors (DRV and ATV). These data have been derived from a number of clinical trials and this table (above) was not included in the previous submission. The sponsor suggests a mechanism for the variable exposure as a combination inductive/inhibitory effect P-gp when DRV or ATV was administered with FTC/TAF as compared with FTC/TAF alone and this effect is more pronounced when there multiple-dose co-administration, rather than a single dose as occurred in the Phase I pharmacokinetic study.

The sponsor has provided an appropriate response to this question. The data and explanation are acceptable. The essential issue in this question is the apparently differential absorption of TAF in the presence of RTV as presented in the PBMC Study of GS-US-120-0118. The table below indicates this differential exposure to TAF.

Table 23: TAF Study GS-US-120-0118: Statistical Comparisons of TAF PK Parameter Estimates between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	164.8 (18.1)	91.6 (39.9)	188.92 (155.37, 229.71)
AUC_{last} (ng•h/mL)	162.6 (18.8)	89.5 (40.8)	191.06 (155.08, 235.40)
C_{max} (ng/mL)	146.5 (46.9)	76.8 (29.4)	176.72 (128.19, 243.63)
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
AUC_{inf} (ng•h/mL)	80.5 (30.4)	80.0 (41.8)	104.34 (84.14, 129.39)
AUC_{last} (ng•h/mL)	78.6 (30.9)	77.4 (43.6)	106.27 (83.59, 135.10)
C_{max} (ng/mL)	102.3 (46.5)	73.4 (49.4)	141.80 (96.11, 209.22)
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	122.5 (42.7)	82.7 (34.0)	144.75 (114.15, 183.55)
AUC_{last} (ng•h/mL)	120.8 (43.9)	80.0 (34.1)	146.73 (116.60, 184.65)
C_{max} (ng/mL)	157.5 (39.4)	68.7 (28.7)	218.97 (171.88, 278.97)
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	105.1 (31.7)	100.9 (51.2)	116.62 (93.49, 145.48)
AUC_{last} (ng•h/mL)	103.0 (30.6)	98.5 (53.3)	119.02 (95.83, 147.82)
C_{max} (ng/mL)	83.4 (30.6)	79.9 (60.6)	123.64 (87.79, 174.13)

The sponsor has compared the PK data from HIV-1 infected subjects with TAF PK data from healthy subjects in the studies referred to above. These comparisons determined the PK of TAF in the presence of RTV is comparable to the TAF exposure in the Genvoya PK studies. The population PK studies were not directly conducted with TAF and RTV. However efficacy data from GS-US-311-1089 indicates the same level of virological success when Descovy was administered with a third agent as compared with Truvada. This supports the modelling conducted by the sponsor and the comparison with popPK conducted with healthy subjects in the Genvoya studies. In the GS-US-311-1089 PK analysis intracellular PBMC TFV-DP concentration between F/TAF and FTC/TDF groups were compared after a natural log transformation. A parametric (normal theory) analysis of variance (ANOVA) using a mixed-effects linear model was fitted to the natural logarithmic transformation of PBMC TFV-DP concentration, with the treatment and the third agent stratum as fixed effect. This model appears appropriate as it is supported by the efficacy data demonstrated in the table following where the efficacy of Descovy and Truvada administered with a third agent (either boosted or not depending on the requirement of the third agent) is equivalent:

Table 24: GS-US-311-1089: Percentage of Virologic Success and Virologic Failure at Week 48 across Quartiles of TAF Exposure (TAF PK/PD Analysis Set)

Quartile	TAF AUC_{tau} Quartile Range (ng*h/mL)	N	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis)	Percentage of Virologic Failure at Week 48 (HIV-1 RNA ≥ 50 copies/mL, Snapshot Analysis)
1	30.3 to 87.6	73	93.2	0
2	87.6 to 129.5	73	95.9	0
3	129.8 to 173.1	73	97.3	0
4	173.8 to 466.7	73	95.9	1.4[a]

In summary, the evaluator accepts the reasoning of the sponsor that the differential exposure TAF when administered by RTV or COBI is most likely determined by the influence of the third agent that is administered at the same time.

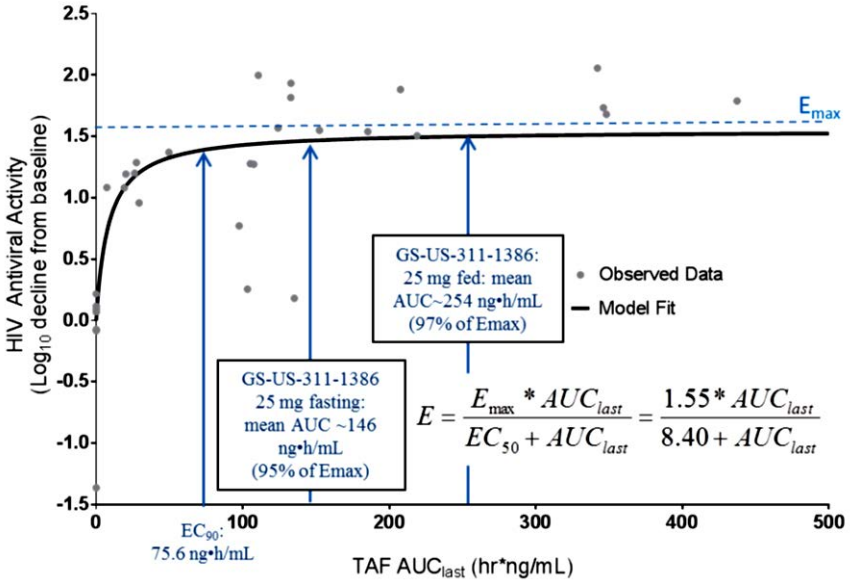
Can the sponsor explain the inconsistencies of boosting by ritonavir and why all studies have been conducted in fed populations when it is noted that TAF exposure increases by around 80% in the fed state as compared with the fasted state.

11.1.1.3. Response by sponsor

As an NRTI-backbone to be used in combination with third agents, F/TAF will be administered under the food condition dictated by the co-administered third agent (that is, with or without food, or without regards to food). The F/TAF 200/10 mg tablet is recommended to be used with boosted protease inhibitors (PIs), which are to be taken with food. The F/TAF 200/25 mg tablet is expected to be used in combination with third agents that are not co-administered with a pharmaco-enhancer. Most of those third agents are to be taken without regard to food (dolutegravir [DTG], raltegravir [RAL], nevirapine [NVP], and maraviroc [MVC]), with specific food restrictions that apply only for rilpivirine (RPV) (taken with a meal) and EFV (taken on an empty stomach).

In Study GS-US-120-0104, a TAF AUC of approximately 115 ng*h/mL with TAF 25 mg administered without food was associated with a near maximal decrease in human immunodeficiency virus type 1 (HIV-1) RNA of 1.46 log10 copies/mL, which was an approximately 0.5 log10 copies/mL greater reduction compared with TDF 300 mg. In addition, the final TAF exposure-response E_{max} model showed that E_{max} was predicted to be approximately −1.55 log10 copies/mL change from baseline with an EC_{50} of 8.4 ng*h/mL and EC_{90} of 75.6 ng*h/mL.

Figure 4: GS-US-120-0104: TAF Exposure-Response Model for AUC_{last} and HIV Antiviral Activity



The results from the F/TAF GS-US-311-1089 Phase III study PK/PD analysis, where virologically suppressed subjects switched to F/TAF from emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; co-formulated; Truvada), were similar to those from the E/C/F/TAF studies. In this study, the study drugs (F/TAF and FTC/TDF) were administered without regard to food. TAF AUCs from Study GS-US-311-1089 were estimated from a TAF population PK model. Based on the population PK model as well as the observed plasma concentration data from GS-US-311-1089, post-hoc predicted individual PK parameters were estimated and utilised to simulate TAF concentration-time profiles that were subsequently used for non-compartmental analysis to obtain individual AUC and C_{max} values for evaluable subjects. TAF AUCs were estimable for 292 subjects in Study GS-US-311-1089.

Across a wide range of TAF exposures (range: 30 to 467 ng*h/mL), which correspond to 78% to 98% of E_{max} of the TAF exposure-response model, the rates of virologic success were uniformly high across quartiles of TAF exposures (range: 93.2 to 97.3%). There were also no apparent trends with virologic failure and TAF exposure (only 1 subject had virologic failure at Week 48, and the TAF exposure was in Quartile 4; this subject developed M184V in reverse transcriptase with reduced susceptibility to emtricitabine at virologic failure [Week 36]). These data further demonstrate high rates of virologic success in virologically suppressed patients across exposures of TAF, including the F/TAF 25 mg administered without regard to food (fasting) and in the absence of a P-gp inhibitor.

Table 25: GS-US-311-1089: TAF PK Exposure and Virologic Success at Week 48 Using Snapshot Algorithm and HIV-1 RNA < 50 copies/mL by Third Agent (Full Analysis Set)

			F/TAF+3rd Agent with Available PK Data		FTC/TDF+3rd Agent (N = 330)	
Third Agent	n	Mean (%CV) TAF AUC_{tau} (ng*h/mL)	n	Percent of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL)	n	Percent of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL)
ATV/r	44	149.6 (50.8)	53	90.6	50	94.0
DRV/r	72	73.5 (41.0)	84	90.5	82	91.5
DTG	25	155.6 (18.5)	26	96.2	23	91.3
EFV	6	141.6 (18.7)	8	100	6	83.3
LPV/r	15	89.8 (25.0)	18	100	18	100
MVC	1	191.3 (NA)	1	100	6	100
NVP	67	167.4 (32.1)	74	97.3	66	98.5
RAL	61	170.8 (37.2)	66	95.5	73	89.0
RPV	1	273.1 (NA)	3	100	6	83.3

NA = not applicable

11.1.1.4. Evaluator's conclusion

In response to the evaluator's questions the sponsor has submitted data that was not previously available. This is the first time data has been submitted for Study GS-US-311-1089 which is the pivotal safety and efficacy study comparing FTC/TAF with FTC/TDF plus a third agent in a switch design for virally supressed patients. This study supports the administration and efficacy of Descovy with a third agent where the food recommendation is determined by the third agent rather than by Descovy. The evaluator accepts the sponsor's explanation and agrees that because there is inconsistency regarding patients' adherence to recommendations regarding specific meal types, food effect should not be used as a recommendation for dose-related administration of Descovy. This is an appropriately conservative approach by the sponsor and supported by the evaluator.

> *Furthermore, there are no PK studies in the adolescent population for which the sponsor is seeking approval, especially given the possibility of dose adjustment requirements in young adolescent populations.*

11.1.1.5. Response by sponsor

The sponsor referred to pharmacokinetic data which is available in the adolescent population for E/C/F/TAF (Genvoya150/150/200/10 mg; Study GS-US-292-0106), and the submission for F/TAF is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1473 and GS-US-311-1472) that provide a pharmacokinetic (PK) bridge between the 2 F/TAF FDC tablet strengths (200/25 mg and 200/10 mg) and Gilead's FDC tablet E/C/F/FAF. Both studies have demonstrated bioequivalent exposure of F/TAF when compared to E/C/F/TAF within the guidance specified bioequivalence limit of 80.00 – 125.00% for the ratio of the product averages, therefore in line with current guidance additional special population studies are not required for F/TAF. Genvoya was approved by the TGA on 12 January 2016 for use in adults and adolescents aged 12 years of age and older with body weight at least 35 kg.

11.1.1.6. Evaluator's conclusions

The evaluator remains concerned that no specific PK studies have been conducted in adolescents with the third agents which will be used with Descovy. While it is accepted that the PK studies with Genvoya indicate appropriate PK dynamics when Descovy is administered with EVG/COBI, there are no data when Descovy is administered with third agents (except for

EVG/COBI) either administered alone or boosted with RTV. While this issue may not be critical enough to restrict the use of Descovy to adults, the sponsor's rationale for responding by requoting data that has already been reviewed and formed the basis for the evaluators concern is not entirely acceptable. It is, however, reasonable to extrapolate the PK data from the GS-US-311-1089 study to adolescents, given there is no major differences between PK data from the Genvoya clinical study in adolescents (GS-US-292-0106) and the 1089 study. Therefore, the evaluator accepts that Descovy may be used in adolescents ages 12 to 18 years old, using the same criteria as approved for Genvoya.

Regarding study GS-US-311-1089 the results of F/TAF with the boosted third agents indicate the intracellular concentration of TFV-DP is around 2-3 times the concentration seen with FTC/TDF, rather than the four fold difference noted by the sponsor in the Genvoya studies. It is also noted that the concentration seems to be independent of the level of boosting agent used as the PBMC concentration is marginally lower with 200 mg of RTV (LPV/r) compared with boosting with RTV 100 mg (ATV+RTV and DRV+RTV). As the 95% CIs are so wide for many of the results, it would be useful to also have the median values. It appears the exposure of TAF does not have a proportional relationship with the intracellular TFV-DP concentration and may be interpreted as not totally dependent of boosting with RTV at the dose of 10 mg and that taking the 10 mg dose with food may have the same PBMC intracellular effect.

11.1.1.7. Sponsor's response

Gilead would like to clarify that the intracellular concentrations of TFV-DP from TAF administration with the boosted third agents ATV+RTV, DRV+RTV and LPV/r, were 5.44-, 3.38- and 3.09 fold higher than the respective FTC/TDF arms (Table 6), and an overall comparison of the boosted regimens showed that the F/TAF arm yielded TFV-DP concentrations that are 3.92 fold higher than the TDF arm [GLSM ratio (90% CI): 391.99 (322.62, 476.26)], Similarly, overall intracellular concentrations of TFV-DP from TAF administration with unboosted third agents yielded TFV-DP concentrations that are 4.38 fold higher than the TDF arm [GLSM ratio (90% CI): 438.31 (359.57, 534.296)].

As requested the median values of the intracellular TFV-DP concentrations in Study GS-US-311-1089 are provided below.

Table 26: GS-US-311-1089: Median Intracellular TFV-DP Concentrations between Test and Reference Treatments by Co-administered Third Agent (PBMC PK Analysis Set)

Intracellular PBMC TFV-DP concentration ($pg/10^6$ cells)	F/TAF (Test)		FTC/TDF (Reference)	
	n	Median	n	Median
Overall unboosted	156	154.500	148	32.650
+DTG	24	104.000	19	34.900
+EFV	8	50.900	6	31.200
+MVC	1	268.000	5	28.200
+NVP	65	157.000	56	32.650
+RAL	55	159.00	57	31.700
+RPV	3	271.000	5	21.800
Overall boosted	148	92.450	117	23.000
+ATV+RTV	50	133.000	34	23.050
+DRV+RTV	82	71.850	69	21.000
+LPV/r	16	86.650	14	37.650

11.1.1.8. Evaluator's conclusions

The sponsor has presented data from the pivotal clinical trial GS-US-311-1089 to support their response. These data were not presented in the first round submission. The evaluator accepts the sponsor's response and concludes that the median values are consistent with the sponsor's pharmacokinetic summaries, albeit these data were not included to provide this evidence in the original submission. The above table indicates the higher intracellular concentration of TFV-DP when administered as F/TAF as compared with FTC/TDF.

> *The study GS-US-311-1386 conducted in healthy adult patients investigated the effect of fed and fasted conditions on the exposure to TAF and FTC. This study demonstrated that the exposure of TAF 25 mg in a fed condition was increased by 75%. This is about the same level of increased exposure that was observed with boosted TAF. It is therefore unclear as to why the dose of TAF of 25 mg is recommended for unboosted, when it would seem biologically plausible that a 10 mg dose with a meal would result in similar exposure to TAF as would be gained by administration of a 25 mg dose. This discrepancy should be explained by the sponsor. The sponsor is requested to explain why all studies have been conducted in fed populations, rather than assessing the effect of food on the pharmacodynamics as it appears the increased exposure of TAF in the fed state, as compared with the fasted state as this may be an important factor in determining the intracellular concentration of TAF.*

11.1.1.9. Sponsor's response

While the magnitude of food effect under extreme conditions (standardised high fat meal versus overnight fasting) was characterised in well-controlled clinical studies, food is not considered a reliable nor consistent factor to be used to boost antiretroviral exposures as food intake can vary widely in a given patient. Therefore Gilead does not consider dosing F/TAF 200/10 mg with food to be equivalent to dosing with a pharmaco-enhancer (RTV or COBI), and that TAF 25 mg can be taken without regard to food for unboosted third agents to achieve consistently efficacious TAF exposures. To offer patients the flexibility and simplicity that maximise adherence to chronic therapy, it is important to allow F/TAF (25 mg or 10 mg) to be taken. In conclusion, F/TAF 25 mg and F/TAF 10 mg given with a pharmaco-enhancer without regard to food provides adequate exposure for efficacy.

The studies presented by the sponsor to support the above response are shown below.

Table 27: Summary of TAF AUC across Studies

Study Number	Study Description	Arm	Mean (90% CI) TAF AUClast (ng•h/mL)	% Emax* Based on TAF AUClast
GS-US-311-1386	Effect of food on TAF administered as F/TAF (25 mg)	Fed (n = 38) Fasted (n = 40)	254.4 (225.4, 283.4) 145.8 (129.5,162.1)	> 90% > 90%
GS-US-292-0110 (Genvoya: PM-2014-04011-1-2)	Effect of food on TAF administered as E/C/F/TAF (10 mg)	Fed (light meal) (n = 42) Fed (high fat meal) (n = 42) Fasted (n = 42)	250.3 (229.5, 271.1) 251.4 (232, 270.8) 222.5 (197, 248.1)	> 90% > 90% > 90%
GS-US-292-0104 and GS-US-292-0111 (Genvoya: PM-2014-04011-1-2)	E/C/F/TAF Pivotal Studies	Fed (n = 539)	206.4 (195.9, 216.9)	> 90%
GS-US-311-1089	F/TAF Ph3 Switch study	Without regards to food (n = 292)	137.2 (116.2, 129.8)	> 90%
GS-US-120-0104	Proof of concept	Fasted 25 mg (n = 8)	115.2 (92.9, 137.5)	> 90%

11.1.1.10. Evaluator's conclusions

The sponsor has presented data analysed from clinical trial GS-US-311-1089 to demonstrate that the exposure of TFV-DP is dependent on administration of the third agent in a fed or fasted

state, rather than to TAF. This is accepted by the evaluator. More details are presented in response to the second question above). As with the other responses by the sponsor data from Study GS-US-311-1089 are presented as an important evidential component. This is agreed by the evaluator.

> *The efficacy of F/TAF has not been shown in this submission, other than as a component of Genvoya. The efficacy of F/TAF should be reported in the results of a Phase III clinical trial. It is necessary for the sponsor to provide evidence of efficacy of F/TAF in combination with antiretrovirals, other than EVG and boosted with other than COBI.*

11.1.1.11. Sponsor's response

Scientific advice on the development of F/TAF was sought from the Medicinal Products Agency (MPA), Medicines and Healthcare products Regulatory Agency (MHRA), National Agency of Medicine and Health Products Safety (ANSM), and Medicines Evaluation Board (MEB), as well as in consultation with the US FDA. As a result of these discussions, and in accordance with the industry guidance, the registration strategy for F/TAF is based on 2 pivotal bioequivalence studies that pharmacokinetically bridge the exposure of the parent drugs, FTC and TAF, between each of the F/TAF FDC tablet strengths (F/TAF 200/25 mg and F/TAF 200/10 mg) to the E/C/F/TAF FDC tablet, which has been shown to be efficacious, safe, and well tolerated in a broad spectrum of HIV-infected patients.

Gilead considers that the efficacy of F/TAF has been established via Phase III studies of E/C/F/TAF and bioequivalence studies. In multiple comparative studies of E/C/F/TAF (GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109) or other F/TAF-containing regimens (GS-US-299-0102), the only difference between the randomised groups was the nucleos(t)ide analogue (NUC) backbone, F/TAF vs F/TDF, with the third agents fixed (that is, either EVG/co or DRV/co). These designs allow the direct comparison between F/TAF and F/TDF. From an efficacy standpoint, the interpretation of these studies is that F/TAF is non-inferior to F/TDF in achieving or maintaining plasma virologic suppression. Gilead considers that it is reasonable to expect similar efficacy between F/TAF and F/TDF each with the same third agent.

The development program to register F/TAF tablets based on pivotal bioequivalence studies is a similar strategy that was implemented for the registration of Truvada tablets (300 tenofovir disoproxil fumarate /200 mg emtricitabine), AUST R 107072, which was supported by the efficacy and safety profiles of the individual components of Truvada (FTC+TDF) in combination with EFV established in Phase III clinical studies in addition to several pharmacokinetic and bioequivalence studies. No studies with Truvada in combination with other third agents were provided in support of the registration application. Truvada has been registered in Australia since 2005 and is currently the most commonly prescribed guideline-recommended N(t)RTI backbone for ART-naive patients antiretroviral back bone in the United States, as well as Australia. It is anticipated that F/TAF will replace Truvada with its improved renal and bone safety profile compared with TDF-containing backbones, while maintaining the advantages of TDF over other NRTIs.

Although the initial bioequivalence-based submission did not include clinical data from a clinical study using F/TAF with third agents other than EVG+COBI, those data have become available since then. In response to the TGA Clinical evaluator's questions, a copy of the interim Week 48 results from Study GS-US-311-1089 is included with this response and the summary of the efficacy data from this study is provided.

Evaluator comment

It is interesting to note that while the sponsor contends that, because the Genvoya data should be applied to all submissions, an efficacy and safety Phase III clinical is not required for a Registration application in Australia and in other overseas jurisdictions. In fact, the sponsor has conducted just such a comparative Study GS-US-311-1089 to determine the non-inferiority of

TAF with TDF. This study forms the basis of the sponsor's response to most questions raised by the evaluator in the first round assessment. Considering the sponsor regarded this clinical trial as unnecessary, it is also interesting to note how comprehensive and involved it is; in terms of patient numbers, investigations and ancillary measurements such as Health economics and quality-of-life and so on.

11.1.1.12. GS-US-311-1089

Title of Study: A Phase III, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed on Regimens Containing FTC/TDF

Investigators: This is a multicentre study.

Study Centres: Subjects were enrolled in a total of 78 study sites: 1 in Belgium, 4 in Canada, 5 in France, 2 in Italy, 6 in United Kingdom, and 60 in United States.

Publications: No publications at the time of this clinical study report.

Study period:

06 May 2014 (First Subject Screened)

12 August 2015 (Last Subject Observation for the Primary Endpoint)

21 August 2015 (Last Subject Observation for this Report)

Phase of development: Phase III

Objectives: Study GS-US-311-1089 was conducted to evaluate the efficacy, safety, and tolerability of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in virologically suppressed human immunodeficiency virus type 1 (HIV-1) infected subjects.

The primary objective of this study was as follows:

- To evaluate the efficacy of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF, as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives of this study were as follows:

- To evaluate the bone safety of 2 regimens as determined by the percentage change from baseline in hip and spine bone mineral density at Week 48
- To evaluate the efficacy, safety, and tolerability of 2 regimens through Week 48
- To evaluate the pharmacokinetics (PK) of TAF and TFV

The current report describes the 48-week results for all subjects.

Methodology

This is a randomised, double-blind, multicentre, active-controlled study to evaluate the efficacy and safety of switching FTC/TDF to F/TAF versus continuing FTC/TDF in HIV-1 positive subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing FTC/TDF and 1 of the protocol-specified third agents.

All eligible subjects were randomised in a 1:1 ratio to 1 of the following 2 treatment groups:

- *Treatment Group 1 (referred to herein as F/TAF+3rd Agent):*

  F/TAF + Placebo-to-match FTC/TDF; third agent remains the same (planned N = 330); a TAF dose of 10 or 25 mg was administered based on the general recommendation that F/TAF 200/25 mg should be used with unboosted third agents and F/TAF 200/10 mg should be used with boosted third agents

- *Treatment Group 2 (referred to herein as FTC/TDF+3rd Agent):*

FTC/TDF + Placebo-to-match F/TAF; third agent remains the same (planned N = 330)
Randomization was stratified by the third agent (boosted protease inhibitors vs any other protocol allowed third agents) in a subject's existing regimen.

Following the screening and Day 1 visits, subjects returned for study visits at Weeks 4, 8, and 12, and then every 12 weeks through Week 96. After Week 96, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded, at which point all subjects will return for an unblinding visit and will be given the option to receive open-label F/TAF and attend visits every 12 weeks until F/TAF is commercially available, or until Gilead Sciences terminates the F/TAF clinical development program. Subjects who complete the study through Week 96 and do not wish to continue to participate will be required to return to the clinic 30 days after the completion of the study drug for a 30-Day Follow-up Visit.

Number of subjects (Planned and Analysed)

Planned: 660 (330 subjects each in Treatment Arm 1 and Treatment Arm 2)

Analysed (by analysis set)

Table 28: Patients analysed by analysis set

Subjects n (%)	F/TAF+3rd Agent	FTC/TDF+3rd Agent	Total
Randomized	334	334	668
Week 48 Full Analysis Set (FAS)	333	330	663
Week 48 Protocol (PP) Analysis Set	304	305	609
PBMC PK Analysis Set	308	271	579
Safety Analysis Set	333	330	663
Hip DXA Analysis Set	321	317	638
Spine DXA Analysis Set	321	320	641

DXA = dual-energy x-ray absorptiometry; FAS = Full Analysis Set; PBMC = peripheral blood mononuclear cells; PP = per protocol
The denominator for percentages was based on the number of subjects in the Randomized Analysis Set.

Diagnosis and main criteria for inclusion: Subjects enrolled in this study were HIV-infected adults who for at least 6 consecutive months prior to the screening visit received an antiretroviral regimen containing FTC/TDF in combination with 1 of the protocol-specified third agents and maintained plasma HIV-1 RNA levels < 50 copies/mL. Subjects were also required to have HIV-1 RNA < 50 copies/mL at the screening visit and an estimated glomerular filtration rate (eGFR) as calculated by the Cockcroft-Gault equation (eGFRCG) ≥ 50 mL/min at screening.

Duration of treatment: Subjects will receive blinded study drug for at least 96 weeks. After Week 96, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded, at which point all subjects will return for an unblinding visit and will be given the option to receive open-label F/TAF and attend visits every 12 weeks until F/TAF is commercially available, or until Gilead Sciences terminates the F/TAF clinical development program.

Test product, dose, mode of administration, and lot no

F/TAF tablet (200/10 mg, 200/25 mg, or placebo-to-match) administered orally in combination with a third ARV agent, once daily in the morning at approximately the same time each day.

F/TAF 200/10 mg Lot Numbers:	CR1308B1, CR1407B1, and CR1411B1
F/TAF 200/10 mg Placebo-to-Match Lot Number:	CR1312B1
F/TAF 200/25 mg Lot Numbers:	CR1305B1, CR1408B1, and CR1412B1

F/TAF 200/25 Placebo-to-Match Lot Number: CR1312B1

Reference therapy, dose, mode of administration, and lot no

FTC/TDF tablet (200/300 mg or placebo-to-match) administered orally in combination with a third ARV agent, once daily in the morning at approximately the same time each day

FTC/TDF 200/300 mg Lot Numbers: V1206B1 and V1207B1

FTC/TDF 200/300 mg Placebo-to-Match Lot Number: V1107B1

Criteria for evaluation

Efficacy

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot algorithm.

The secondary efficacy endpoints evaluated for the Week 48 analysis were as follows:

- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 48 as defined by the FDA snapshot algorithm
- The change from baseline in CD4 cell count at Week 48

The tertiary efficacy endpoints evaluated for the Week 48 analysis were as follows:

- Pure virologic failure (PVF) with HIV-1 RNA cut-off at 50 copies/mL by Week 48
- The proportion of subjects with HIV 1 RNA < 50 copies/mL at Week 48 as defined by 2 different missing-data imputation methods (Missing = Failure [M = F] and Missing = Excluded [M = E])
- The change from baseline in CD4% at Week 48

Safety

Baseline and post-baseline safety assessments included adverse events (AEs), BMD using dual-energy x-ray absorptiometry (DXA), physical examinations, ECG, vital signs, weight, and clinical laboratory tests (chemistry, haematology, urinalysis, and pregnancy testing) including type 1 collagen C-telopeptide (CTx), procollagen type 1 N-terminal propeptide (P1NP), parathyroid hormone (PTH), serum creatinine, eGFRCG and eGFR Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine method (eGFRCKD-EPI, creatinine), proteinuria by urinalysis and quantitative assessment (protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR]), and renal biomarkers (retinol binding protein [RBP] to creatinine ratio, beta-2-microglobulin to creatinine ratio, renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate [TmP/GFR], fractional excretion of phosphate [FEPO4], and fractional excretion of uric acid [FEUA]).

Two key safety endpoints were defined as follows:

- Percentage change from baseline in hip BMD at Week 48
- Percentage change from baseline in spine BMD at Week 48

Patient-reported outcomes

The following questionnaires were implemented: Health Utilization Assessment, Medical Outcome Study Short Form-36 (SF-36), and the EQ-5D-3L health questionnaire. The SF-36 and EQ-5D-3L questionnaires were administered at Day 1, Week 24, and every 24 weeks thereafter, and at the Early Study Drug Discontinuation (ESDD) visit. The Health Utilization Assessment was administered at Day 1 and every post-baseline visit.

Statistical methods

Efficacy

The analysis purpose of the primary efficacy endpoint was to assess the non-inferiority of treatment with F/TAF+3rd Agent relative to treatment with FTC/TDF+3rd Agent. Non-inferiority was assessed using a conventional 95% confidence interval (CI) approach, with a non-inferiority margin of 10%. For the interim analyses performed by the IDMC at Weeks 12 and 24, an alpha penalty of 0.00001 was applied for each interim IDMC meeting. Therefore, the significance level for the 2-sided test in the primary analysis at Week 48 was 0.04998 (corresponding to 95.002% CI). It was concluded that switching to F/TAF was non-inferior to maintaining FTC/TDF if the lower bound of the 2-sided 95.002% CI of the difference (F/TAF+3rd Agent group – FTC/TDF+3rd Agent group) in the response rate was greater than −10%. The primary analysis used the full analysis set (FAS). The stratum-weighted difference in the response rate (P1 – P2) and its 95.002% CI were calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion, where the stratum was defined by the third agents: boosted protease inhibitors versus others.

If non-inferiority of F/TAF+3rd Agent versus FTC/TDF+3rd Agent was established, the same 95.002% CI used in evaluating non-inferiority at Week 48 was used to evaluate superiority. If the lower bound of the 95.002% CI was greater than 0, superiority of F/TAF+3rd Agent over FTC/TDF+3rd Agent was established. The third agent stratum-stratified, 2-sided CMH test was also used to assess superiority as a secondary assessment. The FAS was used for the superiority evaluation.

The secondary efficacy endpoint of the proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 48 was analysed using the same methods as for the primary endpoint, except that CIs were constructed at a 95% level.

Time to PVF was analysed using the Kaplan-Meier method by treatment group using the FAS. The log rank test was performed to compare the difference in time to PVF between the 2 randomised treatment groups stratified by the third agents (boosted protease inhibitors versus others).

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL (M = F and M = E methods), and changes from baseline in CD4 cell count and CD4% were summarised by visit using descriptive statistics for the FAS.

Pharmacokinetics/pharmacodynamics

Plasma concentration data for TAF and TFV were listed for all subjects by visit. Intracellular PBMC TFV-DP concentration between F/TAF and FTC/TDF groups were compared after a natural log transformation. A parametric (normal theory) analysis of variance (ANOVA) using a mixed-effects linear model was fitted to the natural logarithmic transformation of PBMC TFV-DP concentration, with the treatment and the third agent stratum as fixed effects.

Safety

The Safety Analysis Set included all randomised subjects who received at least one dose of study drug. Adverse events were coded using Version 18.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Safety data were summarized by treatment group using descriptive statistics.

Percentage change from baseline in hip BMD and spine BMD are the 2 key secondary safety endpoints. They were summarized by treatment group and visit using descriptive statistics for subjects in the Hip DXA and Spine DXA Analysis Sets, respectively, and compared between the 2 treatment groups at each post-baseline visit using ANOVA, which included the third agent randomization stratum and treatment as fixed effects.

If non-inferiority of the primary efficacy endpoint was established, multiplicity adjustments were planned for the following 2 key safety endpoints with a fall-back procedure in the sequential order given below with pre-specified 2-sided alpha levels: (1) hip BMD (alpha = 0.02) and (2) spine BMD (alpha = 0.02998).

Adverse events were summarised by the third agent stratum (that is, boosted protease inhibitors and others).

Patient-reported outcomes

Patient-reported outcome measures were summarised by treatment group and visit using the Safety Analysis Set.

Summary of results

Subject disposition

In this study, 780 subjects were screened in this study, of whom 668 were randomised, and 663 received at least 1 dose of study drug (F/TAF+3rd Agent 333 subjects; FTC/TDF+3rd Agent 330 subjects). A total of 5 randomised subjects either withdrew consent or discontinued the study per investigator's discretion before receiving study drug (F/TAF+3rd Agent 1 subject; FTC/TDF+3rd Agent 4 subjects).

Through the data cut-off date, 621 subjects are continuing study drug treatment (F/TAF+3rd Agent 93.7%, 312 subjects; FTC/TDF+3rd Agent 93.6%, 309 subjects) and 631 subjects are continuing in the study (F/TAF+3rd Agent 94.6%, 315 subjects; FTC/TDF+3rd Agent 95.8%, 316 subjects). Forty-two subjects (6.3%) discontinued study drug (F/TAF+3rd Agent 6.3%, 21 subjects; FTC/TDF+3rd Agent 6.4%, 21 subjects) and 4.8% (32 subjects) prematurely discontinued from the study (F/TAF+3rd Agent 5.4%, 18 subjects; FTC/TDF+3rd Agent 4.2%, 14 subjects) prior to the data cutoff date. The most common reasons subjects prematurely discontinued study drug were withdrew consent (F/TAF+3rd Agent 3.0%, 10 subjects; FTC/TDF+3rd Agent 3.0%, 10 subjects), AE (F/TAF+3rd Agent 2.1%, 7 subjects; FTC/TDF+3rd Agent 0.9%, 3 subjects), and protocol violation (F/TAF+3rd Agent 0 subjects; FTC/TDF+3rd Agent 1.2%, 4 subjects).

Subject demographics and baseline disease characteristics

Demographic and general baseline characteristics were similar between the 2 treatment groups with the exception of ethnicity; a statistically significantly higher percentage of subjects in the FTC/TDF+3rd Agent group were Hispanic or Latino (23.6%, 78 subjects) compared with the F/TAF+3rd Agent group (14.4%, 48 subjects; p = 0.003). Most subjects in the Safety Analysis Set were male (84.6%), with a median age of 49 years (range: 22 to 79 years); most were either white (75.0%) or black (20.5%), and most were not Hispanic/Latino (81.0%). The median (Q1, Q3) value for body mass index at baseline was 26.3 (23.7, 29.7) kg/m^2. Most subjects (98.8%) in the Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL. The median (Q1, Q3) baseline CD4 count was 646 (491, 835) cells/µL, with approximately three-quarters (74.2%) of subjects having a baseline CD4 count ≥ 500 cells/µL. The most common HIV risk factor category was homosexual sex (68.5%); 25.2% of subjects reported heterosexual sex as the mode of infection.

The distributions of third agents were similar between the 2 treatment groups (boosted PI: F/TAF+3rd Agent 46.5%, 155 subjects; FTC/TDF+3rd Agent 45.5%, 150 subjects; others: F/TAF+3rd Agent 53.4%, 178 subjects; FTC/TDF+3rd Agent 54.5%, 180 subjects). Most subjects (91.1%) had no proteinuria (Grade 0 by dipstick) on urinalysis. Values for eGFR (as measured by CG or by either of the CKD-EPI methods) were similar between the 2 treatment groups.

11.1.1.13. Sponsor's response to efficacy question by evaluator

Summary of GS-US-311-1089 efficacy results

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm. Virologic success rates at Week 48 were high in both groups using the FAS (F/TAF+3rd Agent 94.3%; FTC/TDF+3rd Agent 93.0%; difference in percentages: 1.3%, 95.002% CI: −2.5% to 5.1%). Because the lower bound of the 2-sided 95.002% CI of the difference in response rate was greater than the pre-specified −10% margin, switching to F/TAF was non-inferior to maintaining FTC/TDF at Week 48.

Table 29: GS-US-311-1089: Virologic Outcome at Week 48 Using Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Full Analysis Set)

	F/TAF+ 3rd Agent (N = 333)	FTC/TDF+ 3rd Agent (N = 330)	F/TAF vs. FTC/TDF	
			P-value[a]	Difference in Proportions (95.002% CI)[b]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	314 (94.3%)	307 (93.0%)	0.50	1.3% (−2.5% to 5.1%)
Virologic Failure at Week 48	1 (0.3%)	5 (1.5%)		
HIV-1 RNA ≥ 50 copies/mL	0	5 (1.5%)	—	—
Discontinued Study Drug Due to Lack of Efficacy	0	0	—	—
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[c]	1 (0.3%)	0	—	—
Added New ARV	0	0	—	—
No Virologic Data in Week 48 Window	18 (5.4%)	18 (5.5%)	—	—
Discontinued Study Drug Due to AE/Death	7 (2.1%)	3 (0.9%)	—	—
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	10 (3.0%)	15 (4.5%)	—	—
Missing Data During Window but on Study Drug	1 (0.3%)	0	—	—

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by third agent (ritonavir-boosted protease inhibitors vs. others).
b Difference in percentages of virologic success between treatment groups and its 95.002% CI were calculated based on the MH proportions adjusted by the third agent stratum.
c Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.
Week 48 window is between Day 294 and 377 (inclusive).

Virologic success rates were also similar between treatment groups using the Week 48 PP Analysis Set (F/TAF+3rd Agent 100%, 304 of 304 subjects; FTC/TDF+3rd Agent 98.4%, 300 of 305 subjects; difference in percentages: 1.6%, 95.002% CI: 0.0% to 3.3%) and support the conclusion for the primary analysis that switching to F/TAF+3rd Agent was non-inferior to maintaining FTC/TDF+3rd Agent at Week 48.

The percentages of subjects with virologic failure at Week 48 were low in the F/TAF+3rd Agent group and the FTC/TDF+3rd Agent group, using the FAS (F/TAF+3rd Agent 0.3%, FTC/TDF+3rd Agent 1.5%). Similar percentages of subjects in each treatment group had no virologic data at Week 48 (F/TAF+3rd Agent 5.4%, FTC/TDF+3rd Agent 5.5%). Regarding virologic success rates for predefined subgroups (age, sex, race, geographic regions, prior treatment regimen, and study drug adherence), the 95% CIs for the differences in response rates included 0 for all subgroups, suggesting no differences between treatment groups. Although not predefined, virologic success rates were also similar between treatment groups across all third agents as noted in the table below.

Table 30: GS-US-311-1089: Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48 Using Snapshot Algorithm by 3rd agent (Full Analysis Set)

	n	F/TAF+3rd Agent (N = 333)	n	FTC/TDF+3rd Agent (N = 330)
DRV/r	84	90.5%	82	91.5%
ATV/r	53	90.6%	50	94.0%
LPV/r	18	100%	18	100%
NVP	74	97.3%	66	98.5%
RAL	66	95.5%	73	89.0%
DTG	26	96.2%	23	91.3%
EFV	8	100%	6	83.3%
RPV	3	100%	6	83.3%
MVC	1	100%	6	100%

A high percentage of subjects in both treatment groups had virologic success defined as HIV-1 RNA < 20 copies/mL at Week 48 using the FDA snapshot algorithm for the FAS (F/TAF+3rd Agent 91.6%, FTC/TDF+3rd Agent 90.9%; difference in percentages: 0.7%, 95% CI: –3.7% to 5.1%) or PP Analysis Set (F/TAF+3rd Agent 97.4%, FTC/TDF+3rd Agent 96.1%; difference in percentages: 1.3%, 95% CI: –1.7% to 4.3%).

The rates of virologic success as assessed in the Missing = Failure (M = F) and Missing = Exclusion (M = E) analyses for the percentages of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48, were high and similar in both treatment groups (M = F: F/TAF+3rd Agent 95.8%, FTC/TDF+3rd Agent 95.2%; M = E: F/TAF+3rd Agent 100%, FTC/TDF+3rd Agent 98.4%; stratum-weighted difference in response rate between treatment groups at Week 48: M = F: 0.7%, 95% CI: −2.6% to 3.9%; M = E: 1.6%, 95% CI: 0.0% to 3.2%).

The proportions of subjects who were pure virologic responders at Week 48 were high and similar in both treatment groups (F/TAF+3rd Agent 98.8%, 329 of 333 subjects; FTC/TDF+3rd Agent 97.9%, 323 of 330 subjects).

The mean (SD) changes in CD4 cell counts were similar between groups through Week 48, with both groups having slight increases from baseline. Using observed data (that is, M = E), the mean (SD) changes from baseline at Week 48 in CD4 cell counts were 20 (161.8) cells/µL in the F/TAF+3rd Agent group and 21 (152.7) cells/µL in the FTC/TDF+3rd Agent group (difference in LSM: –1 cells/µL, 95% CI: −26 to 24 cells/µL).

The resistance analysis population comprised 3 subjects who experienced confirmed virologic rebound in the first 48 weeks of study: 2 subjects (0.6%) from the F/TAF+3rd Agent group and 1 subject (0.3%) from the FTC/TDF+3rd Agent group. In the F/TAF+3rd Agent group, 1 subject developed an NRTI resistance mutation to FTC (M184V), while 1 subject had pre-existing NNRTI resistance mutations detected. In the FTC/TDF+3rd Agent group, 1 subject had a pre-existing primary PI resistance mutation (Q58E) detected without phenotypic resistance to the 3rd agent (DRV/r). The development of resistance mutations was rare after 48 weeks of treatment across the F/TAF+3rd Agent and FTC/TDF+3rd Agent groups.

11.1.1.14. Evaluator's conclusions

The sponsor has responded to the evaluator's concerns regarding efficacy of Descovy with third agents by submitting the results of a Phase III clinical trial that determined the non-inferiority of Descovy, with a broad range of third agents, compared to Truvada with a similar broad range of third agents. The demographic, epidemiologic, clinical and laboratory baseline characteristics of both cohorts were comparable. The preliminary analysis at 48 weeks indicates that Descovy with third agents is non-inferior to Truvada and both therapies are equally efficacious. The

Evaluator is satisfied that the sponsor has responded to the question of lack of Phase III efficacy data in the original Round one submission. The efficacy of Descovy is accepted as non-inferior to Truvada.

The safety of F/TAF is implied in this submission, but requires controlled Phase III clinical trial scrutiny to document safety in the target population.

11.1.1.15. Sponsor's response

Gilead considers that the safety of F/TAF has been established via Phase III studies of E/C/F/TAF and bioequivalence studies. As there is no reason to believe that EVG+COBI (or DRV+COBI) would mask any safety signal of F/TAF, the safety data from E/C/F/TAF studies are directly relevant to F/TAF. As such, the safety of F/TAF can be considered to have been extensively assessed at the time of initial submission when used as part of E/C/F/TAF or D/C/F/TAF. In particular, the Phase III studies of E/C/F/TAF were conducted in a broad range of HIV-infected patients, including those who are ART-naive, virologically suppressed, renally impaired, or adolescents. In total, 2497 HIV-1 infected patients received F/TAF-containing regimen administered as E/C/F/TAF or D/C/F/TAF in Phase II and III studies (E/C/F/TAF: n=2394 with median exposure 48.1 weeks; D/C/F/TAF: n=103 with median exposure 68.0 weeks). Gilead considers that this number of patients and duration of exposure exceeds the requirements outlined in the ICH E1 Guidance: *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-life-threatening Conditions,* which states 300 to 600 patients should be treated for 6 months at dosage levels intended for clinical use, in order to characterise the pattern of adverse events.

Summary of GS-US-311-1089 safety results

In subjects switching from their baseline regimen, F/TAF+3rd Agent was generally well tolerated through a median of 48.3 weeks of exposure, as evidenced by the infrequent discontinuations due to AEs and the absence of study drug related SAEs. In subjects who stayed on their baseline regimen, study drugs were generally well tolerated through a median of 48.2 weeks of exposure.

Adverse rvents

Similar percentages of subjects in each group had any AE reported (F/TAF+3rd Agent 84.4%, 281 of 333 subjects; FTC/TDF+3rd Agent 79.4%, 262 of 330 subjects) or had SAEs (F/TAF+3rd Agent 5.4%, 18 subjects; FTC/TDF+3rd Agent 4.2%, 14 subjects). Adverse events that led to study drug discontinuation were uncommon in both groups (F/TAF+3rd Agent 2.1%, 7 subjects; FTC/TDF+3rd Agent 0.9%, 3 subjects). A similar percentage of subjects in each group had any AE considered by the investigator as related to study drug (F/TAF+3rd Agent 9.3%, 31 subjects; FTC/TDF+3rd Agent 12.1%, 40 subjects).

One subject in the F/TAF+3rd Agent group died during the study as a result of lymphoma and increased lipase; these events were considered by the investigator as not related to study drug. The death occurred in a 49 year old male patient with advanced HIV who presented at the Week 12 study visit with elevated lipase, lymphadenopathy, hepatosplenomegaly and icterus. A large mass of coalescent lymph nodes was found in the abdomen. A diagnosis of aggressive lymphoma was made, and the patient died 40 days after diagnosis. No AE that led to study drug discontinuation was reported for more than 1 subject in either group. Most of the AEs leading to discontinuation of study drug were non-serious; 2 SAEs led to discontinuation in the F/TAF+3rd Agent group (lymphoma and elevated lipase resulting in death and alprazolam overdose; neither considered related to study drug). One subject in the F/TAF+3rd Agent group had a confirmed pregnancy.

Common AEs were consistent with those expected in the study population, the known safety profiles of the study drugs, and with previous clinical study experience with FTC+TAF in combination with either EVG+COBI or DRV+COBI, administered as E/C/F/TAF or D/C/F/TAF,

respectively. The most common AEs (≥ 5% of subjects in either treatment group) by treatment group were as follows:

1. *F/TAF+3rd Agent*: diarrhoea and upper respiratory infection (9.0%, 30 of 333 subjects each); headache (8.1%, 27 of 333 subjects); nasopharyngitis (7.5%, 25 of 333 subjects); bronchitis, back pain, and cough (6.3%, 21 of 333 subjects each); arthralgia (5.7%, 19 of 333 subjects); and fatigue (5.4%, 18 of 333 subjects)
2. *FTC/TDF+3rd Agent*: upper respiratory infection (13.6%, 45 of 330 subjects), diarrhoea (10.0%, 33 of 330 subjects), sinusitis (6.7%, 22 of 330 subjects), nasopharyngitis (6.1%, 20 of 330 subjects), and bronchitis (5.2%, 17 of 330 subjects)

Overall, the rates and types of AEs observed in this study were similar in the 2 groups.

11.1.1.16. Evaluator comment

The two key issues of safety for Descovy are the potential amelioration in bone mineral density and renal adverse outcomes that have been observed in patients treated with Stribild. The reduction in these parameters formed the basis for the Genvoya clinical safety studies. The safety of Descovy in relation to BMD and renal outcomes is the genesis of the question raised by the Evaluator.

Bone safety

Similar percentages of subjects in each group had a fracture event (F/TAF+3rd Agent 0.3%, 1 subject; FTC/TDF+3rd Agent 0.6%, 2 subjects; p = 0.62). All reported fracture AEs were the result of trauma, considered by the investigator as unrelated to the study drugs, and none resulted in permanent discontinuation of study drugs. There were no reported fragility fractures.

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for this study, respectively. Statistical analysis using the fall-back procedure confirmed significance using adjusted alphas, which were dependent on the results from preceding tests.

There were increases from baseline in mean (SD) BMD at the hip and at the spine in the F/TAF+3rd Agent group compared with minimal changes from baseline in both parameters in the FTC/TDF+3rd Agent group ($p < 0.001$ for the differences between groups at Weeks 24 and 48).

Differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were also statistically significant ($p < 0.001$ at Weeks 24 and 48). At Week 48, more subjects in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent had a ≥ 3% increase from baseline in hip (F/TAF+3rd Agent 16.7%; FTC/TDF+3rd Agent 8.6%) or spine BMD (F/TAF+3rd Agent 30.3%; FTC/TDF+3rd Agent 13.7%).

Table 31: GS-US-311-1089: Bone Mineral Density (Observed Data, Hip or Spine DXA Analysis Set)

		F/TAF+ 3rd Agent	FTC/TDF+ 3rd Agent	F/TAF vs FTC/TDF	
				P-Value[a]	Diff in LSM (95% CI)[a]
Hip BMD[b]					
Baseline	N	321	317	0.64	0.005 (−0.015, 0.025)
	Mean (SD)	0.982 (0.1290)	0.977 (0.1288)		
% Change at Week 24	N	309	305	< 0.001	0.625 (0.274, 0.977)
	Mean (SD)	0.573 (2.1720)	−0.053 (2.2656)		
% Change at Week 48	N	300	303	< 0.001	1.287 (0.864, 1.710)
	Mean (SD)	1.135 (2.7526)	−0.152 (2.5317)		
Spine BMD[c]					
Baseline	N	321	320	0.76	0.004 (−0.022, 0.030)
	Mean (SD)	1.081 (0.1669)	1.077 (0.1663)		
% Change at Week 24	N	310	310	< 0.001	1.473 (1.022, 1.924)
	Mean (SD)	0.852 (2.8881)	−0.612 (2.8473)		
% Change at Week 48	N	300	306	< 0.001	1.735 (1.223, 2.246)
	Mean (SD)	1.527 (3.1816)	−0.206 (3.2233)		

% Change = Change from baseline at a postbaseline visit/baseline × 100%; Diff = difference

a For baseline, p-value and difference in least squared means (Diff in LSM), and its 95% CI were from an ANOVA model including treatment as a fixed effect. For postbaseline visits, p-values, difference in least squared means (Diff in LSM), and its 95% CI were from an ANOVA model including treatment and third agent randomization stratum as fixed effects.

b Only subjects with nonmissing baseline hip BMD were included in the Hip DXA Analysis Set.

c Only subjects with nonmissing baseline spine BMD were included in the Spine DXA Analysis Set.

Figure 5: GS-US-311-1089: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)

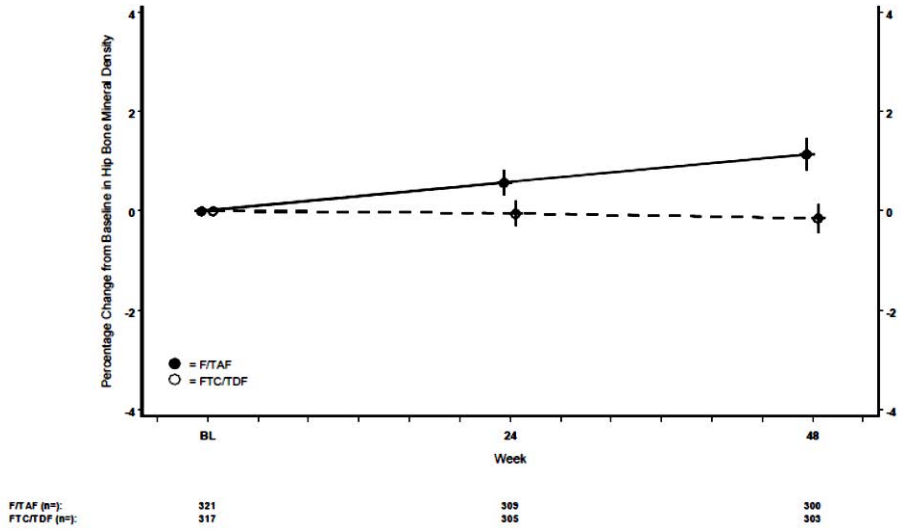
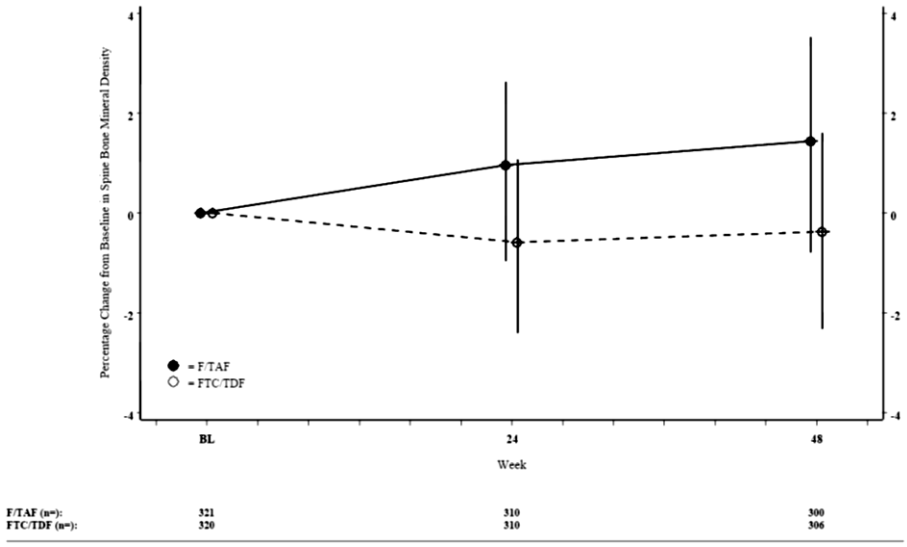


Figure 6: GS-US-311-1089: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)



Bone laboratory parameters

There was a decrease in bone turnover after switching from FTC/TDF to F/TAF. Decreases from baseline were observed in serum levels of the bone formation biomarker P1NP and also in PTH, a hormone involved in bone formation and resorption, in the F/TAF+3rd Agent group compared with minimal changes in both parameters in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). In addition, decreases from baseline were observed in serum levels of the bone resorption biomarker CTx, which were greater in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent at Week 48 ($p < 0.001$) for the differences between groups at Weeks 24 and 48).

Differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were also statistically significant ($p < 0.001$ at Weeks 24 and 48). At Week 48, more subjects in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent had a ≥ 3% increase from baseline in hip (F/TAF+3rd Agent 16.7%; FTC/TDF+3rd Agent 8.6%) or spine BMD (F/TAF+3rd Agent 30.3%; FTC/TDF+3rd Agent 13.7%).

There was a decrease in bone turnover after switching from FTC/TDF to F/TAF. Decreases from baseline were observed in serum levels of the bone formation biomarker P1NP and also in PTH, a hormone involved in bone formation and resorption, in the F/TAF+3rd Agent group compared with minimal changes in both parameters in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). In addition, decreases from baseline were observed in serum levels of the bone resorption biomarker CTx, which were greater in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent at Week 48 ($p < 0.001$).

Renal safety

In the F/TAF+3rd Agent group, none of the subjects had renal AEs that were considered serious, resulted in discontinuation of study drug, or considered by the investigator as related to study drug. In the FTC/TDF+3rd Agent group, 1 subject had an SAE of nephrolithiasis considered by the investigator as related to study drug and 1 subject had a non-serious renal AE of creatinine increased that led to study drug discontinuation (considered by the investigator as related to study drug).

There were no AEs of proximal renal tubulopathy (including Fanconi Syndrome) reported during the study.

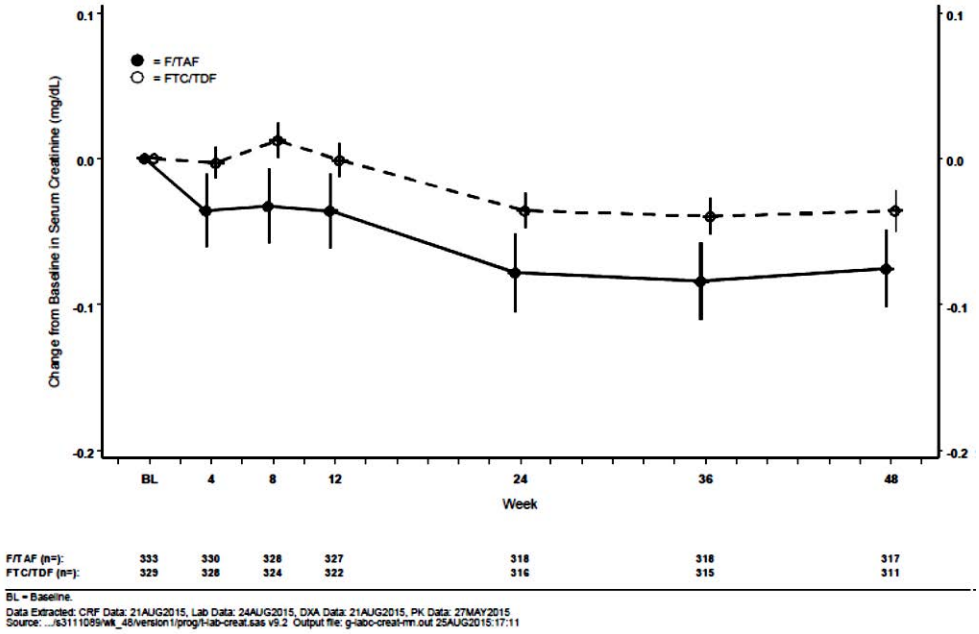
For subjects who switched to F/TAF+3rd Agent, there were decreases from baseline in serum creatinine at most time points as compared with minimal changes from baseline among subjects who remained on an FTC/TDF+3rd Agent regimen. At Week 48, the mean (SD) changes from baseline in serum creatinine were as follows: F/TAF+3rd Agent –0.08 [0.238] mg/dL; FTC/TDF+3rd Agent –0.04 [0.126] mg/dL (p = 0.005).

At Week 24, the distribution of proteinuria adjusted for baseline status was significantly different between treatment groups (p < 0.001), but not at Week 48. The findings at Week 24 were largely driven by improvement in proteinuria in the F/TAF+3rd Agent group.

All AEs of proteinuria were Grade 1 or 2 in severity and none resulted in discontinuation of study drugs.

There were decreases from baseline in UPCR, UACR, and in urine RBP to creatinine and beta-2-microglobulin to creatinine ratios in the F/TAF+3rd Agent group compared with increases from baseline in the FTC/TDF+3rd Agent group in all of these parameters at Week 48 (p < 0.001 for the differences between groups).

Figure 7: GS-US-311-1089: Mean (95% CI) of Change from Baseline in Serum Creatinine (mg/mL) by Visit (Observed Data; Safety Analysis Set)



There were increases from baseline in eGFRCG values in the F/TAF+3rd Agent group compared with minimal changes from baseline in the FTC/TDF+3rd Agent group at Weeks 4 through 48. Median changes from baseline at Week 48 were as follows: F/TAF+3rd Agent 8.4 mL/min, FTC/TDF+3rd Agent 2.8 mL/min; p < 0.001. Similar findings were observed in change from baseline in $eGFR_{CKD\text{-}EPI,\ creatinine}$ in both groups.

Table 32: GS-US-311-1089: Changes from Baseline in Estimated GFR at Week 48 (Safety Analysis Set)

	F/TAF+3rd Agent (N = 333)			FTC/TDF+3rd Agent (N = 330)			
	N	Median	Q1, Q3	N	Median	Q1, Q3	P-Value[a]
$eGFR_{CG}$ (mL/min)							
Baseline	333	99.4	83.8, 120.3	329	100.2	83.8, 121.2	0.74
Change at Week 48	317	8.4	0.2, 15.6	310	2.8	−5.1, 10.9	< 0.001
$eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 m^2)							
Baseline	333	85.9	74.4, 97.4	329	86.9	76.1, 98.7	0.74
Change at Week 48	317	5.5	−1.3, 11.4	311	2.4	−2.6, 8.8	< 0.001

a P-values comparing the 2 treatment groups were from the 2-sided Wilcoxon rank sum test.
For postbaseline visits, p-values were from rank analysis of covariance adjusting for baseline value and the third agent randomization stratum for treatment comparison.

Laboratory abnormalities

There were no clinically relevant changes from baseline within groups, or differences between the treatment groups in median values for haematology or clinical chemistry parameters. With the exception of lipase, which was measured only for subjects with elevated amylase, all median values were within normal ranges.

The majority of subjects had at least 1 laboratory abnormality (F/TAF+3rd Agent 90.0%, 298 subjects; FTC/TDF+3rd Agent 84.5%, 278 subjects). The majority of reported abnormalities were Grade 1 or 2. The percentage of laboratory abnormalities of any grade was balanced in both treatment groups for most chemistry, haematology, and urinalysis parameters. Similar percentages of subjects in the F/TAF+3rd Agent group and the FTC/TDF+3rd Agent group had Grade 3 or 4 abnormalities (F/TAF+3rd Agent 21.5%, FTC/TDF+3rd Agent 18.8%).

Metabolic laboratory parameters

There were increases from baseline in fasting values of total cholesterol, LDL cholesterol, and triglycerides in the F/TAF+3rd Agent group, while these parameters had little change in the FTC/TDF+3rd Agent group at both Week 24 and Week 48 ($p < 0.001$ for the differences between groups for total cholesterol and LDL cholesterol; $p = 0.016$ at Week 24 and $p = 0.002$ at Week 48 for triglycerides).

Median (Q1, Q3) changes from baseline at Week 48 for the F/TAF+3rd Agent group compared with FTC/TDF+3rd Agent group were as follows: total cholesterol 14 (−2, 33) mg/dL vs 1 (−17, 15) mg/dL; LDL cholesterol 13 (−1, 28) mg/dL vs 4 (−9, 16) mg/dL; HDL cholesterol 2 (−4, 8) mg/dL vs. −1 (−6, 5) mg/dL; and triglycerides 10 (−22, 46) mg/dL vs −2 (−30, 31) mg/dL. The changes were not considered clinically relevant.

Consistent with these results, of subjects with non-missing data at Week 48, higher percentages in the F/TAF+3rd Agent group than the FTC/TDF+3rd Agent group had the following categorical shifts from baseline based on NCEP ATP III classifications: total cholesterol (< 200 mg/dL to ≥ 200 mg/dL: F/TAF+3rd Agent 30.7%; FTC/TDF+3rd Agent 15.1%); LDL cholesterol (< 130 mg/dL to ≥ 130 mg/dL: F/TAF+3rd Agent 32.4%; FTC/TDF+3rd Agent 15.7%); HDL cholesterol (< 40 mg/dL to ≥ 40 mg/dL: F/TAF+3rd Agent 42.4%; FTC/TDF+3rd Agent 37.3%); and triglycerides (< 200 mg/dL to ≥ 200 mg/dL: F/TAF+3rd Agent 13.9%; FTC/TDF+3rd Agent 8.5%).

In general, AEs and laboratory abnormalities related to lipids were more commonly reported in the F/TAF+3rd Agent group than the FTC/TDF+3rd Agent group. All of the AEs were non-serious, and none led to discontinuation of study drugs.

There were no clinically relevant findings in other safety-related assessments.

Evaluator's conclusions

The sponsor has submitted comprehensive safety data from clinical trial GS-US-311-1089 that was not included when the first round was submitted. These data indicate that Descovy has a very similar safety profile to Truvada, when administered with a range of third agents. The main difference between the safety profiles of Descovy as compared with Truvada, as demonstrated in this clinical trial relates to the amelioration of reduction in bone mineral density and renal dysfunction in the cohort which was administered Descovy. The results of the trial indicate a statistically significant improvement in BMD and an amelioration in renal function in the Descovy cohort as determined by a reduction in serum creatinine. The evidence indicates that switching from Truvada to Descovy has a significant safety advantage while retaining efficacy as per the results of GS-US-311-1089. The evaluator agrees with the conclusions of the sponsor that Descovy provides safety advantages over Truvada while retaining non-inferiority. It should be noted that there were statistically significant increases in fasting cholesterol and triglycerides in the Descovy cohort when compared with the Truvada cohort. These differences were present at both Weeks 24 and 48 analysis. The pathogenesis of this increase is uncertain and should be monitored over the longer-term study results.

The association between TAF 25 mg and spontaneous abortion should be clarified.

11.1.1.17. Sponsor's response

The suspected unexpected serious adverse reaction (SUSAR) of spontaneous abortion following a single dose of F/TAF occurred 2 weeks after a dose taken in the fasting state. The first positive pregnancy test was 7 days after the single dose of F/TAF. Gilead does not believe that any conclusion can be drawn from this single report in a healthy volunteer given the background rate of spontaneous abortion of 8-20% in the general population. Spontaneous abortion is the most common complication of early pregnancy. In a study of 221 healthy women who were attempting to conceive, daily urinary hCG assays were performed. The results showed the total rate of pregnancy loss after implantation was 31%.

Although there has been limited use of TAF-containing products in pregnant women, animal data indicate that TAF does not cause reproductive or embryo-foetal toxicity. In addition, a large number of pregnancy outcomes have been collected following exposure to TDF in the Antiretroviral Pregnancy Registry (APR). APR defines spontaneous abortion as foetal death or expulsion of products of conception prior to 20 weeks gestation. From the latest interim APR report issued in December 2015 (data to 31 July 2015), the frequency of spontaneous abortion was 7.8% (242 out of 3106 pregnancy outcomes) for N(t)RTI-containing regimen (approximately 98% on TDF-containing regimens and 2% on adefovir dipivoxil-containing regimens). This frequency is consistent with the background rate in the population.

In conclusion, Gilead concurs with the evaluator that the spontaneous abortion from Study GS-US-311-1386 appears to have been a coincidental finding given the high background rate and that there is no data to support TAF being associated with an increased risk of spontaneous abortion.

11.1.1.18. Evaluator's conclusion

As stated by the sponsor, there is concurrence that the single case of spontaneous abortion was most probably due to the background prevalence of miscarriages and was misinterpreted as due to Descovy by the Phase I study clinician.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Descovy in the proposed usage are:

- Non-inferior to Truvada when administered with a broad range of third agents.
- Statistically significant safety advantages over Truvada in terms of improvement in bone mineral density. There was a decrease in bone turnover after switching from FTC/TDF to F/TAF. Decreases from baseline were observed in serum levels of the bone formation biomarker P1NP and also in PTH, a hormone involved in bone formation and resorption in the F/TAF+3rd Agent group compared with minimal changes in both parameters in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). In addition, decreases from baseline were observed in serum levels of the bone resorption biomarker CTx, which were greater in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent at Week 48 ($p < 0.001$),

12.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Descovy in the proposed usage are:

- There is a lack of specific clinical evidence for efficacy and safety in an adolescent population. However, data presented by the sponsor related to Genvoya and evidence from the clinical trial GS-US-311-1089, indicates that efficacy and safety of Descovy should be similar to that of Truvada and probably also have the same BMD and renal advantages of Descovy, when used with third agents. Study GS-US-292-0106 involved administering Genvoya to ART naïve adolescents and demonstrated similar efficacy (91.3%) to Descovy administered with third agents to HIV-1 infected adults and also to ART naïve adults. The similarity of both efficacy and safety in these populations provides a level of confidence that Descovy, when administered with third agents to adolescents, will have a similar level of efficacy and safety. While this level of confidence is reasonable, it is supported by inference, not by direct clinical trial evidence.
- There were increases from baseline in fasting values of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in the F/TAF+3rd Agent group, while these parameters had little change in the FTC/TDF+3rd Agent group at both Week 24 and Week 48 ($p < 0.001$ for the differences between groups for total cholesterol, LDL cholesterol, and HDL cholesterol; $p = 0.016$ at Week 24 and $p = 0.002$ at Week 48 for triglycerides). However, because TDF is known to reduce blood lipids, the apparent 'increases' in blood lipids observed with Descovy in GS-US-311-1089, compared with Truvada may be due to blood lipids returning to their pre-Truvada levels.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Descovy, given the proposed usage, is favourable.

13. Second round recommendation regarding authorisation

The evaluator recommends authorisation of Descovy.

13.1. Second round comments on clinical aspects of the draft PI

The sponsor provided new clinical information after the first round but did not change any clinical aspects of the draft PI. After consideration of the new clinical information, the PI comments are revised as follows:

The PI should be up-dated to include clinical and safety data from Study GS-US-311-1089 as these data are more relevant to Descovy than the previous PI which included only data from the Genvoya studies. At this time it appears there is no mention of this pivotal clinical trial in the currently submitted PI.

13.2. Second round comments on clinical aspects of the draft CMI

The sponsor provided new clinical information after the first round but did not change any clinical aspects of the draft CMI. After consideration of the new clinical information, the CMI comments are revised as follows:

The sponsor appears not to have up-dated the CMI with addition of safety and efficacy data from the GS-US-311-1089 clinical trial.

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