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APPLICATION NUMBER:

207561Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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NDA	207561
Submission Type	NME
Applicant Name	Gilead
Submission Dates	11/5/2014
Generic Name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF)
Dosage Form (Strength)	Tablet (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide)
Indication	Treatment of HIV-1
Review Team	Mario Sampson, PharmD, Islam Younis, PhD

This memo concerns additional analyses that were conducted after submission of the Clinical Pharmacology review of this application.¹

Time course of lipid changes during treatment with E/C/F/TAF

Compared to baseline, week 48 total cholesterol, LDL, and triglyceride values were significantly increased for subjects in the E/C/F/TAF arms of pivotal studies 104 and 111 in treatment naïve subjects, and less of an increase was noted for subjects in the E/C/F/TDF arms (Table 1). Lipid values were collected at weeks 24, 48, and 72 in studies 104 and 111. In the E/C/F/TAF and E/C/F/TDF arms of these studies, peak lipid changes occurred by week 24, and no further increase was observed at weeks 48 or 72 (Tables 2-3). The data suggests progressive lipid increases during long-term treatment are not expected.

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Table 1. Change from baseline lipid values in studies 014 and 111.

	[TRADENAME] N=866		STRIBILD N=867	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change ^b	mg/dL	Change ^b
Total Cholesterol (fasted)	162 [N=757]	+30 [N=757]	166 [N=742]	+13 [N=742]
HDL-cholesterol (fasted)	46 [N=757]	+7 [N=757]	45 [N=742]	+4 [N=742]
LDL-cholesterol (fasted)	104 [N=753]	+15 [N=753]	107 [N=744]	+3 [N=744]
Triglycerides (fasted)	113 [N=757]	+29 [N=757]	119 [N=742]	+10 [N=742]
Total Cholesterol to HDL ratio	3.7 [N=757]	0.2 [N=757]	3.9 [N=742]	0 [N=742]

a. Excludes subjects who received lipid lowering agents during the treatment period.

b. The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.

Source: Draft E/C/F/TAF US prescribing information (version 8/7/2015). Tradename = E/C/F/TAF.

Table 2. Mean change from baseline in lipid values in subjects who received E/C/F/TAF in studies 0104 and 0111.

Lipid	Week 24	Week 48	Week 72
LDL	14 (-22, 60) N=832	13 (-23, 55) N=821	15 (-27, 58) N=127
Cholesterol	26 (-15, 75) N=835	29 (-16, 80) N=823	27 (-19, 72) N=128
Triglycerides	15 (-67, 125) N=825	17 (-72, 171) N=823	15 (-96, 165) N=128
HDL	7 (-10, 24) N=835	7 (-9, 25) N=823	7 (-10, 25) N=128

Source: reviewer's analysis. Values are median (5th, 95th percentiles).

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Table 3. Mean change from baseline in lipid values in subjects who received E/C/F/TDF in studies 0104 and 0111.

Lipid	Week 24	Week 48	Week 72
LDL	4 (-31, 44) N=841	2 (-36, 48) N=815	3 (-34, 37) N=117
Cholesterol	10.5 (-32, 55) N=840	13 (-33, 63) N=812	8 (-32, 58) N=117
Triglycerides	8 (-86, 108.5) N=840	6 (-84, 125) N=813	11 (-63, 188) N=117
HDL	3.5 (-12, 19) N=840	3 (-11, 20) N=813	3.5 (-13, 19) N=116

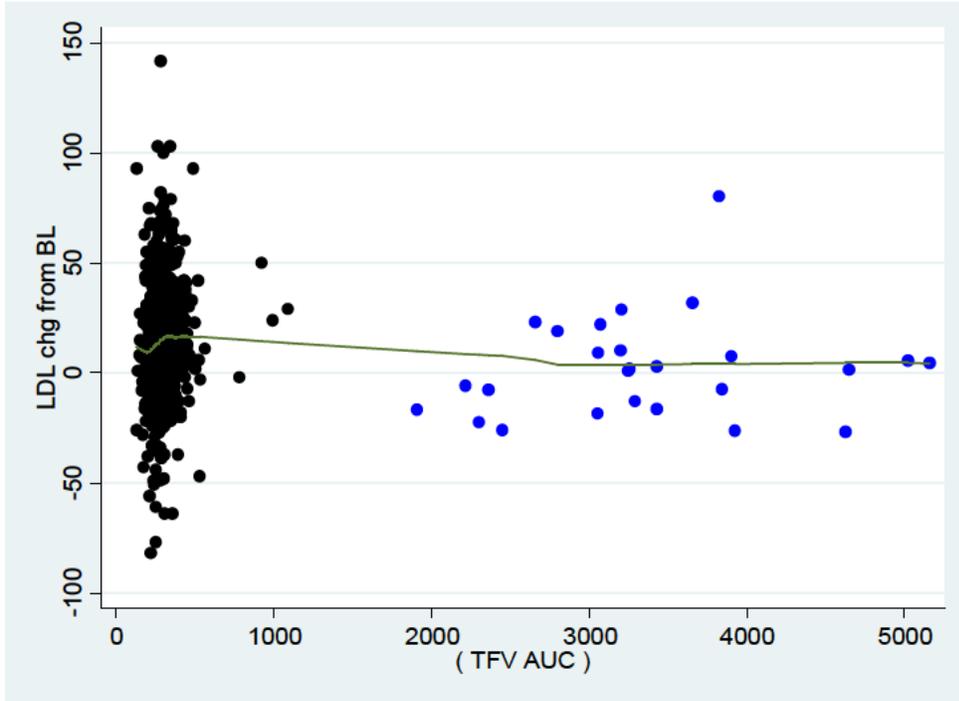
Values are median (5th, 95th percentiles) change from baseline

Tenofovir exposure-responses analyses

The PK/PD analyses conducted in the full E/C/F/TAF Clinical Pharmacology review focused on exposure-response analyses limited to subjects who received E/C/F/TAF in studies 104 and 111 (n=841 subjects with sparse sampling). In an exploratory analysis, we extended this analysis to include the small number of subjects (n=29) who received E/C/F/TDF in studies 104 and 111 and were enrolled in an intensive PK substudy. In spite of the much higher TFV exposures in the E/C/F/TDF arm relative to the E/C/F/TAF arm, no exposure-response relationships were observed for lipid values, serum creatinine, or bone mineral density (representative data shown in Figures 1-2). However, the small PK sample size in the E/C/F/TDF arm may prevent the detection of possible exposure-response relationships.

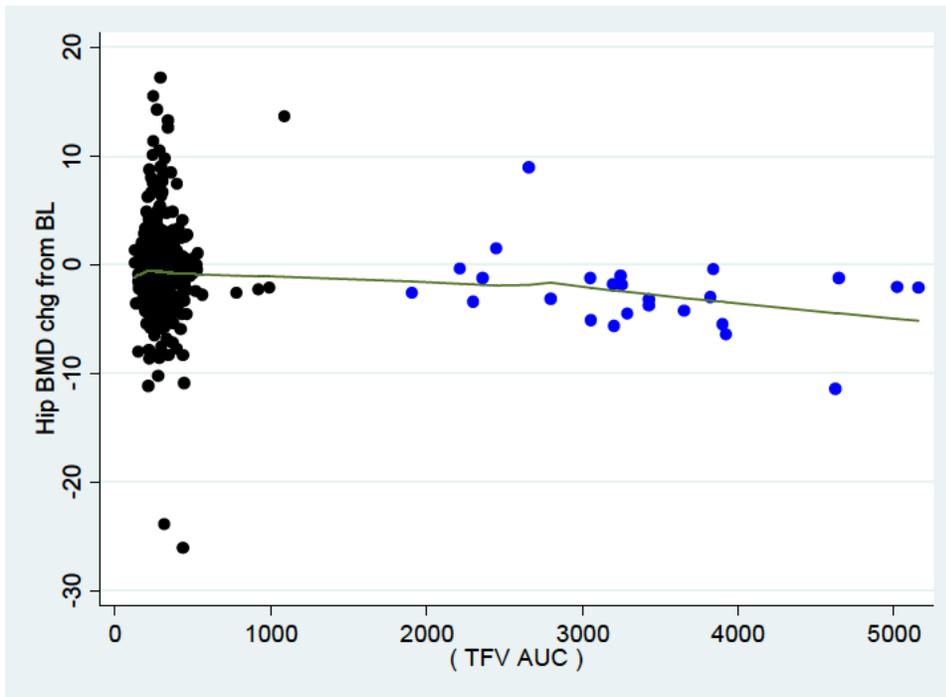
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Figure 1. TFV exposure-response relationship for LDL change from baseline.



Source: reviewer's analysis. E/C/F/TAF = black; E/C/F/TDF = blue.

Figure 2. TFV exposure-response relationship for hip bone mineral density change from baseline.



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Pharmacokinetics of E/C/F/TAF in renal impairment

Study 292-0112 was a phase 3 E/C/F/TAF study in HIV-infected subjects with mild to moderate renal impairment (n=260). As there was no cohort with normal renal function, the PK analysis consisted of comparing E/C/F/TAF PK in subjects with CrCL <50 mL/min versus those with CrCL ≥50 mL/min. In order to inform the impact of renal impairment on E/C/F/TAF exposures, we asked the sponsor to repeat the analysis by comparing PK data from this renal impairment study (test) relative to PK data from HIV-infected subjects with normal renal function (historical control). This data was included in the label in section 12.3 (Table 4).

Table 4. E/C/F/TAF PK in subjects with normal renal function and renal impairment.

Creatinine Clearance (mL per minute)	AUC _{tau} (microgram-hour per mL) Mean (CV%)		
	≥90 (N=18) ^a	60–89 (N=11) ^b	30–59 (N=18) ^b
Elivitegravir	22.6 (35.8)	24.2 (35.0)	29.0 (29.6)
Cobicistat	9.4 (35.0)	10.0 (47.5)	9.9 (45.0)
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)
Tenofovir Alafenamide*	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)

Source: Draft E/C/F/TAF US prescribing information (8/7/2015 version)

*AUC_{last}

- a.  (b) (4)
- b. 

Other labeling issues

The following clinical pharmacology-related labeling issues were identified after completion of the full Clinical Pharmacology review and are summarized in Table 5.

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Table 5. Other E/C/F/TAF clinical pharmacology-related labeling issues.

Section(s)	Issue	Outcome
2.3 Dosage adjustment in patients with renal impairment	We asked the sponsor to propose (b) (4)	Sponsor proposed to consider (b) (4) . The FDA review team decided discontinuation criteria is not necessary. The statement that use of E/C/F/TAF in patients with CrCL <30 mL/min is not recommended was deemed to be sufficient.
6.1 Adverse Reactions from Clinical Trials Experience	We asked the sponsor not to use the descriptors “normal, mild, moderate, etc” when describing stages of renal function, and instead use CrCL values. The reason is because the current definitions differ from the categories as defined in the renal impairment studies.	The sponsor accepted our proposal.
7.4 Drugs affecting renal function	We inserted this paragraph, which is in the E/C/F/TDF label, because improved renal safety of TAF versus TDF has not yet been demonstrated, FTC is also renally eliminated, and there are no safety or drug interaction data with drugs with active tubular secretion.	Sponsor accepted
7.5 Established and other potentially significant interactions	Ledipasvir/sofosbuvir was placed in section 7.6 “Drugs without clinically significant interactions with E/C/F/TAF”. A drug interaction study was done and submitted to the ledipasvir/sofosbuvir NDA. No clinically significant interaction was noted.	Sponsor accepted
12.3 Pharmacokinetics	We proposed placing the PK properties information in a table instead of text due to the long length of the section in text form, which is related to the fact that this product contains four components.	Sponsor accepted

References

1. NDA 207561 Clinical Pharmacology Review. FDA. 7/10/2015. DARRTS reference ID 3790589.

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/s/

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10/13/2015

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10/14/2015

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	207561
Submission Type; Code:	NME
Applicant Name:	Gilead
Submission Dates:	11/5/2014
Brand Name:	Genvoya
Generic Name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Dosage Form:	Fixed dose combination tablet
Dosage Strengths:	150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide
Proposed Indication:	Treatment of HIV-1 in ages \geq 12 years
OCP Division:	IV
Review Team:	Mario Sampson, PharmD, Jeffry Florian, PhD, Islam Younis, PhD

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1 EXECUTIVE SUMMARY

Elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/tenofovir alafenamide fumarate (TAF) (E/C/F/TAF) is a fixed dose combination (FDC) (b) (4) tablet. The proposed indication is treatment of HIV-1 in patients ≥ 12 years. The tablet contains EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg. EVG, COBI, and FTC are approved at the dosages included in E/C/F/TAF. TAF is a prodrug of tenofovir (TFV). This is the first NDA application for a product containing TAF. Tenofovir disoproxil fumarate (TDF) is an approved prodrug of TFV with warnings for new onset or worsening renal impairment in addition to decreased bone mineral density. E/C/F/TDF is an approved product with the same components (and doses) as E/C/F/TAF with the exception of the TFV prodrug. The presumed medical rationale for development of TAF was lower TFV concentrations and a potentially improved bone and renal safety profile.

The E/C/F/TAF development program consisted of clinical studies in treatment-naïve (n=1733), virologically suppressed (n=1196), virologically suppressed with mild to moderate renal impairment (n=242), and adolescent (n=23) populations. Per the sponsor's analysis, the fraction of subjects with HIV RNA < 50 copies/mL at week 48 (efficacy outcome) was $> 90\%$ for each of the E/C/F/TAF studies, and in studies with a comparator arm, results in both arms were similar (Table 2).¹ FDA findings regarding efficacy, safety, and resistance are described elsewhere.²⁻⁴

1.1 Recommendations

The clinical pharmacology information submitted in the NDA application supports the approval of E/C/F/TAF for treatment of HIV-1 in patients ≥ 12 years of age.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Note: Figures and tables are from the sponsor's clinical study reports (CSRs) unless otherwise indicated.

1.3.1 Clinical pharmacology of TAF

TAF is readily absorbed and can be detected in plasma. TAF is primarily eliminated by metabolism to TFV by cathepsin A in peripheral blood mononuclear cells (PBMC, the site of action) and carboxylesterase 1 in hepatocytes (Figure 11). TFV is intracellularly phosphorylated to the active moiety TFV-diphosphate (TFV-DP).

TAF anti-HIV activity was established in a monotherapy study in which HIV-infected subjects were administered TDF 300 mg, TAF 8 mg, TAF 25 mg, and TAF 40 mg for 10 days. Relative to TDF, anti-HIV activity (log reduction in HIV RNA) was similar for TAF 8 mg and increased for the TAF 25 mg and 40 mg groups. The TAF 25 mg dose was selected for phase 2 and phase 3 studies. TAF 10 mg was included in the E/C/F/TAF tablet because it provides similar exposure to TAF 25 mg when coadministered with COBI 150 mg.

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When E/C/F/TAF is administered with food to HIV-infected subjects, TAF T_{max} is 1 hour. Relative to fasting conditions, administration of E/C/F/TAF with a light meal or high fat meal results in TAF AUC increased 15% and 18%, respectively. In samples collected during clinical trials, ex-vivo binding of TAF to plasma proteins was ~80%.

TAF is a substrate of efflux transporters Pgp and BCRP, in addition to uptake transporters OATP1B1 and OATP1B3. TAF is a weak inhibitor of CYP3A; it does not inhibit or induce other CYPs and does not inhibit any transporters. TAF exposure is increased by COBI as it is a Pgp, BCRP, and OATP1B1/1B3 inhibitor.

Upon multiple doses of single agent TAF at doses of 8 mg, 25 mg, and 40 mg, exposure increased more than proportionally with dose. In HIV-infected subjects, TFV AUC was reduced ~90% in subjects administered E/C/F/TAF (TAF 10 mg contains 6.0 mg of TFV) versus E/C/F/TDF (TDF 300 mg contains 136 mg of TFV), while the intracellular AUC in PBMCs of the active metabolite TFV-diphosphate (TFV-DP) was similar.

1.3.2 Exposure-response

Efficacy

With the exception of COBI (used as a CYP3A inhibitor), each of the individual agents included in E/C/F/TAF were associated with near-maximal antiviral activity based on monotherapy studies. In phase 3 studies as part of combination therapy, exposure-response relationships for efficacy of EVG (evaluated in E/C/F/TDF development), TAF (Figure 2), and TFV (evaluated in E/C/F/TAF development) were flat.

Safety

In treatment-naïve subjects administered E/C/F/TAF in phase 3 trials, TAF and TFV C_{max} and AUC were estimated by population PK. TAF and TFV exposures in subjects administered E/C/F/TAF were not associated with commonly observed AEs (nausea, diarrhea, vomiting, and GI/abdominal pain), known bone and renal toxicities of TFV (bone mineral density, maximum increase from baseline in serum creatinine), or change from baseline in lipid values (Figure 6, Figure 7, Figure 8, Figure 9, Figure 10).

In the E/C/F/TDF program, EVG, COBI, and FTC exposures were not associated with rates of common AEs (headache, nausea, and diarrhea) or changes in serum creatinine (Figure 3, Figure 4, Figure 5).⁵ In the FTC development program, a dose-response relationship was not observed in relation to frequency or severity of common AEs (included asthenia, nausea, headache, pharyngitis, and rhinitis).⁶

Comparing subjects administered E/C/F/TAF versus E/C/F/TDF in studies 104 and 111, mean declines from baseline bone mineral density were significantly smaller in the E/C/F/TAF group.⁷

1.3.3 Drug-drug interactions

Drug-drug interaction information related to EVG and COBI was primarily transferred from the E/C/F/TDF label. FTC has minimal drug-drug interaction potential. Three drug-drug interaction studies were submitted as part of this NDA.

A drug-drug interaction study with E/C/F/TAF and sertraline (study GS-US-292-1316) found exposure changes of <16% for each component of E/C/F/TAF and sertraline.

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Based on flat exposure-response relationships, no dose adjustment is recommended for based on a <16% exposure change.

Coadministration of EVG/COBI and carbamazepine in drug-drug interaction study GS-US-216-0137 resulted in EVG AUC decreased 69%, COBI AUC decreased 84%, carbamazepine AUC increased 43%, and carbamazepine-10,11-epoxide (CYP3A-mediated active metabolite of carbamazepine) AUC decreased 35%. Based on significant EVG exposure decreases, coadministration of E/C/F/TAF and carbamazepine is contraindicated.

Coadministration of TAF and COBI in drug-drug interaction study GS-US-311-0101 resulted in TAF AUC increased 2.7-fold and TFV AUC increased 3.3-fold. This drug interaction was addressed by a dose reduction of the TAF dose from 25 mg to 10 mg in the E/C/F/TAF tablet.

Within the E/C/F/TAF regimen, drug-drug interactions occur via COBI-mediated CYP3A and Pgp inhibition, resulting in increased exposures of EVG (CYP3A substrate) and TAF (Pgp substrate). EVG and TAF exposures may also be increased via inhibition of BCRP, OATP1B1, and OATP1B3 as EVG, TAF, and COBI are substrates of these transporters and COBI is an inhibitor of these transporters.

1.3.4 Adolescents

The primary endpoint intended to support approval of E/C/F/TAF in adolescents in study GS-US-292-0106 (age >12 - <18 years) was exposure matching with adults. Twenty-four HIV-infected adolescents were administered E/C/F/TAF and steady-state PK was evaluated. Compared to adults (pooled dataset with HIV-infected and healthy adults) administered E/C/F/TAF, adolescent exposures were decreased for EVG C_{trough} (C_{trough} >45 ng/mL is associated with antiviral activity)⁸, TAF, and COBI (Table 16). Though adolescent EVG C_{trough} was decreased compared to adults, all adolescents had values above the target (Figure 12). When compared only to HIV-infected adults (a more clinically relevant comparison than the pooled dataset), adolescent EVG exposures (including C_{trough}) were similar, while TAF and COBI exposures remained lower (Table 17). TAF has flat exposure-response relationships for efficacy, thus 30% reduced exposures are acceptable. COBI exposures are of secondary importance, as the purpose of COBI is to increase the exposure of EVG (it also increases TAF exposures). In conclusion, while exposures from administration of E/C/F/TAF were decreased in adolescents compared to adults, based on exposure-response relationships, exposures were overall acceptable and support approval for adolescents.

1.3.5 Hepatic impairment

In subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment, after a single TAF dose, TAF and TFV AUC increased <13% compared to matched healthy controls, which was deemed not clinically significant (Table 18). No dose adjustment is recommended for mild to moderate hepatic impairment.

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1.3.6 Renal impairment

Mild to moderate

The use of TDF is associated with renal impairment, including cases of acute renal failure and Fanconi syndrome; therefore, E/C/F/TDF is not recommended in patients with $\text{CrCL} < 70$ mL/min and should be discontinued if CrCL declines below 50 mL/min. TAF results in ~90% lower TFV exposures relative to TDF and can potentially have an improved safety profile in subjects with renal impairment. To establish safety of E/C/F/TAF in subjects with $\text{CrCL} \geq 30$ mL/min, phase 3 study GS-US-292-0112 enrolled virologically-suppressed HIV-infected subjects with mild to moderate renal impairment (estimated GFR [eGFR] Cockcroft-Gault of 30-69 mL/min, inclusive). Subjects were switched to E/C/F/TAF daily for 96 weeks. The interim 24 week study reports was submitted to the NDA. Evaluation of baseline renal function was complicated by COBI and RTV-mediated inhibition of creatinine tubular secretion, potentially resulting in artificially high creatinine values and thus lower estimated GFR values using the Cockcroft-Gault equation (eGFR_{CG}). Therefore baseline renal function was estimated by both the creatinine and Cystatin C. Baseline eGFR_{CG} versus Cystatin C using the CKD-Epi equation differed significantly (Table 19). However, the discrepancy between mean eGFR measured by creatinine versus Cystatin C was present for subjects on COBI or RTV at baseline versus those not on COBI/RTV (Table 19). In addition, in a PK substudy of this trial, baseline eGFR was closer to actual GFR (aGFR) for creatinine versus Cystatin C (Table 20). Thus the use of creatinine and the Cockcroft-Gault equation that was used to determine baseline renal function in the trial was considered acceptable.

FTC is labeled to be dosed 200 mg every other day in subjects with creatinine clearance (CrCL) of 30-49 mL/min. This is based on findings from a single dose PK study in subjects with renal impairment, where relative to subjects with normal renal function, FTC exposure was increased 2-fold in subjects with CrCL 30-49 mL/min. The E/C/F/TAF label (E/C/F/TAF also contains FTC 200 mg) proposes no dose adjustment for subjects with CrCL of ≥ 30 mL/min. The basis for the proposed E/C/F/TAF dosing is study GS-US-292-0112, which enrolled 242 HIV virologically-suppressed subjects with mild (CrCL of 50-69 mL/min, n=162) to moderate (CrCL of 30-49 mL/min, n=80) renal impairment. Compared to PK data from a phase 2 study in HIV-infected subjects with normal renal function, subjects with moderate renal impairment had ~2-fold increased FTC and TFV AUC values (Table 21, Table 22).

In subjects without renal impairment administered E/C/F/TDF (includes FTC 200 mg daily), FTC exposure-response relationships for safety appeared to be flat (Figure 5). Study GS-US-292-0112 is the first safety study in which FTC 200 mg daily was administered to subjects with renal impairment. In this study, FTC was only measured in intensive PK substudy participants; only TAF and TFV were measured in the single PK sample collected in all subjects. Thus FTC exposure-safety relationships have not been evaluated in HIV patients with renal impairment and the clinical significance of 2-fold increased FTC exposures is unclear. Please refer to the Clinical review for the evaluation of overall safety in this study, which will likely form the basis for acceptability of dosing E/C/F/TAF in subjects with CrCL of ≥ 30 - < 50 mL/min.²

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Severe

PK study GS-US-120-0108 enrolled HIV- and HBV-negative subjects with severe renal impairment (Cockcroft-Gault CrCL ≥ 15 mL/min to ≤ 29 mL/min) and matched subjects with normal renal function (Cockcroft-Gault CrCL ≥ 90 mL/min) and administered a single dose of TAF 25 mg. Relative to healthy controls, subjects with severe renal impairment had TAF AUC increased 92% and TFV AUC increased 5.7-fold; TFV renal clearance was reduced 75% (Table 23). Given flat exposure-response relationships for TAF, the increase in TAF exposure is not considered clinically relevant. Although following administration of TAF 25 mg to subjects with severe renal impairment resulted in TFV AUC increased almost 6-fold, exposures are still lower than observed after administration of TDF 300 mg to subjects without renal function. However, due to the FTC component (discussed above), the minimum CrCl at which E/C/F/TAF is being considered for administration is either 30 mL/min or 50 mL/min.

1.3.7 Increased lipid values in subjects administered E/C/F/TAF versus E/C/F/TDF

In phase 3 studies, mean change from baseline in week 48 LDL values for subjects administered E/C/F/TAF versus E/C/F/TDF was +15 mg/dL versus +4 mg/dL, respectively (Table 4). This was attributed to a postulated lipid-lowering effect of TFV that has been observed in several studies.^{9, 10} The mechanism of the effect of TFV on lipids is not known; bioanalytical interference of the components of E/C/F/TAF with quantification of lipids has not been ruled out experimentally. As mentioned in section 1.3.2, TAF and TFV exposures were not associated with lipid values.

1.3.8 Bioanalytical methods

E/C/F/TAF results in ~90% reduced systemic exposure to TFV versus E/C/F/TDF while resulting in similar concentrations of the active intracellular moiety TFV-DP. The sponsor proposed labeling stating (b) (4)

we disagree with including

(b) (4)

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2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

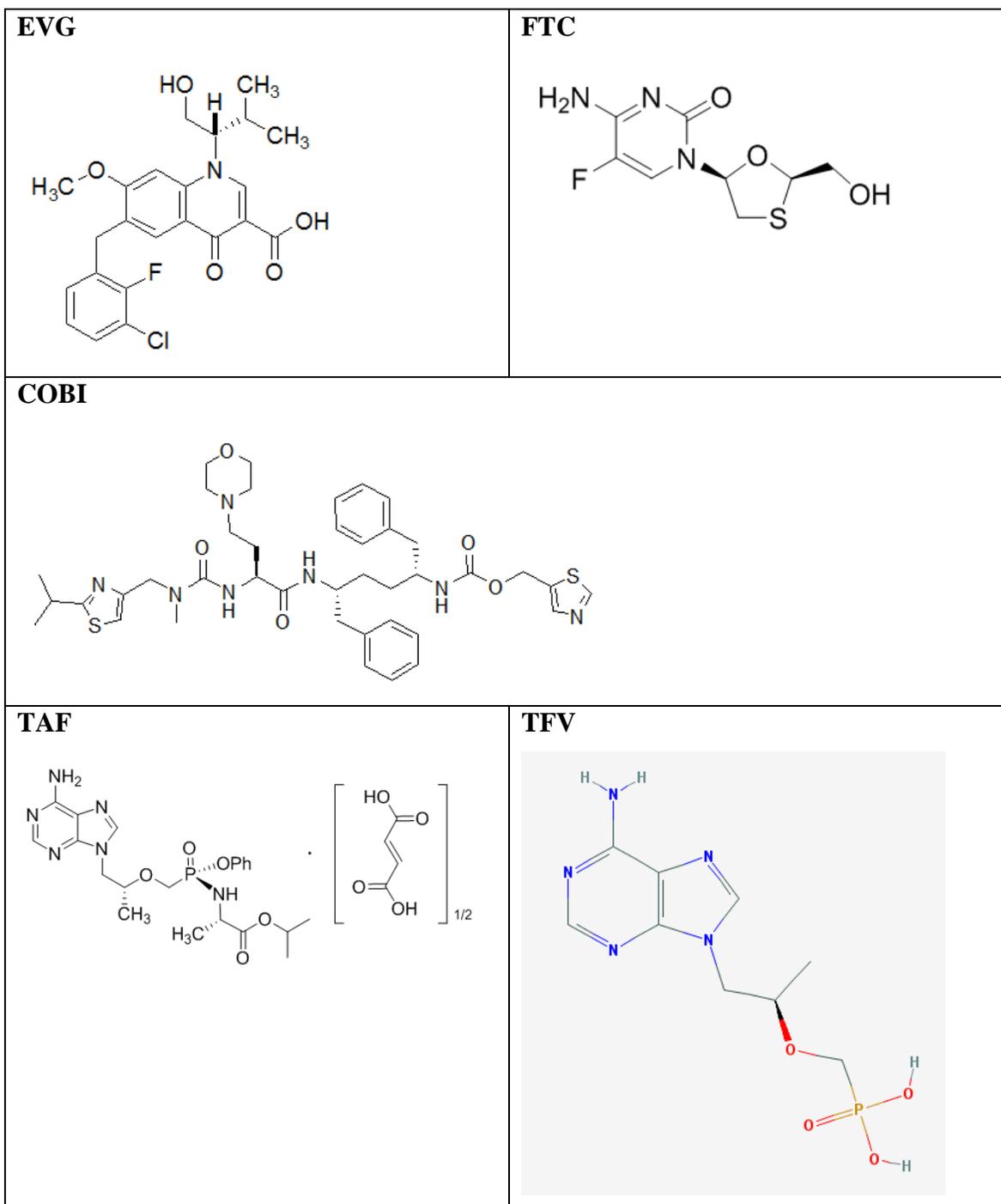
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The E/C/F/TAF formulation is a fixed dose combination (FDC) (b) (4) tablet containing EVG, COBI, FTC, and TAF fumarate (Figure 1, Table 1). TAF monofumarate (1:1 ratio of TAF to fumarate) and TAF fumarate (i.e. hemifumarate form with 2:1 ratio of TAF to fumarate) were used in phase 1 studies. TAF fumarate was selected for commercialization and incorporation into E/C/F/TAF FDC, which was then used in phase 2 and phase 3 studies.

The tablets include the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, silicon dioxide, sodium lauryl sulfate, and magnesium stearate. The tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine aluminum lake, and iron oxide yellow.

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Figure 1. Chemical structures of the components of E/C/F/TAF.^{11, 12}



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Table 1. Physicochemical characteristics of the components of E/C/F/TAF.¹¹

Drug	MW	BCS class*
EVG	447.9	2
COBI	776.0	2
FTC	247.25	1
TAF (includes fumarate)	534.5	3

Table prepared by reviewer. BCS class: 1 = high solubility, high permeability; 2 = low solubility, high permeability; 3 = high solubility, low permeability.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Per the proposed labeling, “[TRADENAME] is a four-drug combination of elvitegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs) and is indicated for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.”

2.1.3 What are the proposed dosages and routes of administration?

Each tablet for oral administration contains 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF. The dosage regimen is one tablet by mouth daily with food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

The E/C/F/TAF development program consisted of clinical studies in several HIV-infected populations (Table 2). E/C/F/TAF clinical pharmacology studies are summarized in Table 3.

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Table 2. Summary of clinical studies.

Study #	Design	Primary Objectives	Population	Treatments	Fraction of subjects with HIV RNA <50 copies/mL*
292-0104	1:1 randomized, double-blind, active-controlled (n=1733)	Safety, efficacy, PK	Treatment-naïve	<ul style="list-style-type: none"> E/C/F/TAF + placebo E/C/F/TDF (test) 	E/C/F/TAF: 93.1%
292-0111				<ul style="list-style-type: none"> E/C/F/TDF + placebo E/C/F/TAF (active control) 	E/C/F/TAF: 91.6%
292-0109	2:1 randomized, open-label (n=1196)		Virologically suppressed	<ul style="list-style-type: none"> Switch to E/C/F/TAF Stay on FTC/TDF + 3rd agent 	E/C/F/TAF: 95.6%
292-0112	Open-label (n=242)		Virologically suppressed, mild to moderate renal impairment	E/C/F/TAF	FTC/TDF + 3 rd agent: 92.9%
292-0106	Open-label (n=23)		Adolescents	E/C/F/TAF	E/C/F/TAF: 93.0% (week 24)
		Antiviral activity, safety, and PK			NA

Table prepared by reviewer. *Sponsor's analysis; week 48 endpoint unless otherwise indicated).

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Table 3. Summary of clinical pharmacology studies submitted in the E/C/F/TAF NDA.

Study #	Design	Population	Rationale	Treatments
120-0104	Randomized, partially-blinded, active- and placebo-controlled	HIV	Single and multiple PK and antiviral activity	TAF 8 mg, TAF 25 mg, TAF 40 mg, TDF 300 mg, or placebo for 10 days without food
120-0109	Open-label	Healthy	Mass balance	Single TAF 25 mg radiolabeled dose without food
292-0102	Randomized, double-blind, active- and placebo-controlled	HIV	Steady-state intensive PK substudy	E/C/F/TAF or E/C/F/TDF for 48 weeks
292-0103	Randomized, open-label	Healthy	Single and multiple dose PK of E/C/F/TAF FDC versus single agents	E/C/F/TAF or EVG/COBI or FTC + TAF for 12 days
292-0106	Open-label	HIV, adolescents	Multiple dose PK	E/C/F/TAF for 48 weeks
120-0108	Open-label, parallel	Severe renal impairment, healthy matched controls	Single dose PK	Single TAF 25 mg dose
120-0114	Open-label, parallel	Mild to moderate hepatic impairment, matched healthy controls	Single dose PK	Single TAF 25 mg dose without food
292-0108	Open-label	Healthy Japanese and Caucasians	Single and multiple dose PK	Single dose on day 1 and days 8-19
292-0112	Open-label	HIV-infected with mild to moderate renal impairment, healthy matched controls	Steady-state intensive PK substudy	E/C/F/TAF for 96 weeks
216-0137	Open-label, cross-over	Healthy	DDI: EVG/COBI and carbamazepine	EVG+COBI for days 1-10, CBZ (BID) for days 11-31, EVG+COBI+CBZ (BID) for days 32-41
292-0110	Open-label, randomized, cross-over	Healthy	PK, food effect	E/C/F/TAF on days 1, 8, and 15 under each of three conditions: fasted, low fat meal, high fat meal
292-1316	Open-label, cross-over	Healthy	DDI: E/C/F/TAF and SER	SER on day 1, E/C/F/TAF on days 1-12, SER + E/C/F/TAF on day 13
311-0101	Open-label, cross-over	Healthy	DDI: TAF and COBI	TAF on days 1-12, TAF+COBI on days 13-22

Table prepared by reviewer. Population refers to adults except study 292-0106. All treatments were dosed orally once daily with food except where indicated. SER=sertraline.

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2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

With the exception of study 120-0104 (PK and antiviral activity study), the primary endpoint in all of the clinical pharmacology studies was PK. In exposure-response analyses, HIV-1 RNA concentration was the response endpoint as it is a validated surrogate endpoint for antiretroviral (ARV) efficacy. Efficacy in clinical phase 3 trials was demonstrated based on showing noninferiority to the active control in the proportion of subjects with HIV-1 RNA <50 copies/mL after 48 weeks of treatment.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In plasma (and urine in certain studies), EVG, COBI, FTC, TAF, and TFV were measured in several studies, along with other analytes in select studies (iohexol, carbamazepine, carbamazepine-10,11-epoxide, and sertraline) using validated LC/MS/MS methods. TFV-DP was measured using methods that were not fully validated.

2.2.3.1 What are the characteristics of the exposure-response relationships for efficacy?

Exposure-response analyses were only conducted for TAF and TFV as part of the E/C/F/TAF development program. EVG and FTC exposure-response relationships were derived from monotherapy or E/C/F/TDF studies. COBI lacks antiviral activity.

EVG

EVG C_{min} is the PK parameter associated with antiviral activity.⁸ Mean C_{min} values from EVG 150 mg in monotherapy and dose ranging studies were in the flat portion of the exposure-antiviral activity curve.⁵ Also, in the E/C/F/TDF development program, efficacy was similar (~90%) across all four quartiles of EVG C_{min}.

COBI

Exposure-efficacy analyses were not described in the COBI development program, because COBI lacks antiviral activity and is used as a CYP3A inhibitor.

FTC

The relationship between FTC dose and antiviral activity was relatively flat at doses of 50-400 mg per day.⁵ FTC is intracellularly phosphorylated to the active FTC-triphosphate; steady-state intracellular FTC concentrations in PBMCs appear to be associated with antiviral activity.⁵

TAF and TFV

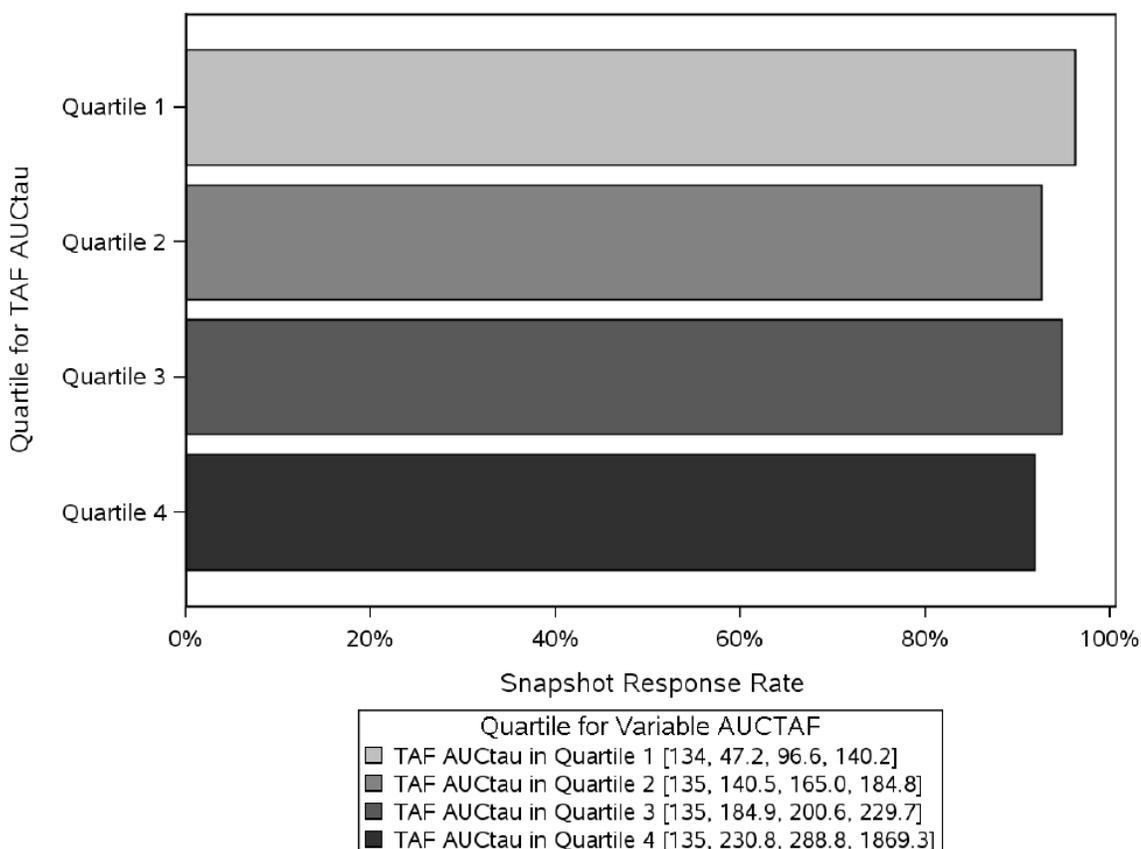
In TAF monotherapy study GS-US-120-0104, antiviral activity was associated with TAF dose (8-40 mg daily) and TFV-DP concentrations (when pooled across treatment groups). Similar activity was seen with TAF 8 mg compared with TDF 300 mg.

In the E/C/F/TAF phase 3 trials in the treatment-naïve population, TAF and TFV PK C_{max} and AUC were estimated by population PK. Virologic success was >93% across

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quartiles of TAF and TFV C_{max} and AUC, suggesting a likely flat exposure-response relationship for efficacy (Figure 2).

Figure 2. Percent virologic success in studies 104 and 111 by TAF AUC quartile.⁵



The TAF PK/PD analysis set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.

Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.

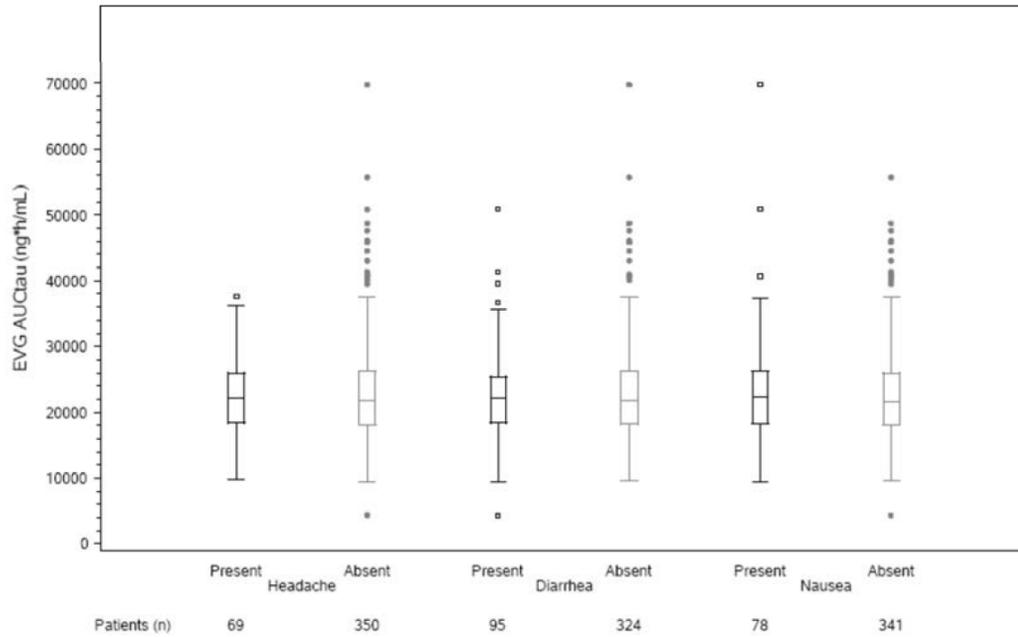
2.2.3.2 What are the characteristics of the exposure-response relationships for safety?

EVG, COBI, FTC

In the E/C/F/TDF program, relationships between EVG, COBI, and FTC AUC and C_{max} were separately evaluated in relation to common AEs (headache, nausea, and diarrhea) along with maximum changes from baseline in serum creatinine; no trends were noted (Figure 3, Figure 4, Figure 5).⁵

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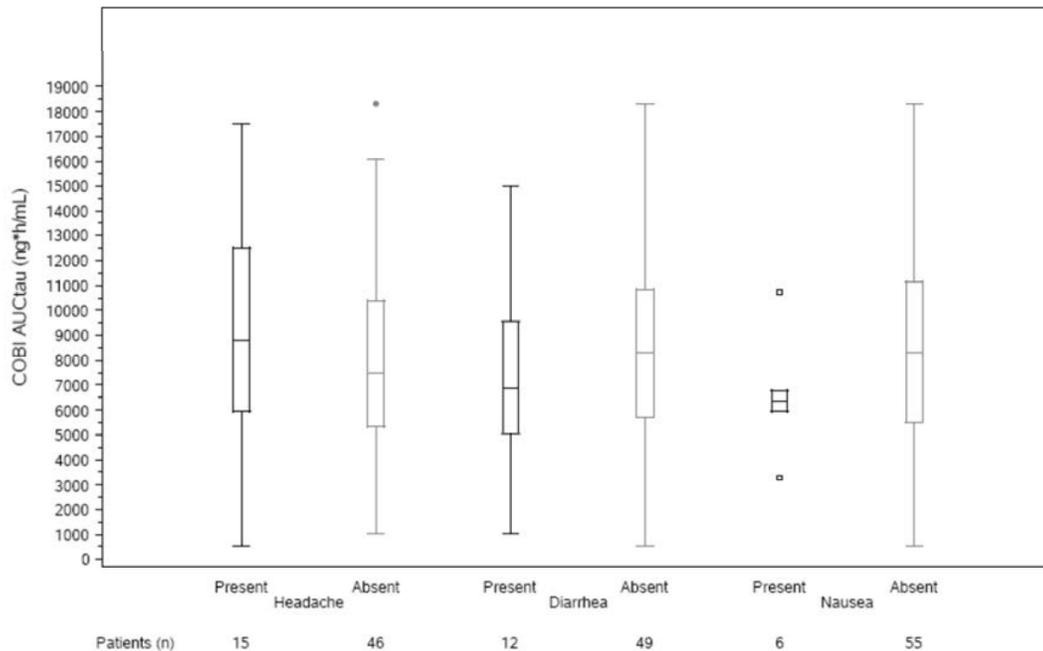
Figure 3. EVG exposure-response relationships for safety.⁵



IQR = interquartile range

Box plots denote median and IQR, whiskers denote maximum and minimum values within $1.5 \times$ IQR, and circles denote outliers $> 1.5 \times$ IQR.

Figure 4. COBI exposure-response relationships for safety.⁵

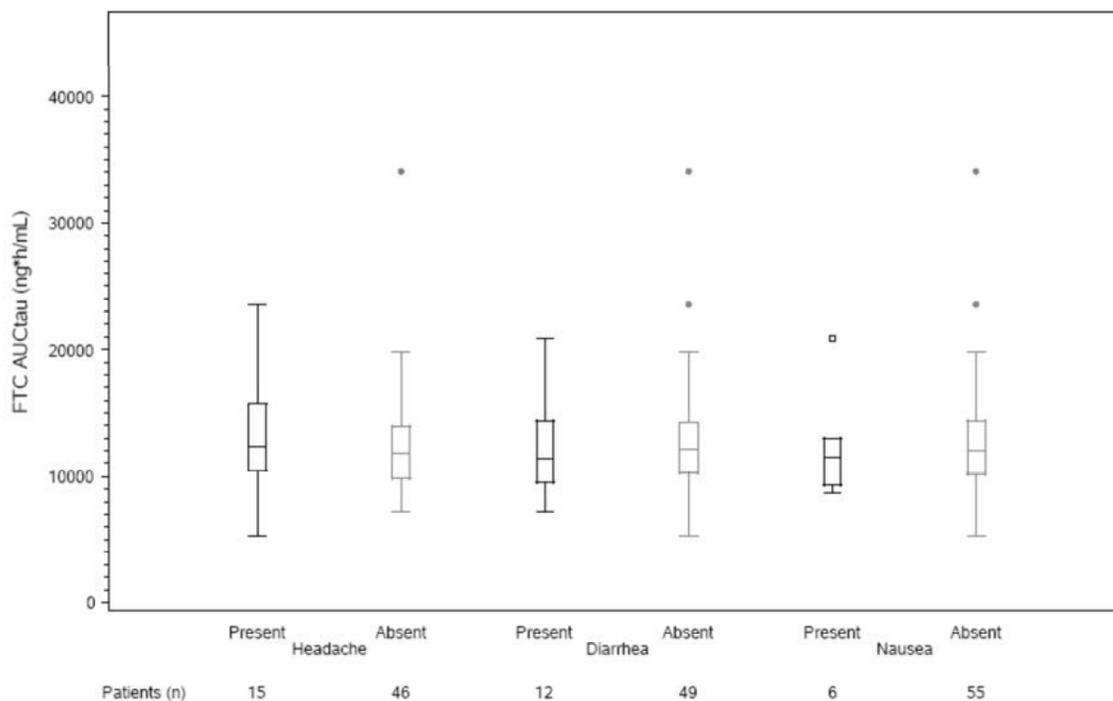


IQR = interquartile range

Box plots denote median and IQR, whiskers denote maximum and minimum values within $1.5 \times$ IQR, and circles denote outliers $> 1.5 \times$ IQR.

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Figure 5. FTC exposure-response relationships for safety.⁵



IQR = interquartile range

Box plots denote median and IQR, whiskers denote maximum and minimum values within $1.5 \times$ IQR, and circles denote outliers $> 1.5 \times$ IQR.

TAF and TFV

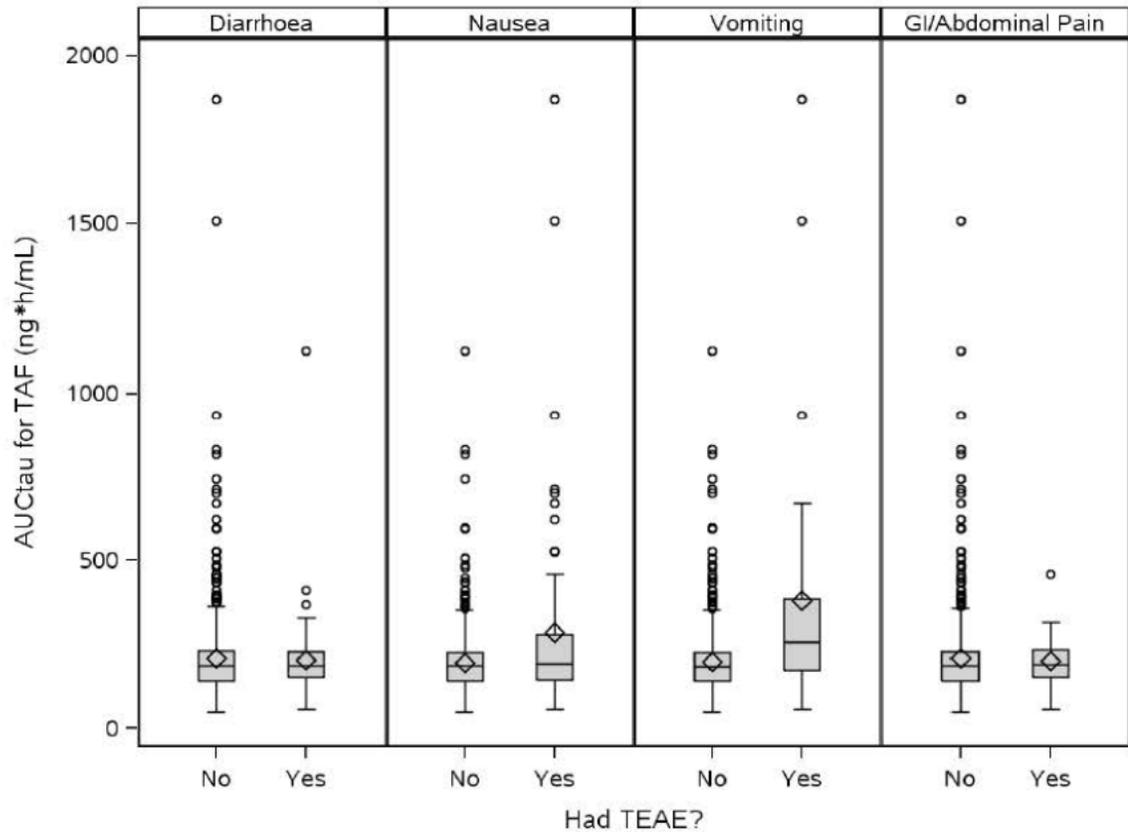
In the E/C/F/TAF phase 3 trials in the treatment-naïve population, TAF and TFV C_{max} and AUC were estimated by population PK.

Commonly observed adverse events (AEs) included nausea, diarrhea, vomiting, and GI/abdominal pain. Diarrhea and GI/abdominal pain were not associated with TAF or TFV exposures. TAF and TFV exposures were comparable in subjects with and without nausea and vomiting (Figure 6, Figure 7), however, logistic regression analysis showed a trend between TAF exposure and nausea at the highest 4% of TAF exposure, and vomiting was associated with the highest 19% of TAF exposure.

TDF-containing products have warnings in their US prescribing information for new onset or worsening renal impairment as well as decreases in bone mineral density (BMD). TAF is purported to result in an improved bone/renal safety due to lower systemic TFV exposure. Using a pooled dataset with subjects administered E/C/F/TAF in phase 3 studies 104 and 111, TAF and TFV C_{max} and AUC were not associated with a significant percent change from baseline in hip or spine week 48 BMD or maximum increase from baseline in serum creatinine (Figure 8, Figure 9). Note that the link between BMD and fracture risk is not established.

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Figure 6. TAF exposure-response relationships for safety.⁵



IQR = interquartile range; TEAE = treatment-emergent adverse event

Diarrhea: No (n = 454), Yes (n = 85); Nausea: No (n = 463), Yes (n = 76); Vomiting: No (n = 508), Yes (n = 31); GI/Abdominal Pains: No (n = 512), Yes (n = 27)

Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within $1.5 \times$ IQR, and circles denote outliers $> 1.5 \times$ IQR.

The TAF PK/PD analysis set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in

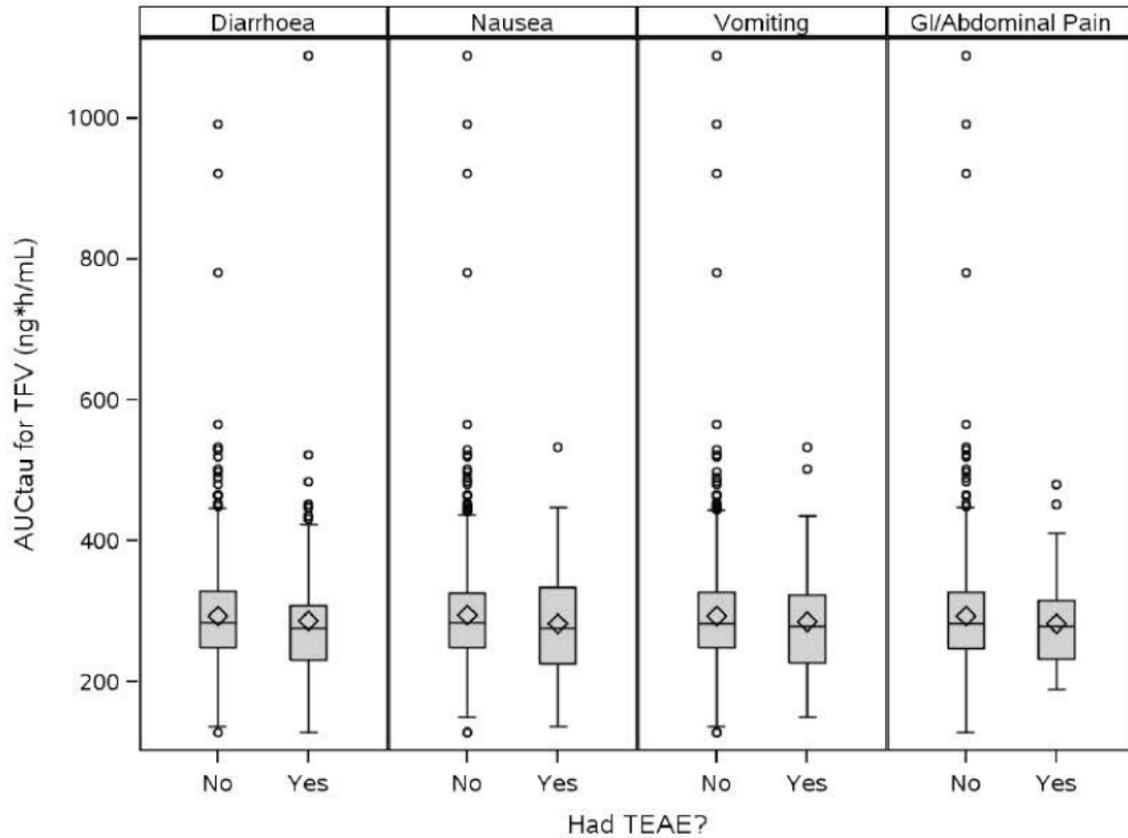
Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.

AEs were coded using MedDRA Version 17.0.

Diarrhoea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).

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Figure 7. TFV exposure-response relationships for safety.⁵



IQR = interquartile range; TEAE = treatment-emergent adverse event

Diarrhea: No (n = 696), Yes (n = 145); Nausea: No (n = 715), Yes (n = 126); Vomiting: No (n = 781), Yes (n = 60);

GI/Abdominal Pains: No (n = 788), Yes (n = 53)

Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within $1.5 \times$ IQR, and circles denote outliers $> 1.5 \times$ IQR.

The TFV PK/PD analysis set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.

AEs were coded using MedDRA Version 17.0.

Diarrhoea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).

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Figure 8. TFV AUC versus percent change from baseline in hip BMD from pooled dataset with subjects administered E/C/F/TAF in phase 3 studies 104 and 111.

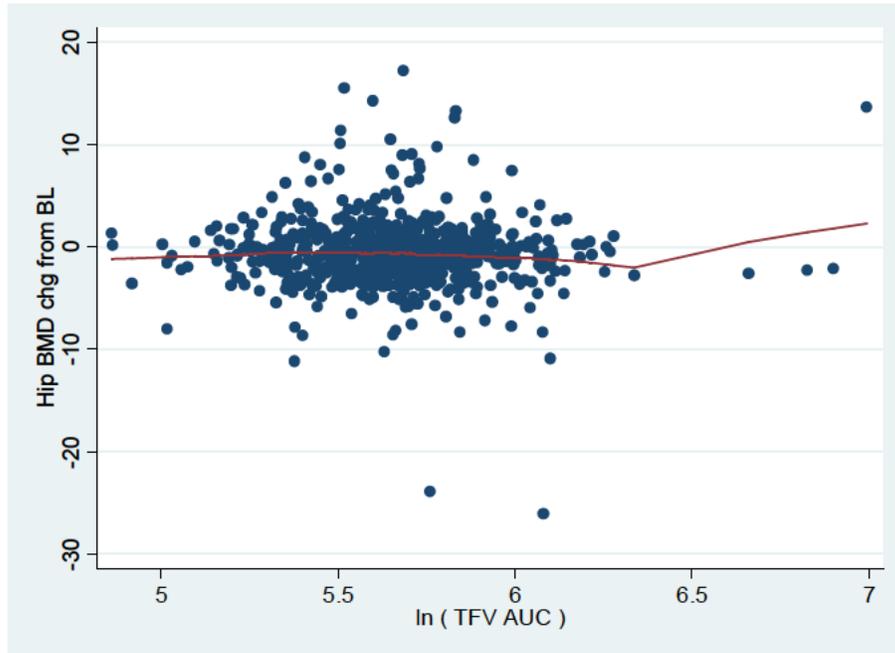


Figure prepared by reviewer. N=769 observations; $p=0.6$; $R^2=0.0004$.

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Figure 9. TFV AUC versus maximum change from baseline in serum creatinine from pooled dataset with subjects administered E/C/F/TAF in phase 3 studies 104 and 111.

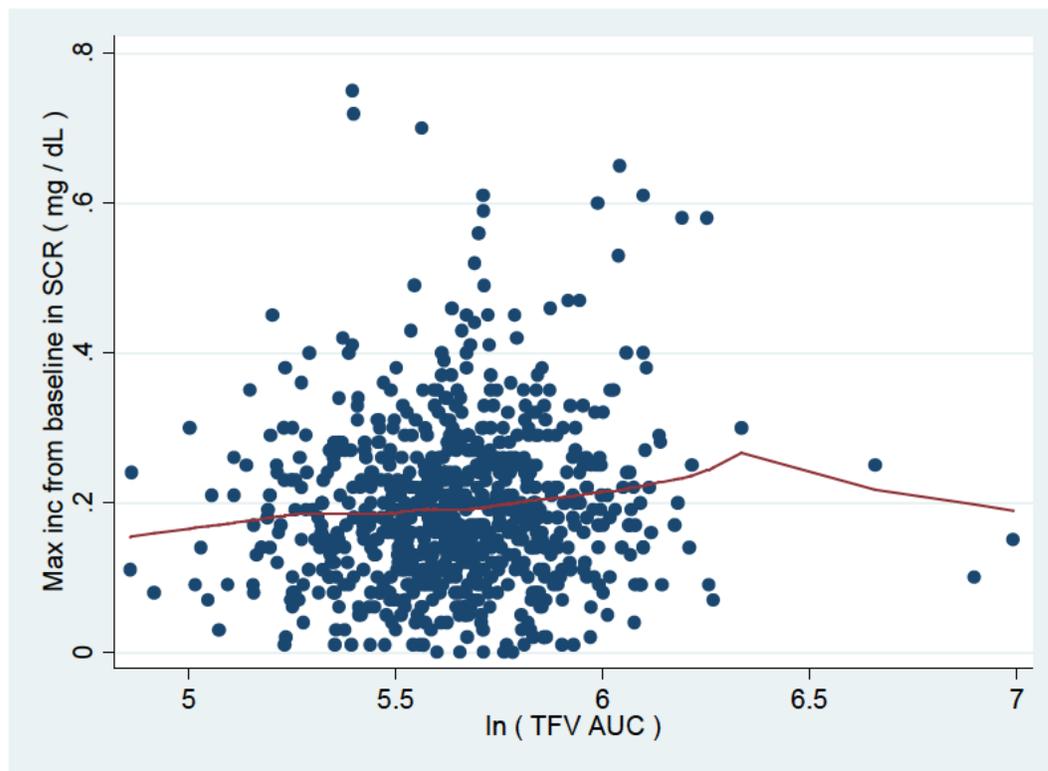


Figure prepared by reviewer. N=817 observations; $p=0.014$; $R^2=0.006$.

Relative to subjects administered E/C/F/TDF in phase 3 studies 104 and 111 in treatment naïve subjects, subjects administered E/C/F/TAF had greater increases in lipid values (Table 4). This was attributed to a postulated lipid-lowering effect of TFV that has been observed in several studies.^{9, 10} The mechanism of the purported effect of TFV on lipids is not known. Bioanalytical interference of the components of E/C/F/TAF with quantification of lipids is a theoretical concern that has not been ruled out experimentally. In subjects administered E/C/F/TAF, the change from baseline in lipid values was not associated with TAF exposure (Figure 10). However, because the only difference between E/C/F/TAF and E/C/F/TDF is TFV exposure, and the large difference in both TFV exposures and change from baseline lipid values between administration of E/C/F/TAF and E/C/F/TDF, increased lipid values appears to be inversely associated with TFV exposure.

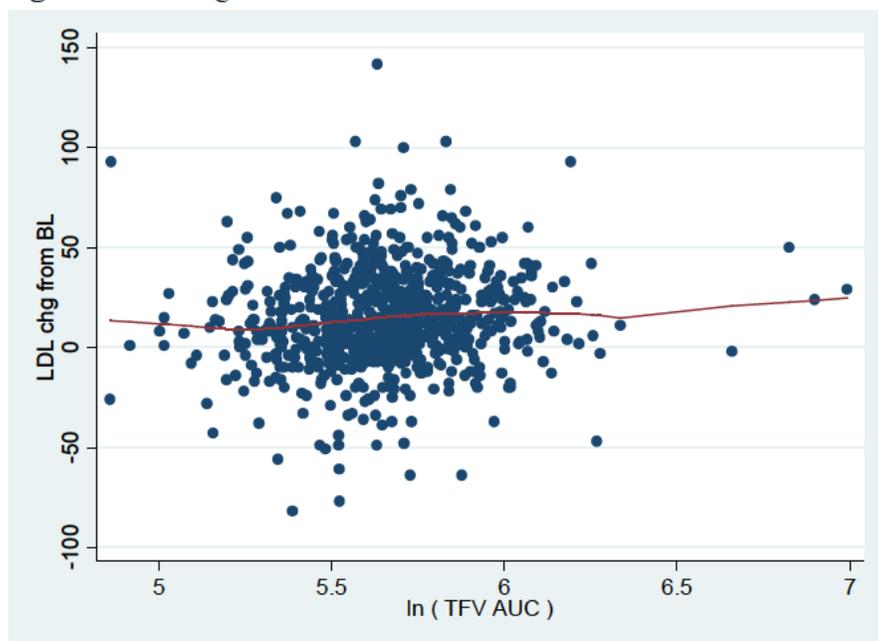
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Table 4. Mean change from baseline in lipid values in the two phase 3 studies in treatment-naïve subjects.

	E/C/F/TAF N=866		E/C/F/TDF N=867	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change ^a	mg/dL	Change ^a
Total Cholesterol (fasted)	(b) (4) [N=(b) (4)]	(b) (4) [N=(b) (4)]	166 [N=(b) (4)]	(b) (4) [N=(b) (4)]
HDL-cholesterol (fasted)	46 [N=(b) (4)]	+7 [N=(b) (4)]	45 [N=(b) (4)]	+4 [N=(b) (4)]
LDL-cholesterol (fasted)	(b) (4) [N=(b) (4)]	+15 [N=(b) (4)]	(b) (4) [N=(b) (4)]	(b) (4) [N=(b) (4)]
Triglycerides (fasted)	(b) (4) [N=841]	(b) (4) [N=789]	(b) (4) [N=(b) (4)]	+10 [N=(b) (4)]

Source: E/C/F/TAF proposed US prescribing information. ^aThe change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.

Figure 10. Change from baseline in LDL versus TFV AUC.



Source: Reviewer's analysis of E/C/F/TAF PK/PD dataset, consisting of subjects administered E/C/F/TAF in studies 104 and 111. N=775 observations, p=0.003, R-squared=0.01.

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Comparison of subjects administered E/C/F/TAF versus E/C/F/TDF in studies 104 and 111

Comparing subjects administered E/C/F/TAF versus E/C/F/TDF in studies 104 and 111, mean declines from baseline bone mineral density were significantly smaller in the E/C/F/TAF group (Table 5).⁷ As bone mineral density changes may not be predictive of fracture risk, the clinical significance of this finding is unclear.

Table 5. Mean declines in bone mineral density in subjects administered E/C/F/TAF and E/C/F/TDF.⁷

	E/C/F/TAF (N=866)	STB (N=867)	E/C/F/TAF vs. STB*	
			p-value	LSM difference (95% CI)
Baseline BMD (g/cm ²) (mean)	1.041	1.028	0.098	
Baseline BMD Z-score (mean)	-0.19	-0.19		
Week 24, n	789	815		
% change from BL, mean (SD)	-0.41 (2.15)	-1.73 (2.24)	<0.001	1.32 (1.11, 1.54)
Week 48, n	780	767		
% change from BL, mean (SD)	-0.66 (3.26)	-2.95 (3.41)	<0.001	2.29 (1.96, 2.62)
Week 72, n	101	88		
% change from BL, mean (SD)	0.74 (4.40)	-2.09 (4.14)	<0.001	2.83 (1.60, 4.06)

* P-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment as fixed effect
Values represent observed data in all patients with nonmissing baseline hip DXA
Sources: ISS Table 20.1.2 and ADDEXA dataset

Comparing subjects administered E/C/F/TAF (n=866) versus E/C/F/TDF (n=867) in studies 104 and 111, the mean \pm SD change from baseline in week 48 serum creatinine (mg/dL) was 0.08 \pm 0.12 and 0.11 \pm 0.22 (p<0.001), respectively.¹³

2.2.3.3 Does this drug prolong the QT/QTc Interval?

The effect of FTC or the combination E/C/F/TAF regimen on the QT interval is not known. In separate thorough QT studies, EVG, COBI, and TAF did not affect the QT/QTc interval.^{5, 14}

2.2.3.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationships?

Yes. Approved doses of EVG, COBI, and FTC were included in E/C/F/TAF. Also, in subjects administered E/C/F/TAF, TAF and TFV exposure-response relationships for efficacy and safety were flat.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters?

In healthy adults administered E/C/F/TAF, PK parameters were calculated after single (TAF and TFV) and multiple dosing (all components) (Table 6, Table 7, Table 8, Table 9).

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Table 6. E/C/F/TAF single and multiple dose PK parameters in healthy adults.

	AUCtau (ng*h/mL)		Cmax (ng/mL)	
	Day 1	Day 12	Day 1	Day 12
TAF	245 (17.2)*	250 (24.7)*	167 (38.6)	177 (35.1)
TFV	317 (27.2)	324 (15.4)	8.7 (13.2)	19.6 (13.9)

Table prepared by reviewer. Values are mean (CV%). *AUClast

Table 7. Multiple dose PK parameters in healthy subjects administered E/C/F/TAF FDC (n=19).

	AUCtau (ng*h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax (h)	T1/2 (h)
EVG	22,067 (26.3)	1,944 (23.9)	422 (54.4)	5.0 (4.0, 5.0)	10.0 (8.5, 11.0)
COBI	11,210 (27.4)	1,561 (26.1)	35 (85.5)	3.5 (3.0, 5.0)	3.4 (2.9, 3.6)
FTC	12,353 (13.5)	1,947 (21.2)	107 (25.8)	3.0 (2.0, 3.0)	10.0 (8.8, 18.5)
TAF	250 (24.7)*	177 (35.1)	Not detectable	1.5 (1.5, 2.0)	0.6 (0.4, 0.6)
TFV	324 (15.4)	19.6 (13.9)	11.4 (17.8)	2.0 (2.0, 3.0)	47 (35, 54)

Table prepared by reviewer. Values are mean (CV%) except for Tmax and t1/2, which are median (Q1, Q3). *AUClast. Source: study GS-US-292-0103.

Single dose PK was not evaluated in HIV-infected subjects administered E/C/F/TAF FDC. In HIV-infected subjects administered TAF 25 mg (equivalent exposure to TAF 10 mg coadministered with COBI 200 mg in E/C/F/TAF FDC) in monotherapy study GS-US-120-0104, single dose TAF and TFV PK parameters were calculated (Table 8). In phase 2 study GS-US-292-0102, multiple dose PK parameters of all components of E/C/F/TAF were calculated (Table 9). Subjects enrolled in intensive PK substudies in phase 3 studies GS-US-292-0104 (n=15) and GS-US-292-0111 (n=21) had similar multiple dose TAF and TFV PK parameters as in study GS-US-292-0102 and thus these studies were not reviewed.

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Table 8. TAF and TFV single dose PK parameters in HIV-infected subjects administered TAF 25 mg.

PK parameter	AUC* (ng*h/mL)	Cmax (ng/mL)	Cmin (ng/mL)
TAF	139.7 (57.8)	231.8 (76.8)	Not detectable
TFV	195.9 (27.2)	6.5 (40.1)	2.4 (23.5)

Table prepared by reviewer. Values are mean (CV%). *AUClast for TAF, AUCinf for TFV. Source: study GS-US-120-0104.

Table 9. Multiple dose PK parameters in HIV-infected subjects administered E/C/F/TAF FDC (n=19).

	AUCtau (ng*h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax (h)	T1/2 (h)
EVG	22,797 (34.7)	2113 (33.7)	287.3 (61.7)	3.9 (2.0, 4.0)	6.6 (6.2, 7.6)
COBI	9,459 (33.9)	1,450 (28.4)	20.6 (85.2)	3.0 (2.0, 4.0)	3.0 (2.8, 3.4)
FTC	11,714 (16.6)	2,056 (20.2)	95.2 (46.7)	1.5 (1.1, 2.0)	6.4 (5.8, 7.0)
TAF	227 (47.3)*	233 (64.6)	Not detectable	1.0 (0.75, 1.5)	0.47 (0.4, 0.9)
TFV	362 (14.8)	18.2 (12.4)	11.4 (17.9)	3.0 (1.5, 4.0)	38 (33, 46)

Table prepared by reviewer. Values are mean (CV%) except for Tmax and t1/2, which are median (Q1, Q3). *AUClast. Source: study GS-US-292-0102.

2.2.4.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

In healthy subjects and HIV-infected subjects administered E/C/F/TAF, multiple dose PK parameters were comparable (Table 7, Table 9).

2.2.4.3 What are the characteristics of drug absorption?

After multiple dosing, the components of E/C/F/TAF FDC are absorbed in HIV-infected subjects with a median Tmax of 1-4 hours (Table 9).

EVG and COBI are recommended to be administered with food, while FTC may be taken without regard to food. In a food effect study where subjects were administered E/C/F/TAF, only TAF and TFV were measured; relative to the fasted state, TAF and TFV exposures were not significantly altered by administration of E/C/F/TAF following low-fat or high-fat meals (Table 10). In subjects administered E/C/F/TAF and its components as single agents with food in cross-over study 292-0103, PK was comparable for the components of E/C/F/TAF versus single agents, suggesting no difference in food effect for E/C/F/TAF versus single agents. Phase 3 trials administered E/C/F/TAF with food and the the E/C/F/TAF label states that it is to be administered with food.

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After administration of E/C/F/TAF, the bioavailabilities of its components are unknown.

Table 10. TAF and TFV food effect in healthy subjects administered E/C/F/TAF.

	TAF		TFV	
	AUCinf	Cmax	AUCinf	Cmax
Low-fat meal	↑15 (7, 24)	↓32 (21, 41)	↑14 (8, 19)	↓16 (7, 24)
High-fat meal	↑18 (9, 26)	↓37 (27, 45)	↑13 (7, 18)	↓16 (7, 25)

Table prepared by reviewer. Values are percent change (90% CI) relative to the fasted state for healthy subjects administered E/C/F/TAF in study GS-US-292-0110.

2.2.4.4 What are the characteristics of drug distribution?

Protein binding and blood-to-plasma ratios for the components of E/C/F/TAF are described in Table 11.

Table 11. E/C/F/TAF distribution.

	Fraction bound to human plasma proteins	Blood-to-plasma ratio
EVG	98-99%	0.73
COBI	97-98%	0.5
FTC	<4%	1
TAF	80%	0.6 (0.25 h postdose) 2.4 (216 h postdose)
TFV	<0.7%	Not reported

Table prepared by reviewer.

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

In mass balance study GS-US-190-0109 where subjects were administered a single 25 mg dose of radiolabeled TAF, TFV represented 86% and 99% of the radioactivity recovered in urine and feces, respectively (total radioactivity recovery was 84%); <1% of the dose was eliminated in the urine as TAF.

2.2.4.6 What are the characteristics of drug metabolism?

See Table 12 and Figure 11.

2.2.4.7 What are the characteristics of drug elimination?

Route of elimination and metabolic pathways for the components of E/C/F/TAF are summarized in Table 12; elimination half-lives are listed in Table 9.

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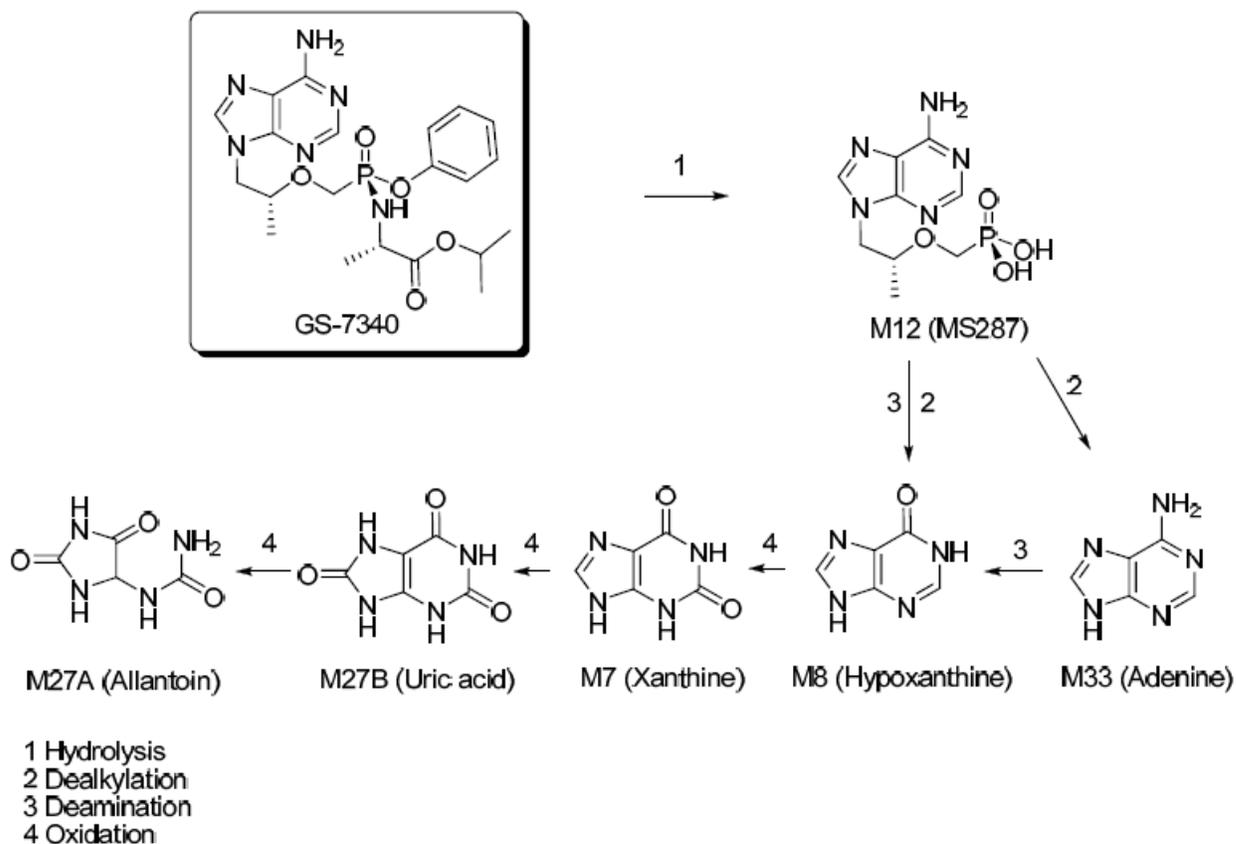
Table 12. E/C/F/TAF elimination.

	Route of elimination	Metabolism
EVG	Hepatobiliary	CYP3A (major), UGT1A1/3 (minor)
COBI	Hepatobiliary	CYP3A (major) and CYP2D6 (minor)
FTC	Renal via glomerular filtration and active tubular secretion	Not significant
TAF	Conversion to TFV	Cathepsin A (PBMCs) and carboxylesterase 1 (hepatocytes)
TFV	Renal via glomerular filtration and active tubular secretion	Not a substrate of CYP enzymes

Table prepared by reviewer. Source: US prescribing information (EVG, COBI, FTC, TFV) and E/C/F/TAF Clinical Pharmacology summary (TAF).

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Figure 11. Tentative TAF biotransformation pathway.



Note: M12 = TFV.

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

Source: Study GS-US-120-0109 CSR.

2.2.4.8 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

See Table 13.

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Table 13. Dose proportionality.

	Product administered	Dose range	Increase in analyte exposure with increasing dose
EVG	EVG single agent	85-150 mg	Less than proportional
COBI	COBI single agent	50-400 mg	Greater than proportional
FTC	FTC single agent	25-200 mg	Proportional
TAF	TAF single agent	8-40 mg	More than proportional
TFV			

Table prepared by reviewer. Sources: EVG, FTC = US prescribing information; COBI = EMA prescribing information; TAF, TFV= study GS-US-120-0104. TFV-DP exposures from study 120-0104 not listed because nonvalidated bioanalytical methods were used.

2.2.4.9 How do the PK parameters change with time following chronic dosing?

In healthy adults administered E/C/F/TAF, TAF and TFV single and multiple dose PK parameters were comparable with the exception of TFV C_{max}, which approximately doubled after multiple dosing (Table 6, Table 7).

In HIV-infected subjects, single and multiple dose parameters were calculated in different studies and PK for all components of E/C/F/TAF were calculated only after multiple doses. After multiple doses, TAF C_{max} was similar and AUC was increased, while all TFV parameters were increased (Table 8, Table 9). TAF accumulation is not expected as it is not detectable beyond 8 hours postdose and has a 0.5 hour half-life, while TFV accumulation is expected due to its long half-life. It is unclear why TFV AUC increased upon multiple doses in HIV-infected subjects but not in healthy subjects.

2.2.4.10 What is the inter- and intra-subject variabilities of PK parameters in healthy volunteers and patients?

Arbitrarily defining CV% variability as low = <30%, moderate = ≥ 30 - <50%, and high = >50%, variability in healthy and HIV-infected subjects was generally low to moderate, with the exception of highly variable EVG and COBI C_{min} in healthy and HIV-infected subjects, and highly variable TAF C_{max} in HIV-infected subjects (Table 14). For all components, relative to healthy adults, variability categories in HIV-infected subjects either stayed the same or increased (Table 14).

There was insufficient data to assess intra-subject variability.

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Table 14. Variability in multiple dose PK parameters.

	Healthy adults (n=19)			HIV-infected subjects (n=19)		
	AUC	Cmax	Cmin	AUC	Cmax	Cmin
EVG	L	L	H	M	M	H
COBI	L	L	H	M	L	H
FTC	L	L	L	L	L	M
TAF	L	M	Not detectable	M	H	Not detectable
TFV	L	L	L	L	L	L

Table prepared by reviewer. L = low, M= moderate, H = high. Data source: Table 7, Table 9.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Race

In study GS-US-292-0108, where E/C/F/TAF was administered to healthy Japanese and Caucasian subjects, steady-state exposures were decreased in Japanese subjects (Table 15). Based on exposure-response relationships, these exposure changes are not clinically relevant.

Table 15. Relative percent exposure change (90% CI) in Japanese versus Caucasians on the most sensitive PK parameter.

Analyte	Single dose	Multiple dose
EVG	AUC ↓17 (-38, +11)	Cmin ↓35 (-59, +2)
COBI	Cmax ↑25 (-12, +77)	Cmin ↓32 (-52, -4)
FTC	Cmax ↑12 (-6, +32)	Cmin ↓24 (-42, -1)
TAF	Cmax ↑44 (+10, +89)	AUC ↓12 (-33, +17)
TFV	Cmax ↑64 (+12, +142)	Cmin ↓23 (-37, -7)

Table prepared by reviewer. Source: study GS-US-292-0108.

Adolescents

Approval of E/C/F/TAF in adolescents (age >12 - <18 years) was based on exposure matching with adults in study GS-US-292-0106, where 24 HIV-infected adolescents were administered E/C/F/TAF and steady-state PK was evaluated. Compared to adults (pooled dataset with HIV-infected and healthy adults) administered E/C/F/TAF, adolescent exposures were decreased for EVG Ctrough (Ctrough >45 ng/mL is associated with

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antiviral activity)⁸, TAF, and COBI (Table 16). Though adolescent EVG Ctrough was decreased compared to adults, all adolescents had values above the target (Figure 12). When compared only to HIV-infected adults (a more clinically relevant comparison than the pooled dataset), adolescent EVG exposures (including Ctrough) were similar, while TAF and COBI exposures remained decreased (Table 17). TAF has flat exposure-response relationships for efficacy, thus 30% reduced exposures are acceptable. COBI exposures are of secondary importance, as the purpose of COBI is to increase the exposure of EVG (it also increases TAF exposures). In conclusion, while exposures from administration of E/C/F/TAF were decreased in adolescents compared to adults, based on exposure-response relationships, exposures were overall acceptable.

Table 16. E/C/F/TAF PK comparison in adolescents versus adults (HIV-infected plus HIV-uninfected).

PK Parameter	GLSMs		GLSM Ratio (%)	90% CI
	GS-US-292-0106 (Test) (N = 24)	GS-US-292-0102, GS-US-292-0103 (Reference) (N = 52)		
EVG				
AUC _{tau} (ng•h/mL)	23128.88	21865.51	105.78	94.66, 118.21
C _{max} (ng/mL)	2186.24	2023.29	108.05	97.87, 119.30
C _{trough} (ng/mL)	234.44	338.24	69.31	52.79, 91.01
TAF				
AUC _{last} (ng•h/mL)	159.50	225.53	70.72	56.12, 89.11
C _{max} (ng/mL)	135.19	173.97	77.71	59.88, 100.85
TFV				
AUC _{tau} (ng•h/mL) ^a	282.64	322.64	87.60	81.23, 94.47
C _{max} (ng/mL)	17.18	18.78	91.50	83.93, 99.75
C _{trough} (ng/mL)	9.73	11.20	86.94	79.73, 94.81
COBI				
AUC _{tau} (ng•h/mL) ^a	7762.56	9832.00	78.95	68.68, 90.75
C _{max} (ng/mL)	1144.60	1456.27	78.60	69.71, 88.62
C _{trough} (ng/mL) ^{b,c}	13.42	22.21	60.41	39.13, 93.26
FTC				
AUC _{tau} (ng•h/mL)	14,007.48	11,964.30	117.08	106.68, 128.49
C _{max} (ng/mL)	2209.14	1947.42	113.44	103.49, 124.35
C _{trough} (ng/mL) ^a	94.98	97.42	97.49	83.42, 113.94

GLSM = geometric least-squares mean

a N = 23 for the Test group

b N = 15 for the Test group

c N = 51 for the Reference group

Source: study GS-US-292-0106.

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Figure 12. EVG C_{trough} in adults and adolescents administered E/C/F/TAF.

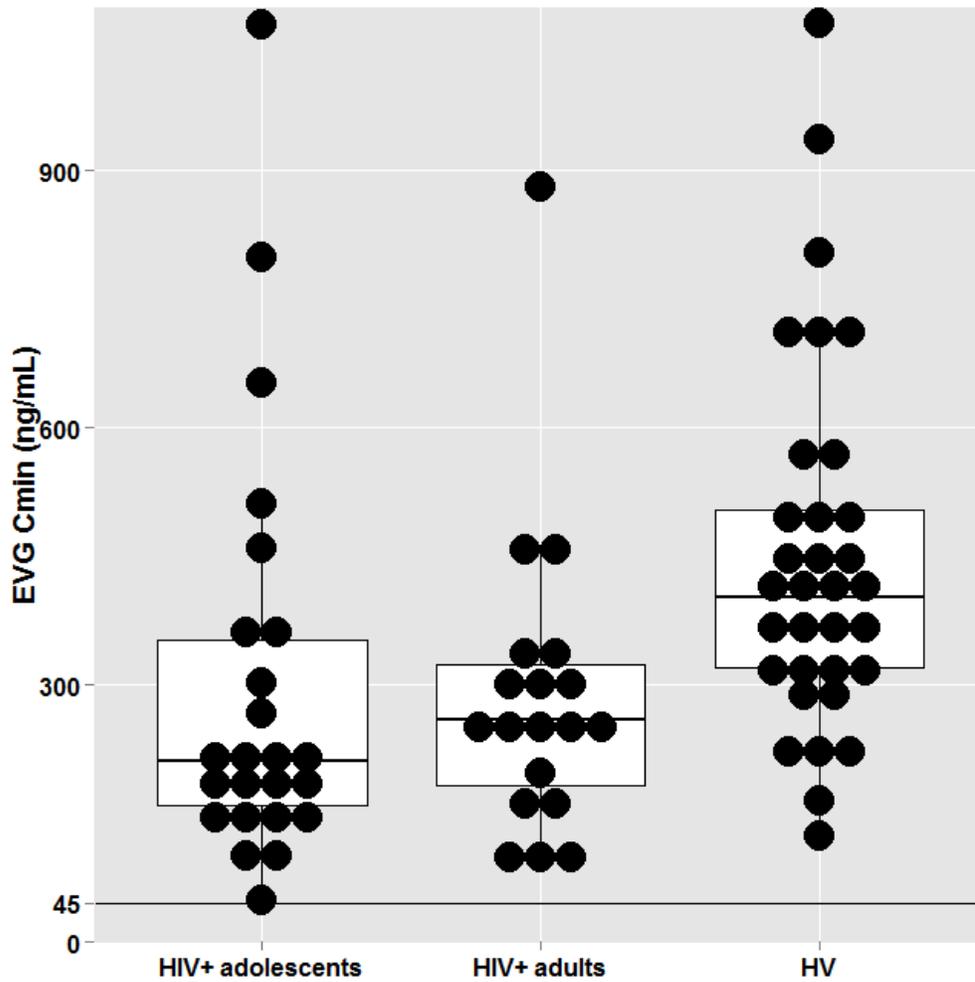


Figure prepared by reviewer.

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Table 17. PK comparison of adolescents versus HIV-infected adults administered E/C/F/TAF.

PK Parameter	GLSMs		GLSM Ratio (%)	90% CI
	Test (Study GS-US-292-0106) (N = 24)	Reference (Historical Control) (N = 19)		
EVG				
AUC _{tau} (ng•h/mL)	23128.88	21553.74	107.31	91.55, 125.78
C _{max} (ng/mL)	2186.24	1997.55	109.45	93.88, 127.59
C _{trough} (ng/mL)	234.44	247.71	94.64	68.45, 130.86
TAF				
AUC _{last}	159.50	206.19	77.35	58.60, 102.12
C _{max}	135.19	191.23	70.69	49.94, 100.07
TFV				
AUC _{tau} (ng•h/mL)	282.64	322.96	87.52	80.22, 95.47
C _{max} (ng/mL)	17.18	18.07	95.13	86.55, 104.55
C _{trough} (ng/mL)	9.73	11.27	86.38	77.96, 95.70
COBI				
AUC _{tau} (ng•h/mL)	7762.56	8975.72	86.48	72.36, 103.36
C _{max} (ng/mL)	1144.60	1400.19	81.75	70.44, 94.86
C _{trough} (ng/mL)	13.42	17.01	78.87	48.20, 129.06
FTC				
AUC _{tau} (ng•h/mL)	14,007.48	11576.55	121.00	108.92, 134.42
C _{max} (ng/mL)	2209.14	2014.35	109.67	97.81, 122.97
C _{trough} (ng/mL)	94.98	89.11	106.58	87.89, 129.25

Source: study GS-US-292-0106. Reference=HIV-infected adults.

Hepatic impairment

In a single dose (TAF 25 mg) study in subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment (study GS-US-120-0114), relative to matched controls, TAF and TFV exposures in subjects with hepatic impairment were altered by ≤13%. Based on exposure-response relationships, these exposure changes are not clinically relevant. We agree with proposed E/C/F/TAF labeling wherein there is no dose adjustment for Child-Pugh A-B, and E/C/F/TAF is not recommend for Child-Pugh C; these hepatic impairment dosing recommendations are equivalent to those for E/C/F/TDF.

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Table 18. Summary of TAF and TFV AUC in hepatic impairment relative to controls.

	TAF	TFV
Hepatic impairment	AUC _{inf} % change (90% CI) relative to controls	AUC _{inf} % change (90% CI) relative to controls
Mild	↓8 (-34, +29)	↓11 (33, 18)
Moderate	↑13 (-13, +45)	↓3 (-23, 23)

Table prepared by reviewer.

Renal impairment

Study GS-US-292-0112 – mild to moderate renal impairment

A study in renally impaired subjects was conducted because two components, TFV and FTC, are primarily renally eliminated. In this study of HIV-infected subjects with mild to moderate renal impairment, baseline eGFR as measured by creatinine using the Cockcroft-Gault equation versus Cystatin C using the CKD-Epi equation differed significantly (Table 19). This difference was hypothesized to be due to inhibition of tubular secretion of creatinine in patients taking cobicistat or ritonavir, resulting in artificially high creatinine values and thus lower eGFR_{CG} values. However, this hypothesis was not supported, as the discrepancy between mean eGFR measured by creatinine versus Cystatin C was present for subjects on COBI or RTV at baseline versus those not on COBI/RTV (Table 19).¹⁵ In addition, in a PK substudy, baseline eGFR was closer to aGFR for creatinine versus Cystatin C (Table 20). Thus the use of creatinine and the Cockcroft-Gault equation used to determine baseline renal function for enrollment was considered acceptable.

Table 19. Baseline eGFR as measured by creatinine versus Cystatin C.¹⁵

	Cockcroft-Gault	CKD-Epi, Creatinine	CKD-Epi, Cystatin C
Mean eGFR (SD)	54.8 (11.6)	54.7 (14.4)	70.5 (21.1)
Baseline COBI/RTV ¹	54.9 (11.3)	55.3 (14.0)	70.4 (19.8)
No baseline COBI/RTV	54.6 (11.9)	54.1 (14.8)	70.6 (22.3)

Baseline COBI/RTV (n=115); No baseline COBI/RTV (n=133).

Table 20. Baseline iohexol aGFR versus creatinine and Cystatin eGFR in PK substudy (n=32).¹⁵

	Mean (SD)	Median (Q1, Q3)
Iohexol GFR	60.1 (19.1)	59.6 (46.2, 71.4)
eGFR		
Cockcroft-Gault	56.7 (11.8)	57.6 (48.3, 64.4)
CKD-Epi, Creatinine	57.8 (17.0)	54.7 (48.3, 65.0)
CKD-Epi, CysC	69.7 (21.0)	72.6 (56.6, 79.9)

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FTC is labeled to be dosed 200 mg every other day in subjects with creatinine clearance (CrCL) of 30-49 mL/min. This is based on findings from a single dose PK study in subjects with renal impairment, where relative to subjects with normal renal function, FTC exposure was increased 2-fold in subjects with CrCL 30-49 mL/min. The E/C/F/TAF label (E/C/F/TAF also contains FTC 200 mg) proposes no dose adjustment for subjects with CrCL of ≥ 30 mL/min. The basis for the proposed E/C/F/TAF dosing is study GS-US-292-0112, which enrolled 242 HIV virologically-suppressed subjects with mild (CrCL of 50-69 mL/min, n=162) to moderate (CrCL of 30-49 mL/min, n=80) renal impairment. Compared to PK data from a phase 2 study in HIV-infected subjects with normal renal function, subjects with moderate renal impairment had ~2-fold increased FTC and TFV AUC values (Table 21, Table 22).

In subjects without renal impairment administered E/C/F/TDF (includes FTC 200 mg daily), FTC exposure-response relationships for safety appeared to be flat (Figure 5). Study GS-US-292-0112 is the first safety study in which FTC 200 mg daily was administered to subjects with renal impairment. In this study, FTC was only measured in intensive PK substudy participants; only TAF and TFV were measured in the single PK sample collected in all subjects. Thus FTC exposure-response relationships for safety have not been evaluated in subjects with renal impairment and the clinical significance of 2-fold increased FTC exposures is unclear. See the Clinical review for the evaluation of overall safety in this study, which will likely form the basis for acceptability of dosing E/C/F/TAF in subjects with CrCL of ≥ 30 - < 50 mL/min.²

Table 21. Summary of PK of E/C/F/TAF in HIV-infected subjects with normal renal function relative to renally impaired subjects in the current study.

Analyte	PK parameter	Normal renal function*	Current study eGFR _{CG} ≥ 30 - < 50 mL/min	Current study eGFR _{CG} ≥ 50 - 69 mL/min
EVG	C _{min} (ng/mL)	287 (62)	425 (83)	332 (72)
COBI	AUC _{tau} (ng*h/mL)	9459 (34)	11,317 (49)	9394 (43)
FTC	AUC _{tau} (ng*h/mL)	11,714 (17)	25,140 (22)	19380 (23)
TAF	AUC _{clast} (ng*h/mL)	228 (47)	341 (60)	227 (44)
TFV	AUC _{tau} (ng*h/mL)	326 (15)	680 (29)	504 (29)

Table prepared by reviewer. *Data from Phase 2 study GS-US-292-0102 (n=19). Values are mean (CV%).

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Table 22. Percent changes in PK parameters of E/C/F/TAF in HIV-infected subjects with renal impairment compared to HIV-infected subjects with normal renal function.

Analyte	PK parameter	Current study eGFR _{CG} 30- <50 mL/min	Current study eGFR _{CG} ≥50- 69 mL/min
EVG	C _{min} (ng/mL)	↑48	↑16
COBI	AUC _{tau} (ng*h/mL)	↑20	↓1
FTC	AUC _{tau} (ng*h/mL)	↑115	↑65
TAF	AUC _{last} (ng*h/mL)	↑50	↔
TFV	AUC _{tau} (ng*h/mL)	↑109	↑55

Table prepared by reviewer. Values are percent change (parameter mean in renally impaired group/parameter mean in normal renal function group*100) relative to subjects with normal renal function (Phase 2 study GS-US-292-0102, n=19).

Study GS-US-120-0108 – severe renal impairment

In this study, subjects with severe renal impairment (CrCL ≥15 mL/min to ≤29 mL/min, n=14) and matched controls (n=13) received a single TAF 25 mg dose. Relative to healthy controls, subjects with severe renal impairment had increased exposures (Table 23). Given flat exposure-response relationships for TAF, the increase in TAF exposure is not considered clinically relevant. Although following administration of TAF 25 mg to subjects with severe renal impairment resulted in TFV AUC increased almost 6-fold, exposures are still lower than observed after administration of TDF 300 mg to subjects without renal function. There is no proposal to dose E/C/F/TAF in patients with severe renal impairment due to the FTC component (discussed above); the minimum CrCl at which E/C/F/TAF is being considered for administration is either 30 mL/min or 50 mL/min.

Table 23. Percent changes or fold change (90% CI) in plasma PK parameters of E/C/F/TAF in subjects with severe renal impairment (n=14) compared to subjects with normal renal function (n=13).

Analyte	AUC _{inf} (ng*h/mL)	C _{max} (ng/mL)
TAF	↑92% (+38%, +167%)	↑16% (+24%, +160%)
TFV	↑5.7-fold (4.6, 7.2)	↑2.8-fold (2.3, 3.4)

Table prepared by reviewer.

Population PK

Nine studies were included in the TAF and TFV population PK analysis. The effect of age, sex, race, weight, BMI, BSA, and CrCL on TAF and TFV exposure were evaluated. There were no significant covariates in the TAF model. Based on statistical criteria, significant covariates in the TFV model were CrCL, HIV status (infected versus healthy), sex, and black race. Each of these covariates resulted in a <2-fold TFV exposure change.

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As TFV exposure from E/C/F/TAF is 90% lower compared to E/C/F/TDF, the <2-fold differences in TFV exposure due to covariate effects are not clinically significant.

2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?

Dose adjustments are not possible as E/C/F/TAF is a FDC tablet with one formulation. E/C/F/TAF can be administered without regard to age (indicated for age ≥ 12 years), weight, race, and gender. In subjects with renal impairment, E/C/F/TAF can be administered to patients with CrCL ≥ 50 mL/min; dosing in CrCL ≥ 30 - < 50 mL/min is under review.² E/C/F/TAF can be administered to patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, and is not recommended in subjects with severe (Child-Pugh C) hepatic impairment.

2.3.3 What pregnancy and lactation use information is there in the label?

See the Pharmacology/Toxicology review for nonclinical data regarding E/C/F/TAF and pregnancy/lactation. The following selected information is from the proposed E/C/F/TAF labeling:

“There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, E/C/F/TAF should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that elvitegravir, cobicistat, and tenofovir are secreted in milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. It is not known whether elvitegravir, cobicistat, or tenofovir alafenamide is excreted in human milk.”

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

As TAF has minimal drug-drug interaction potential as a perpetrator, and the only difference between E/C/F/TAF and E/C/F/TDF is the TAF component, drug interaction labeling for E/C/F/TAF was primarily derived from the E/C/F/TDF US prescribing information, and was therefore previously reviewed by FDA. Several drug-drug interaction studies were conducted as part of the E/C/F/TAF development program, and are described below.

2.4.2 What are the drug-drug interactions?

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. E/C/F/TAF contains components that are inhibitors (COBI) and substrates (all components) of drug metabolizing enzymes and transporters. See details below.

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2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

EVG, COBI, and TAF are enzyme substrates (Table 12). The role of genetics in the metabolism of EVG and COBI has not been assessed.¹⁶⁻¹⁸ A CES1 variant associated with enzyme activity, G143E, has a 2-4% frequency of the heterozygous genotype. Forty-two hepatitis B virus-infected subjects were genotyped for this variant; all subjects possessed the wild-type genotype.¹⁹ As CES1 variants are rare and TAF is also metabolized by CYP2A6, genetics is not likely to significantly impact TAF metabolism.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

EVG and TAF have weak effects on CYP3A that are expected to be outweighed by COBI (Table 24).

Table 24. Components of E/C/F/TAF as an inhibitor of enzymes.

	Enzyme
EVG	Weak inhibitor and inducer of CYP3A
COBI	CYP3A, CYP2D6
FTC	None
TAF	Weak inhibitor of CYP3A
TFV	None

Table prepared by reviewer. Source: US prescribing information (COBI, FTC, TFV), FDA NDA Clinical Pharmacology review (EVG), and E/C/F/TAF Clinical Pharmacology summary (TAF).

2.4.2.4 Is the drug an inhibitor and/or an inducer of PGP transport processes?

COBI and EVG (weak) are Pgp inhibitors.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Yes. EVG and COBI are substrates and inhibitors of transporters BCRP, OATP1B1, and OATP1B3, TAF is a substrate of BCRP, OATP1B1, and OATP1B3, and FTC and TFV are substrates of renal transporters OAT1 (TFV only) and OAT3 (FTC and TFV) (Table 25). In addition, EVG and COBI are inhibitors of BCRP, OATP1B1, and OATP1B3 (Table 26).

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Table 25. Components of E/C/F/TAF as a substrate of transporters.⁵

Transporter	Substrate Assessment (y/n)				
	EVG	COBI	FTC	TAF	TFV
MDR1	y	y	n	y	n
BCRP	y	y	n	y	n
OATP1B1	y	y	ND	y	ND
OATP1B3	y	y	ND	y	ND
OAT1	ND	ND	n	n	y
OAT3	ND	ND	y	n	y
OCT1	n	n	ND	n	n
OCT2	ND	y	n	ND	n
MRP1	ND	ND	ND	ND	n
MRP2	ND	ND	ND	ND	n
MRP3	ND	ND	n	ND	ND
MRP4	ND	ND	ND	ND	y

BCRP = breast cancer resistance protein; MDR1 = multidrug resistance protein 1; MRP1, 2, 3, or 4 = multidrug resistance associated protein 1, 2, or 4; n = no; ND = not determined; OAT1 or 3 = organic anion transporter 1 or 3; OATP1B1 or B3 = organic anion transporting polypeptide 1B1 or B3; OCT1 or 2 = organic cation transporter 1; y = yes

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Table 26. Components of E/C/F/TAF as an inhibitor of transporters.⁵

Transporter	IC ₅₀ (μM)				
	EVG	COBI	FTC	TAF	TFV
MDR1	69.7	36	>100	>100	>1000
BCRP	88.9	59	>100	>100	>100
BSEP	>20	6.5	>100	>100	>100
OATP1B1	>2	3.50	>100	>100	>100
OATP1B3	0.44	1.88	>100	>100	>100
MATE1	2.0	1.87	>100	>100	>300
MATE2-K	ND	33.5	ND	ND	ND
OAT1	>20	>100	>100	>100	33.8 ^a
OAT3	>20	>100	>100	>100	>1000
OCT1	>20	14.7	>100	>100	>100
OCT2	>20	14.4	>100	>100	>300
OCTN1	ND	2.49	ND	ND	ND
MRP1	ND	45-90	ND	ND	>500
MRP2	>20	45-90	>100	ND	>100
MRP4	>20	20.7	>100	ND	>1000 ^b

BCRP = breast cancer resistance protein; BSEP = bile salt excretory pump; MATE1 or 2-K = multidrug and toxin extrusion protein 1 or 2-K; MDR1 = multidrug resistance protein 1; MRP1 2, 3, or 4 = multidrug resistance associated protein 1, 2, or 4; ND = not determined; OAT1 or 3 = organic anion transporter 1 or 3; OATP1B1 or B3 = organic anion transporting polypeptide 1B1 or B3; OCT1 or 2 = organic cation transporter 1; OCTN1 = organic cation transporter novel, type 1

a Binding constant for uptake into CHO cells reported by Cihlar et al, 2009 {2520}

b Imaoka et al 2007 {10260}

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2.4.2.6 Does the label specify co-administration of another drug?

No. However, the tablet contains four drugs, EVG, COBI, FTC, and TAF.

2.4.2.7 What other co-medications are likely to be administered to the target population?

The E/C/F/TAF labeling addresses drug-drug interactions with medications in various drug classes likely administered in adults in the US (includes antihypertensives, antibiotics, statins, oral contraceptives, etc). HCV and opioid dependence medications are more likely to be coadministered in the HIV-infected population. Approximately 25% of HIV-infected persons in the US are also infected with HCV.²⁰ Sofosbuvir/ledipasvir were the only HCV drugs evaluated in drug-drug interaction studies with E/C/F/TAF; the study was not sufficient to provide dosing recommendations for coadministration of E/C/F/TAF with sofosbuvir/ledipasvir. In addition, drugs interactions with opioid dependence medications buprenorphine/naloxone and methadone were addressed in the E/C/F/TAF labeling; no dose adjustment is recommended for either when coadministered with E/C/F/TAF.

As E/C/F/TAF is a complete HIV treatment regimen, drug-drug interactions with other HIV antiretrovirals are not relevant.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Drug-drug interaction information related to EVG and COBI was primarily transferred from the E/C/F/TDF label. FTC has minimal drug-drug interaction potential. Three drug-drug interaction studies were submitted as part of this NDA.

A drug-drug interaction study with E/C/F/TAF and sertraline (study GS-US-292-1316) found exposure changes of <16% for each component of E/C/F/TAF and sertraline. Based on flat exposure-response relationships, no dose adjustment is recommended for based on a <16% exposure change.

Coadministration of EVG/COBI and carbamazepine in drug-drug interaction study GS-US-216-0137 resulted in EVG AUC decreased 69%, COBI AUC decreased 84%, carbamazepine AUC increased 43%, and carbamazepine-10,11-epoxide (CYP3A-mediated active metabolite of carbamazepine) AUC decreased 35%. Based on significant exposure decreases of EVG, coadministration of E/C/F/TAF and carbamazepine is contraindicated.

Coadministration of TAF and COBI in drug-drug interaction study (GS-US-311-0101) resulted in TAF AUC increased 2.7-fold and TFV AUC increased 3.3-fold. This drug interaction was addressed by a dose reduction of the TAF dose ^{(b) (4)} to 10 mg in the E/C/F/TAF tablet.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No.

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2.4.3 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

EVG, COBI, and TAF are substrates of transporters Pgp, BCRP, OATP1B1, and OATP1B3. COBI is an inhibitor of all of these transporters, but is not the strongest known inhibitor of these pathways (Table 27). COBI increases TAF concentrations 2.65-fold. When coadministered with E/C/F/TAF, it is possible that other potentially stronger inhibitors such as cyclosporine could increase EVG, COBI, and TAF concentrations. Based on apparent flat exposure-response relationships for safety of EVG, COBI, and TAF, monitoring is recommended when inhibitors of Pgp, BCRP, OATP1B1, and/or OATP1B3 are coadministered with E/C/F/TAF.

Table 27. Inhibition potential of COBI versus other drugs.

Transporter	Substrate	AUC increase	
		COBI	Potent known inhibitor
Pgp	Oral digoxin	8%	Quinidine: 2.7-fold ²¹
BCRP + OATP1B1/1B3	Rosuvastatin	38%	Cyclosporin: 7.1-fold ²²

2.4.4 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None.

2.5 General Biopharmaceutics

There was no pivotal BE study as the commercial formulation was used in the phase 3 studies. See the NDA 207561 Biopharmaceutics review for details on dissolution and other biopharmaceutics issues.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

All analytes were measured using LC/MS/MS.

2.6.2 Which metabolites have been selected for analysis and why?

TAF metabolites TFV and TFV-DP were measured. This allowed the observation that TAF 10 mg results in 90% reduced TFV concentrations compared to TDF 300 mg while TFV-DP concentrations in PBMCs are comparable. The limitation is that the TFV-DP bioanalytical method was not validated.

2.6.3 For all moieties measured, is free, bound, or total drug measured?

Total.

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2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What is the curve fitting technique?

Standard curve ranges were sufficient to measure PK parameters such as C_{max}, AUC, and C_{min} in the clinical studies and are summarized in Table 28. The curve fitting technique for all analytes was 1/x². Methods were fully validated with the exception of the method for TFV-DP.

Table 28. Standard curves for bioanalytical methods.

Analyte	Matrix	Report #	ULOQ (ng/mL)	LLOQ (ng/mL)
EVG	Plasma	60-0811	20	20000
	Plasma	60-0949	20	10000
	Plasma	60-1343	20	10000
CBZ	Plasma	42-1371	20	20000
CBZE	Plasma	42-1371	5	5000
COBI	Plasma	60-0949	20	10000
	Plasma	60-1343	5	2500
FTC	Plasma	42-0831	5	3000
TAF	Plasma	60-1115	1	1000
	Urine	60-1220	2	1000
TFV	Plasma	42-0831	5	3000
	Plasma	60-1116	0.3	300
	Urine	60-1220	10	5000
	Plasma	60-1352	0.3	300
	Plasma	60-1368	0.3	300
TFV-DP	PBMC	2100-775	1	500

Table prepared by reviewer. CBZ=carbamazepine; CBZE=carbamazepine-10,11-epoxide.

2.6.4.2 What are the lower and upper limits of quantitation?

See Table 28.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Accuracy and precision was within limits recommended by FDA guidance (within 20% at LLOQ, otherwise within 15%).²³

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2.6.4.4 What is the sample stability under conditions used in the study?

Sample stability is summarized in Table 29.

Table 29. Sample stability of the components of E/C/F/TAF in the presence of all components of the FDC tablet in addition to other antiretrovirals.

Drugs present in sample	Analyte	Matrix	Report #	Stability at (b) (4) °C (days)
EVG, COBI, FTC, TAF, TFV, DRV, ATZ, RPV, EFV	EVG	Plasma	60-1325	(b) (4)
	COBI			
	FTC			
	TAF			
	TFV			(methods 42-0831 and 60-1116)

2.6.4.5 What is the QC sample plan?

QCs were included as recommended in FDA guidance²³:

- ≥ 3 QC concentrations, one within three times LLOQ, one in midrange of standard curve, one within 80% of ULOQ
- QCs comprised $\geq 5\%$ of unknown samples in sample analysis runs

2.6.4.6 Are there any other bioanalytical issues?

(b) (4)

Interference

Bioanalytical interference among the components of E/C/F/TAF was evaluated and ruled out with the exception of the effect of TAF on quantification of TFV. Interference of TAF with quantification of TFV was detected at the low QC and was attributed to the presence of TFV-related degradants in the TAF reference materials. Because the low QC is near TFV C_{min}, and at 24 hours postdose (the time corresponding to C_{min}) TAF is undetectable, any effect of TAF on the quantification of TFV would likely have no impact on TFV PK.

Carryover

In several sample analysis reports for several analytes, analyte peaks were seen in extracted blank or carry-over blank chromatograms. Although not discussed in the sample analysis reports, the analytical lab ((b) (4)) had SOPs for addressing carry-over that were provided in a response to an FDA Information Request (dated 5/11/2015). Carry-

CLINICAL PHARMACOLOGY REVIEW

over was assessed in each run by placing an extracted matrix blank after each of the two ULOQ standards. If the blank had a peak area >20% of the LLOQ peak area, a carry-over factor was calculated. This factor was then applied to all samples in the run. If the calculated carry-over value for the preceding sample to the subsequent sample was >5%, the affected sample would be re-run. We consider carry-over to have been sufficiently addressed.

CLINICAL PHARMACOLOGY REVIEW

3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-IV) has reviewed the package insert labeling for XXXXXX and finds it acceptable. We propose the following labeling changes, which will be finalized in upcoming labeling meetings:

- In section 12.3 (PK), the description of the comparison of adolescent versus adult PK parameters from administration of E/C/F/TAF was changed from (b) (4) to “decreased but deemed overall acceptable based on exposure-response relationships”.
- Addition of TAF to Table 1 (drugs contraindicated with E/C/F/TAF) and Table 5 (drug interactions) in situations where COBI concentrations are affected because COBI concentrations affect TAF concentrations.
- Addition of TAF transporter substrate information to section 7.3 (potential for other drugs to affect E/C/F/TAF).
- Addition of EVG, COBI, and TAF as drugs potentially affected by coadministration with cyclosporine (Table 5 – drug interactions).
- (b) (4) with intensive PK parameters from administration of E/C/F/TAF (Table 6).
- Removal of (b) (4)

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4 REFERENCE LIST

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5 APPENDICES

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CLINICAL PHARMACOLOGY REVIEW

5.1 Individual Study Reviews

Appears this way on original

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

NDA Number:	207561
Submission Type; Code:	NME
Applicant Name:	Gilead
Submission Dates:	11/5/2014
Brand Name:	Genvoya
Generic Name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Dosage Form:	Fixed dose combination tablet
Dosage Strengths:	150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide
Proposed Indication:	Treatment of HIV-1 in ages ≥ 12 years
OCP Division:	IV
Review Team:	Mario Sampson, PharmD, Islam Younis, PhD

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2 Notes

Numerical results from analyses, figures, and tables shown in this review are from the sponsor’s study reports unless otherwise indicated. The acceptability of bioanalytical methods for the various human studies were evaluated using criteria from FDA guidance.¹

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

3 Human studies

3.1 Pharmacokinetics

3.1.1 *GS-US-120-0104 – Single and multiple dose PK and antiviral activity study of TAF monotherapy in subjects with HIV-1*

ADMINISTRATIVE	
Study Period	1/19/2011-9/06/2011
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\gs-us-120-0104

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN	
<p>Randomized, partially-blinded study. 40 subjects were randomized 2:2:2:1:2 to the following groups, where study drugs were dosed daily in the fasted state for 10 days:</p> <p>Treatment Group 1 (Blinded GS-7340 8 mg): 9</p> <p>Treatment Group 2 (Blinded GS-7340 25 mg): 8</p> <p>Treatment Group 3 (Blinded GS-7340 40 mg): 9</p> <p>Treatment Group 4 (Open-label TDF 300 mg): 6</p> <p>Treatment Group 5 (Placebo-to-match GS-7340): 8</p>	
Population	HIV-1 infected adults
Study Rationale	PK and antiviral activity of TAF, relation between intracellular TFV-DP concentrations and antiviral effect
Dose Selection Rationale	Based on a prior study, TAF 8 mg and 25 mg were expected to provide comparable TFV-DP concentrations to TDF 300 mg
TAF formulation	Tablet. Doses reflect the free base equivalent of the administered monofumarate form. Lot numbers: CM1002B1 (8 mg), CM1003B1 (25 mg), CM1004B1 (40 mg)
Interfering Substances Excluded	Subjects taking antiretroviral drugs used within 90 days of screening were excluded. Other medications were not mentioned.
Sampling Times	Plasma PK: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose Intracellular PK: 1, 2, 6, and 12 hours postdose
PK Analysis	Noncompartmental

STUDY CONDUCT

Bioanalytical methods

The plasma bioanalytical methods were acceptable; the PBMC method had several deficiencies (Table 1).

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Table 1. Bioanalytical methods.

Analyte	Matrix	Method report #	Sample analysis report #	Deficiencies
TAF	Plasma	60-1115	60-1128A	None
TFV	Plasma	42-0831	60-1128B	
TFV	Plasma	60-1116	60-1128C	
TFV-DP	PBMC	No validated method	60-1128F	<ul style="list-style-type: none"> • No validated method • No stability assessment • For calibration samples at 0.9, 1.8, and 3.6 ng/mL, <75% passed (not within $\pm 20\%$). Thus the LLOQ should be considered 9.0 ng/mL instead of 0.9 ng/mL • No QCs used during runs

Table prepared by reviewer.

Protocol deviations

The following deviations potentially affected the PK/PD analyses:

- Subject 2728-003-4005 missed day 7 and day 8 dosing, and resumed on day 9.
- Subject 0433-004-4032 missed day 5 and day 6 dosing. Also, days 1-4 and day 7 dosing were not at approximately the same time each day.

These two subjects were included in the PK/PD analyses.

An additional two deviations had no effect on the PK/PD analyses.

STUDY RESULTS

Study population

40 subjects were randomized, 38 completed treatment and were included in the safety and PK analyses (two were never dosed), and one subject was lost to follow up after completing dosing. 37 subjects completed the study (Table 2, Table 3).

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 2. Subject demographics.

	TAF 8 mg (n=9)	TAF 25 mg (n=8)	TAF 40 mg (n=8)	TDF 300 mg (n=6)	Placebo (n=7)	Total (n=38)
Age (years)	37 (20-48)	43 (22-57)	30 (28-42)	42 (29-52)	44 (27-49)	39 (20-57)
Male sex	9 (100%)	8 (100%)	7 (87.5%)	6 (100%)	7 (100%)	37 (97.4%)
Race						
White	4 (44.4%)	4 (50%)	4 (50%)	5 (83.3%)	3 (42.9%)	20 (52.6%)
Black	4 (44.4%)	4 (50%)	2 (25%)	0	4 (57.1%)	14 (36.8%)
Native American	0	0	1 (12.5%)	1 (16.7%)	0	2 (5.3%)
Asian	0	0	1 (12.5%)	0	0	1 (2.6%)
Other	0	0	0	0	0	0
	1 (11.1%)	0	0	0	0	1 (2.6%)
Hispanic ethnicity	3 (33.3%)	2 (25%)	2 (25%)	3 (50%)	1 (14.3%)	11 (28.9%)
Weight (kg)	79 (55-109)	89 (59-97)	88 (71-108)	82 (66-87)	84 (70-102)	85 (55-109)
BMI (kg/m ²)	25 (20-34)	27 (20-32)	27 (22-37)	27 (20-29)	27 (21-33)	27 (20-37)

Table prepared by reviewer. Values are median (range) or N (%).

Table 3. Disposition of subjects.

Subject Disposition, n (%)	GS-7340 (8 mg) (n = 9)	GS-7340 (25 mg) (n = 8)	GS-7340 (40 mg) (n = 8)	TDF (300 mg) (n = 6)	Placebo (n = 7)	Total (n = 38)
Subjects Randomized	9	8	9	6	8	40
Subjects Randomized and Never Dosed	0	0	1	0	1	2
Subjects in Safety Analysis Set	9	8	8	6	7	38
Subjects Completing Study Treatment	9 (100.0%)	8 (100.0%)	8 (100.0%)	6 (100.0%)	7 (100.0%)	38 (100.0%)
Subjects Not Completing Study Treatment	0	0	0	0	0	0
Subjects Completing Study	9 (100.0%)	8 (100.0%)	8 (100.0%)	6 (100.0%)	6 (85.7%)	37 (97.4%)
Subjects Not Completing Study	0	0	0	0	1 (14.3%)	1 (2.6%)

Concomitant medications

As TAF is a Pgp substrate, concomitant medications were screened for Pgp inhibitors and inducers using the UW Drug Interaction Database.² Two subjects were administered Pgp inhibitors throughout the study, potentially increasing TAF exposure: subject 0698-4010 in the TAF 40 mg group was administered carvedilol and subject 0407-4031 in the TAF 25 mg group was administered verapamil. These subjects were not excluded from the PK/PD analyses.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Pharmacodynamics

Relative to the TDF group, the day 11 change from baseline in HIV-1 RNA (log₁₀ copies/mL) was statistically unchanged in the TAF 8 mg group and increased for the TAF 25 mg and 40 mg groups (Table 4).

Table 4. Day 11 change from baseline in HIV-1 RNA (log₁₀ copies/mL).

Baseline ^a	GS-7340 (8 mg) (n = 9)	GS-7340 (25 mg) (n = 8)	GS-7340 (40 mg) (n = 8)	TDF (300 mg) (n = 6)	Placebo (n = 7)
n	9	8	7	6	7
Mean (SD)	-0.98 (0.464)	-1.50 (0.412)	-1.74 (0.190)	-0.81 (0.580)	0.15 (0.547)
95% CI	(-1.34, -0.62)	(-1.84, -1.15)	(-1.92, -1.57)	(-1.42, -0.20)	(-0.36, 0.65)
Median	-1.08	-1.46	-1.73	-0.97	-0.07
Q1, Q3	-1.20, -0.96	-1.88, -1.28	-1.88, -1.55	-1.24, -0.62	-0.12, 0.08
Min, Max	-1.57, -0.18	-2.00, -0.77	-2.06, -1.51	-1.30, 0.24	-0.22, 1.36
p-value vs. Placebo	0.001	0.001	0.002	0.038	
p-value vs. TDF	0.77	0.024	0.003		
p-value vs. GS-7340 40 mg	0.002	0.27			
p-value vs. GS-7340 25 mg	0.030				

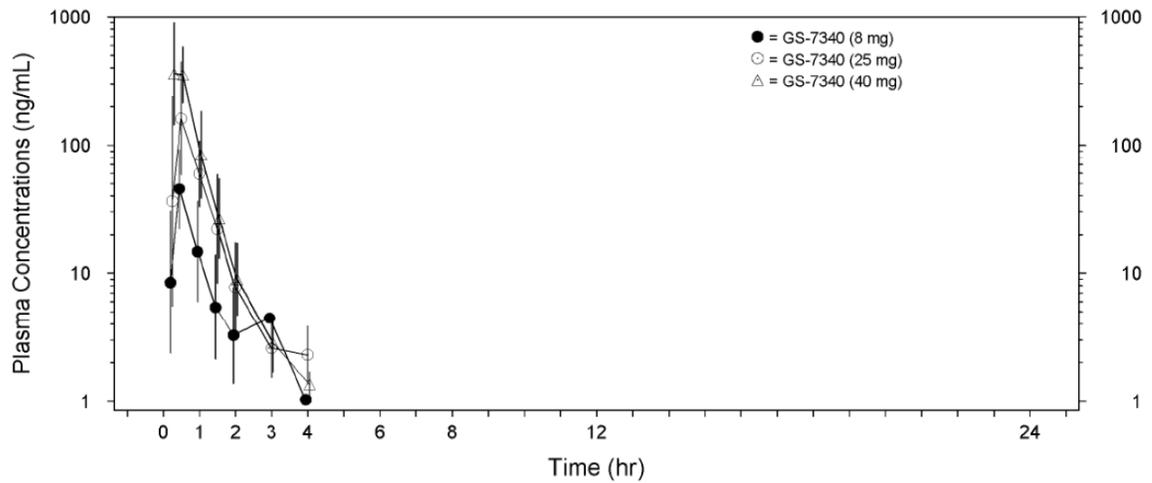
Pharmacokinetics

TAF

At each dose level, TAF PK was similar after single and multiple doses (Figure 1, Figure 2, Table 5). Lack of accumulation was consistent with TAF's short half-life. As there was no accumulation, there is likely no impact of missed doses on the PK of the two affected subjects. Consistent with the potential for increased TAF exposure in the two subjects on concomitant Pgp inhibitors, subject 0407-4031 had the highest C_{max} and AUC in the 25 mg dose group on day 1 and day 10, and subject 0698-4010 had the highest C_{max} and AUC in the 40 mg dose group on day 1 and the second highest on day 2 (Table 6). TAF was detected for only 4 hours postdose in this study, compared to up to 8 hours postdose in other studies. Using a power model, TAF AUC and C_{max} increased more than proportionally with dose (Table 7), consistent with an exploratory analysis (Table 8).

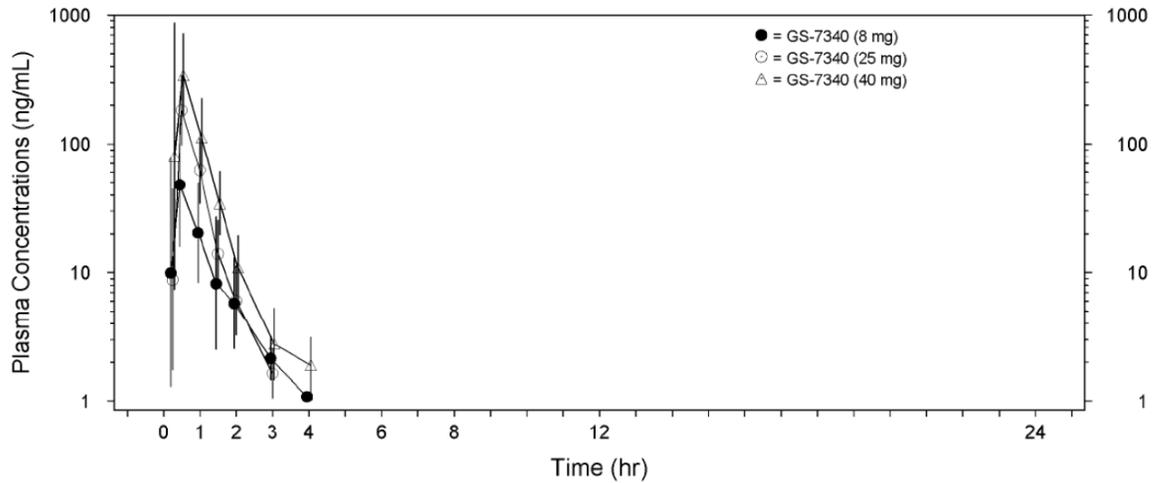
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Figure 1. Single dose TAF plasma concentration-time profiles.



GS-7340 (8 mg)	N=	9	6	1	1
GS-7340 (25 mg)	N=	7	8	6	2
GS-7340 (40 mg)	N=	8	8	7	4

Figure 2. Multiple dose TAF plasma concentration-time profiles.



GS-7340 (8 mg)	N=	9	6	3	1
GS-7340 (25 mg)	N=	8	8	6	6
GS-7340 (40 mg)	N=	8	8	6	3

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Table 5. Single and multiple dose TAF plasma PK parameters.

GS-7340 PK Parameter	GS-7340 Single Dose PK			GS-7340 Multiple Dose PK		
	Day 1			Day 10		
	GS-7340 8 mg (n = 9)	GS-7340 25 mg (n = 8)	GS-7340 40 mg (n = 8)	GS-7340 8 mg (n = 9)	GS-7340 25 mg (n = 8)	GS-7340 40 mg (n = 8)
AUC _{last} (ng•h/mL), Mean (%CV)	38.4 (80.6)	139.7 (57.8)	322.1 (42.0)	54.7 (92.6)	115.2 (33.4)	308.9 (33.6)
AUC _{last} (ng•h/mL), Median (Q1, Q3)	33.0 (18.3, 43.6)	131.9 (71.8, 183.3)	284.4 (221.3, 423.3)	27.5 (20.3, 103.3)	109.1 (101.4, 132.9)	344.2 (213.4, 383.4)
C _{max} (ng/mL), Mean (%CV)	58.3 (61.1)	231.8 (76.8)	598.9 (50.4)	85.8 (116.3)	223.6 (58.8)	629.5 (57.0)
C _{max} (ng/mL), Median (Q1, Q3)	58.4 (29.9, 89.8)	181.7 (95.1 (314.8)	515.2 (364.8, 798.9)	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 (0.38, 0.75)	0.38 (0.25, 0.50)	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)	0.34 (0.33, 0.42)	0.43 (0.30, 0.54)	0.43 (0.38, 0.57)	0.38 (0.26, 0.50) ^a	0.39 (0.34, 0.54)	0.42 (0.32, 0.49)

%CV, percent of coefficient of variation; Q1, first quartile; Q3, third quartile

a n = 8

Note: AUC_{last} is presented for single and multiple dose PK because GS-7340 concentrations are BLQ by approximately 5 hours post dose 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} have been presented. To account for the variability in the data, the mean and median AUC_{last} and C_{max} are presented.

Table 6. TAF PK parameters for subjects taking concomitant Pgp inhibitors.

	Subject 0407-4031		Subject 0698-4010	
	Day 1	Day 10	Day 1	Day 10
Dose (mg)	25		40	
AUC (ng•h/mL)	291.1	185.4	531.8	418.5
C _{max} (ng/mL)	596.4	447.9	1163.9	990

Table prepared by reviewer.

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Table 7. Statistical analysis of TAF dose proportionality.

PK Analyte	PK Parameter	Degree of Freedom	Slope of ln(dose)	SE of Slope	90% CI of slope	P-value
GS-7340 (single-dose)	AUClast (ng*h/mL)	23	1.38	0.170	(1.09, 1.67)	<0.001
	AUCinf (ng*h/mL)	23	1.34	0.164	(1.06, 1.63)	<0.001
	Clast (ng/mL)	23	-0.11	0.121	(-0.32, 0.09)	0.36
	Cmax (ng/mL)	23	1.45	0.198	(1.11, 1.79)	<0.001
GS-7340 (multiple-dose)	AUClast (ng*h/mL)	23	1.23	0.198	(0.89, 1.57)	<0.001
	Clast (ng/mL)	23	-0.13	0.160	(-0.40, 0.14)	0.42
	Cmax (ng/mL)	23	1.38	0.230	(0.99, 1.76)	<0.001
TFV (single-dose)	AUClast (ng*h/mL)	23	1.12	0.070	(1.00, 1.24)	<0.001
	AUCinf (ng*h/mL)	23	1.11	0.094	(0.95, 1.27)	<0.001
	Clast (ng/mL)	23	1.08	0.069	(0.96, 1.20)	<0.001
	Cmax (ng/mL)	23	1.19	0.091	(1.03, 1.34)	<0.001
TFV (multiple-dose)	AUCtau (ng*h/mL)	23	1.16	0.064	(1.05, 1.27)	<0.001
	Ctau (ng/mL)	22	1.20	0.085	(1.05, 1.34)	<0.001
	Cmax (ng/mL)	23	1.19	0.055	(1.10, 1.29)	<0.001

Table 8. Exploratory assessment of TAF dose proportionality.

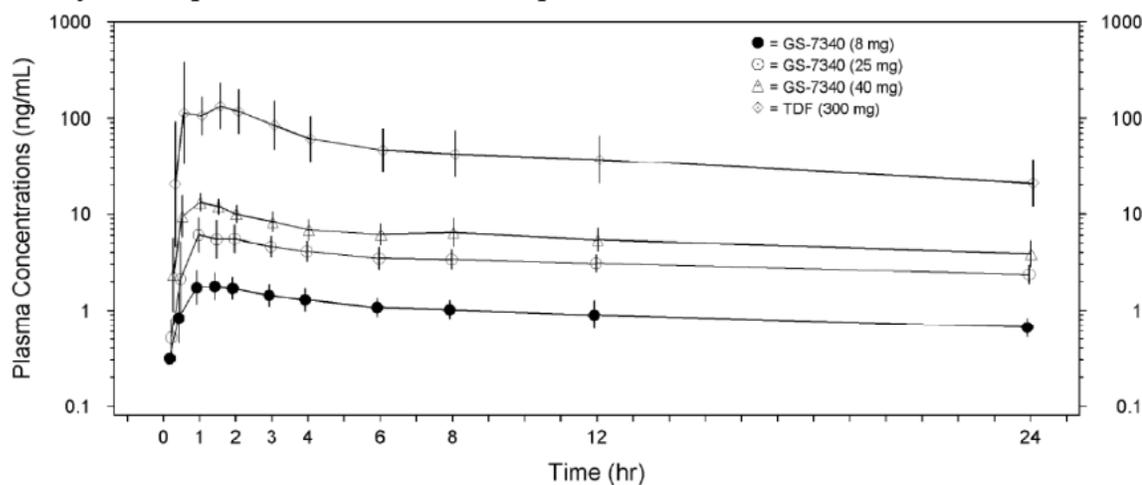
Dose (mg)	Day 1		Day 10	
	Median Cmax/dose	Median AUC/dose	Median Cmax/dose	Median AUC/dose
8	7.3	4.13	5.19	3.438
25	7.27	5.28	7.09	4.36
40	12.9	7.11	15.2	8.61

Reviewer's analysis.

TFV

TFV exposures were less variable than TAF. Relative to the TDF group, systemic TFV concentrations were significantly lower in the TAF dose groups (Figure 3, Figure 4, Table 9).

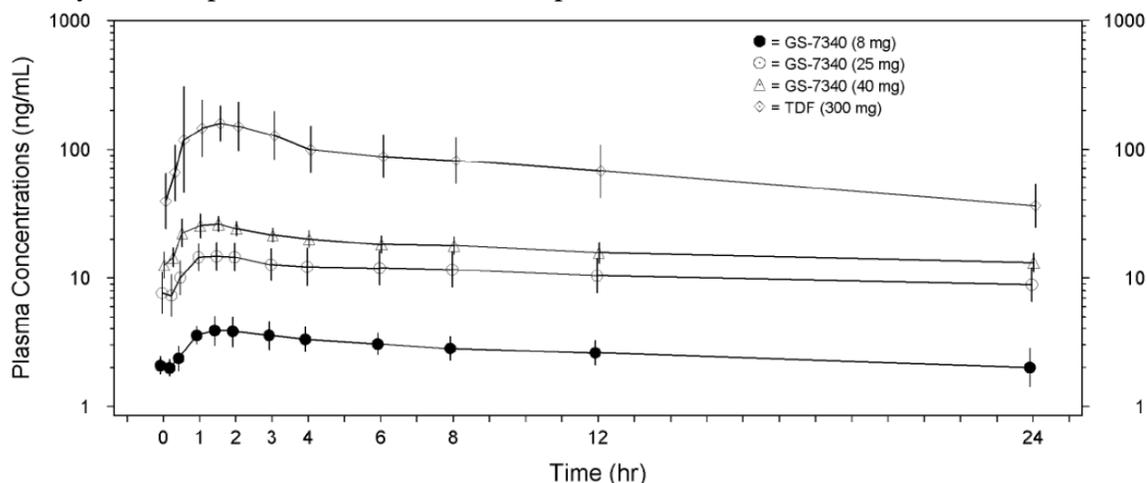
Figure 3. Day 1 TFV plasma concentration-time profiles.



GS-7340 (8 mg)	N=	9	9	9	9	9	9	9
GS-7340 (25 mg)	N=	7	8	8	8	8	8	8
GS-7340 (40 mg)	N=	8	8	8	8	8	8	8
TDF (300 mg)	N=	4	6	6	6	6	6	6

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Figure 4. Day 10 TFV plasma concentration-time profiles.



GS-7340 (8 mg)	N=	8	9	9	9	9	9	9	9
GS-7340 (25 mg)	N=	8	8	8	8	8	8	8	8
GS-7340 (40 mg)	N=	8	8	8	8	8	8	8	7
TDF (300 mg)	N=	6	6	6	6	6	6	6	6

Table 9. Day 1 and day 10 TFV plasma PK parameters.

TFV PK Parameter	TFV Single Dose PK ^a				TFV Multiple Dose PK			
	Day 1				Day 10			
	GS-7340 8 mg (n = 9)	GS-7340 25 mg (n = 8)	GS-7340 40 mg (n = 8)	TDF 300 mg (n = 6)	GS-7340 8 mg (n = 9)	GS-7340 25 mg (n = 8)	GS-7340 40 mg (n = 8)	TDF 300 mg (n = 6)
AUC _{inf} for single dose or AUC _{tau} for multiple dose (ng•h/mL), Mean (%CV)	49.4 (30.3)	195.9 (27.2)	287.3 (33.7)	1719.2 (57.9)	65.5 (23.5)	267.7 (26.7)	405.8 (12.7)	1918.0 (39.4)
C _{max} (ng/mL), Mean (%CV)	2.0 (31.1)	6.5 (40.1)	14.0 (20.3)	181.2 (50.5)	4.2 (24.7)	15.7 (22.1)	28.3 (8.7)	252.1 (36.6)
C _{tau} (ng/mL), Mean (%CV)	0.7 (19.8)	2.4 (23.5)	4.0 (27.2)	23.9 (57.5)	2.1 (33.8)	9.2 (26.1)	13.3 (16.0) ^b	38.7 (44.7)
T _{max} (h), Median (Q1, Q3)	1.00 (1.00, 2.00)	1.50 (1.03, 1.75)	1.00 (0.75, 1.00)	1.25 (0.53, 1.50)	1.50 (1.00, 1.98)	1.50 (1.25, 1.75)	1.29 (1.04, 1.50)	1.25 (0.58, 2.00)
t _{1/2} (h), Median (Q1, Q3)	23.85 (18.32, 37.17) ^b	29.83 (26.87, 44.00) ^b	24.55 (20.33, 28.25)	15.56 (14.17, 17.07)	30.77 (26.90, 55.61) ^c	40.19 (28.98, 44.84)	35.95 (26.38, 42.90) ^b	14.86 (12.18, 16.81)

%CV, percent of coefficient of variation; Q1, first quartile; Q3, third quartile

a AUC_{inf} and C_{24h} are presented for single dose PK

b n = 7

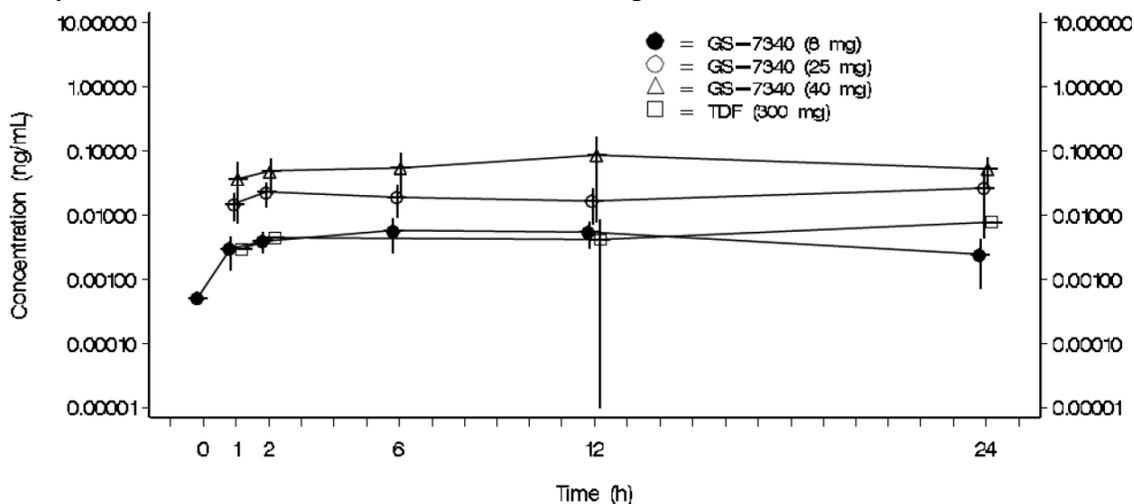
c n = 8

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Intracellular TFV-DP

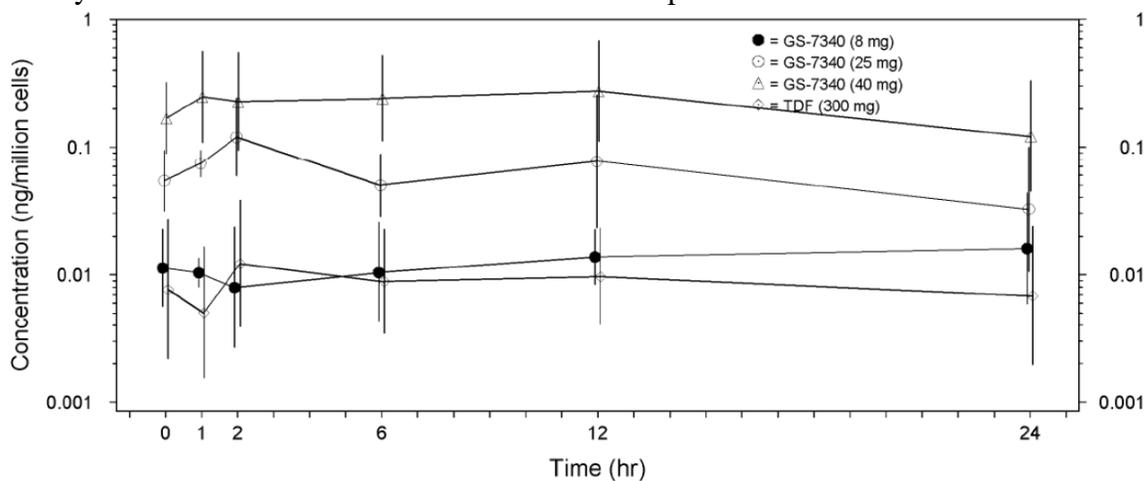
TAF is intracellularly converted to TFV and then TFV-DP, which is the active moiety against the HIV virus. As the TFV-DP bioanalytical method was not sufficiently validated, definitive conclusions cannot be drawn from the TFV-DP PK results. Relative to the TDF group, it does appear at day 1 and day 10 that TFV-DP concentrations are similar in the TAF 8 mg group and higher in the TAF 25 mg and 40 mg groups (Figure 5, Figure 6, Table 10).

Figure 5. Day 1 intracellular TFV-DP concentration-time profile.



GS-7340 (8 mg) (n=):	1	4	5	5	5	6
GS-7340 (25 mg) (n=):		4	4	4	4	4
GS-7340 (40 mg) (n=):		7	6	7	7	7
TDF (300 mg) (n=):		1	1		2	1

Figure 6. Day 10 intracellular TFV-DP concentration-time profile.



GS-7340 (8 mg) N=	6	6	6	6	6	4
GS-7340 (25 mg) N=	4	4	2	4	4	4
GS-7340 (40 mg) N=	7	6	7	7	7	6
TDF (300 mg) N=	4	4	2	4	4	3

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Table 10. Day 10 PBMC TFV-DP PK parameters.

TFV-DP PK Parameter	TFV-DP Multiple Dose PK Day 10			
	GS-7340 8 mg (n = 6)	GS-7340 25 mg (n = 4)	GS-7340 40 mg (n = 7)	TDF 300 mg (n = 4)
AUC _{tau} (μM•h), Mean (%CV)	3.5 (77.1)	21.4 (76.9)	74.5 (92.7)	3.0 (119.6)
AUC _{tau} (μM•h), Median (Q1, Q3)	2.5 (1.6, 5.8)	15.8 (9.6, 33.2)	53.4 (28.3, 104.7)	1.6 (1.0, 4.9)

%CV, percent of coefficient of variation; Q1, first quartile; Q3, third quartile

Note: To account for the variability in the data, the mean and median AUC_{tau} are presented.

PK associations

Among the subjects administered TAF who had TAF, TFV, and TFV-DP AUC values (17/25 subjects administered TAF), plasma TAF and TFV AUC appeared to be associated with PBMC TFV-DP AUC (Figure 7, Figure 8).

Figure 7. Plasma TAF AUC vs PBMC TFV-DP AUC.

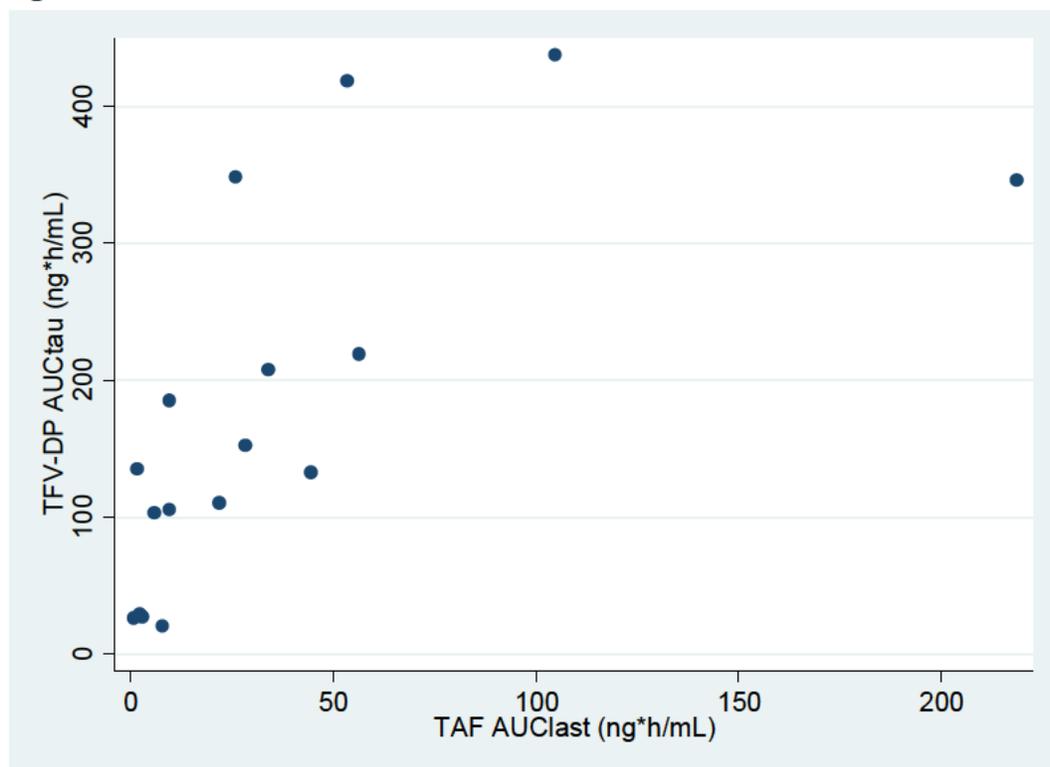


Figure prepared by reviewer. N=17 subjects.

Figure 8. Plasma TFV AUC vs PBMC TFV-DP AUC.

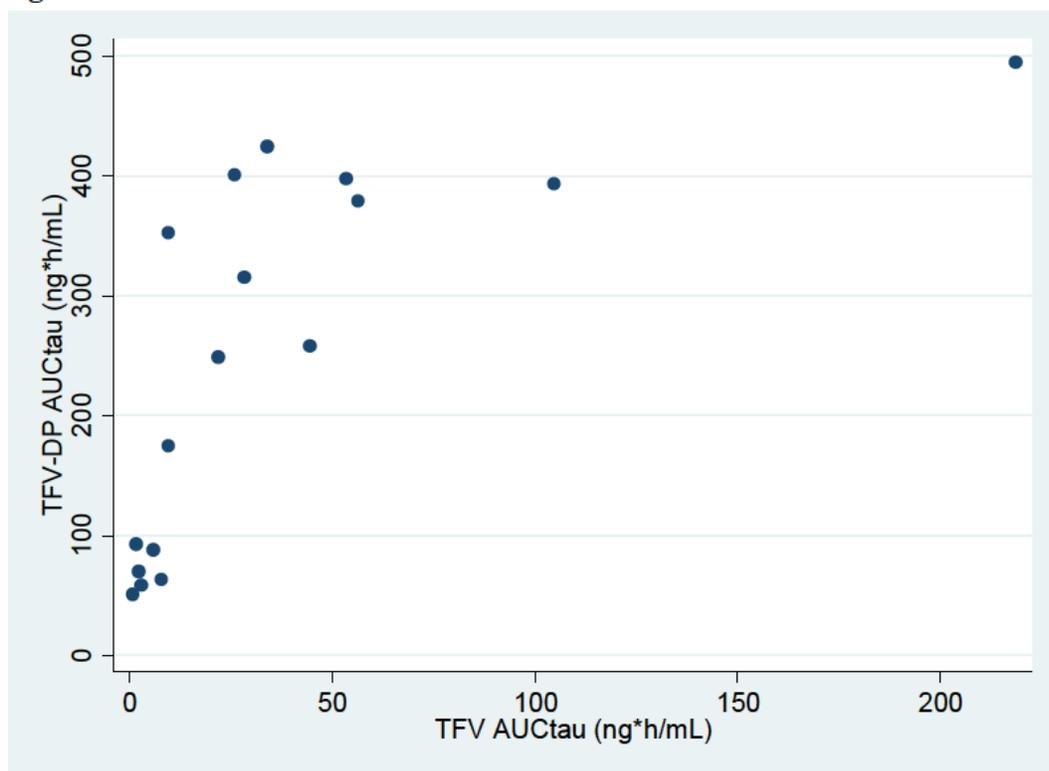


Figure prepared by reviewer. N=17 subjects

PK/PD

When combined across treatment groups, PBMC TFV-DP AUC was associated with the day 11 time-weighted average change from baseline in HIV-1 RNA (Table 11).

Table 11. Correlation between PBMC TFV-DP AUC and day 11 time-weighted average change from baseline in HIV-1 RNA.

TFV-DP PK Parameter	Treatment Group	Number of Data Pairs	Pearson Correlation Coefficient	p-value
AUCtau of TFV-DP in PBMC vs DAVG ₁₁	GS-7340 (8 mg)	6	-0.063	0.906
	GS-7340 (25 mg)	4	-0.701	0.299
	GS-7340 (40 mg)	6	-0.338	0.512
	TDF (300 mg)	3	-0.933	0.234
	All	19	-0.535	0.018

Note: DAVG₁₁ is the time-weighted average change from baseline to study Day 11.

Note: Correlation coefficients and p-values are from the Pearson correlation analysis.

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Safety

There were no SAEs, deaths, or AE-related discontinuations in the study. Eight subjects had treatment-emergent AEs considered to be related to study drug (Table 12). None of the study drug-related AEs occurred in more than 1 subject; they included the following: TAF 8 mg treatment group (dry mouth, haematuria, and proteinuria), TAF 25 mg treatment group (fatigue and headache), TAF 40 mg treatment group (nausea, blood amylase increased, lipase increased, and somnolence), and placebo-to-match TAF group (nausea, diarrhea, fatigue, back pain, headache, and abnormal dreams).

Table 12. Summary of adverse events.

Subjects With any Treatment-Emergent: n (%)	GS-7340 (8 mg) (n = 9)	GS-7340 (25 mg) (n = 8)	GS-7340 (40 mg) (n = 8)	TDF (300 mg) (n = 6)	Placebo (n = 7)
Adverse Event	6 (66.7%)	3 (37.5%)	5 (62.5%)	2 (33.3%)	5 (71.4%)
Grade 3 or 4 Adverse Event	0	0	0	0	1 (14.3%)
Adverse Event Related to Study Drug	1 (11.1%)	2 (25.0%)	2 (25.0%)	0	3 (42.9%)
Grade 3 or 4 Adverse Event Related to Study Drug	0	0	0	0	0
Serious Adverse Event	0	1 (12.5%)	0	0	0
Serious Adverse Event Related to Study Drug	0	0	0	0	0
Adverse Event Leading to Premature Study Drug Discontinuation	0	0	0	0	0

CONCLUSIONS

- Relative to TDF, antiviral activity was similar for TAF 8 mg and increased for the TAF 25 mg and 40 mg groups.
- At the studied TAF doses of 8 mg, 25 mg, and 40 mg, TAF exposure increased more than proportionally with dose.
- Bioanalytical methods for TFV-DP were not sufficiently validated; however, relative to TDF, TFV-DP concentrations appear to be similar for TAF 8 mg and increased for TAF 25 mg and 40 mg. Also, when combined across treatment groups, increased PBMC TFV-DP AUC was associated with greater antiviral activity.
- As this study does not impact the E/C/F/TAF label, PK/PD analyses excluding subjects with missed doses (n=2) or taking concomitant Pgp inhibitors (n=2) was not requested or performed by FDA.

LABEL RECOMMENDATIONS

The E/C/F/TAF label does not contain any data from this study.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

3.1.2 *GS-US-120-0109 – Study of the pharmacokinetics, metabolism and excretion of TAF in healthy males*

ADMINISTRATIVE	
Study Period	5/11/2012-6/22/2012
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-120-0109

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN	
Population	Healthy males
Study Rationale	Determine TAF mass balance, TAF and TFV PK, and TAF metabolite profile
Treatments	Single 25 mg oral dose of radiolabeled [¹⁴ C]-TAF
Dose Selection Rationale	25 mg is the dose in the TAF commercial formulation for treatment of HIV when not coadministered with COBI
Administration	Fasted
Formulation	Capsule containing 24.15 mg nonradiolabeled TAF plus 0.85 mg radiolabeled TAF. Lot numbers: 7340-03-AC-1P and GS002-035-057-C-20120419-PVA
Interfering Substances Excluded	No medications allowed within 28 days of study dosing with the exception of vitamins, acetaminophen, and ibuprofen
Sampling Times	<p><u>Whole blood and plasma:</u> 0 (predose, ≤ 30 minutes prior to dosing) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours postdose. Blood samples for PK analysis were not collected at the 5-hour post-dose time point; rather, blood samples for LSC radioanalysis were collected at this time point.</p> <p><u>Urine:</u> predose, 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 72, and 72 to 96 hour intervals postdose. After 96 hours post-dose, urine was collected</p> <p><u>Stool:</u> predose, 0 to 24, 24 to 48, 48 to 72, and 72 to 96 hour intervals postdose and at 24-hour intervals until subjects met discharge criteria.</p> <p>After the 96-hour postdose time point, additional blood, urine, and stool samples were collected at 24-hour intervals up to Day 22 or until radioactivity levels decreased to near background radioactivity.</p>
PK Analysis	Noncompartmental
Statistical Analysis	None

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY CONDUCT

Bioanalytical methods

Bioanalytical methods were acceptable (Table 13).

Table 13. Bioanalytical methods used for study GS-US-120-0109.

Analyte	Method type	Method #	Matrix
Total radioactivity	Liquid scintillation counting		Blood, plasma, urine, stool
TAF	LC/MS/MS	60-1115	Plasma
TFV		60-1116	Plasma
TAF and TFV		60-1220	Urine

Table prepared by reviewer.

Protocol deviations

None reported.

STUDY RESULTS

Study population

Eight subjects were enrolled (Table 14). All were dosed and included in the safety and PK analyses. Two subjects withdrew consent following dosing.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 14. Demographics for study GS-US-120-0109.

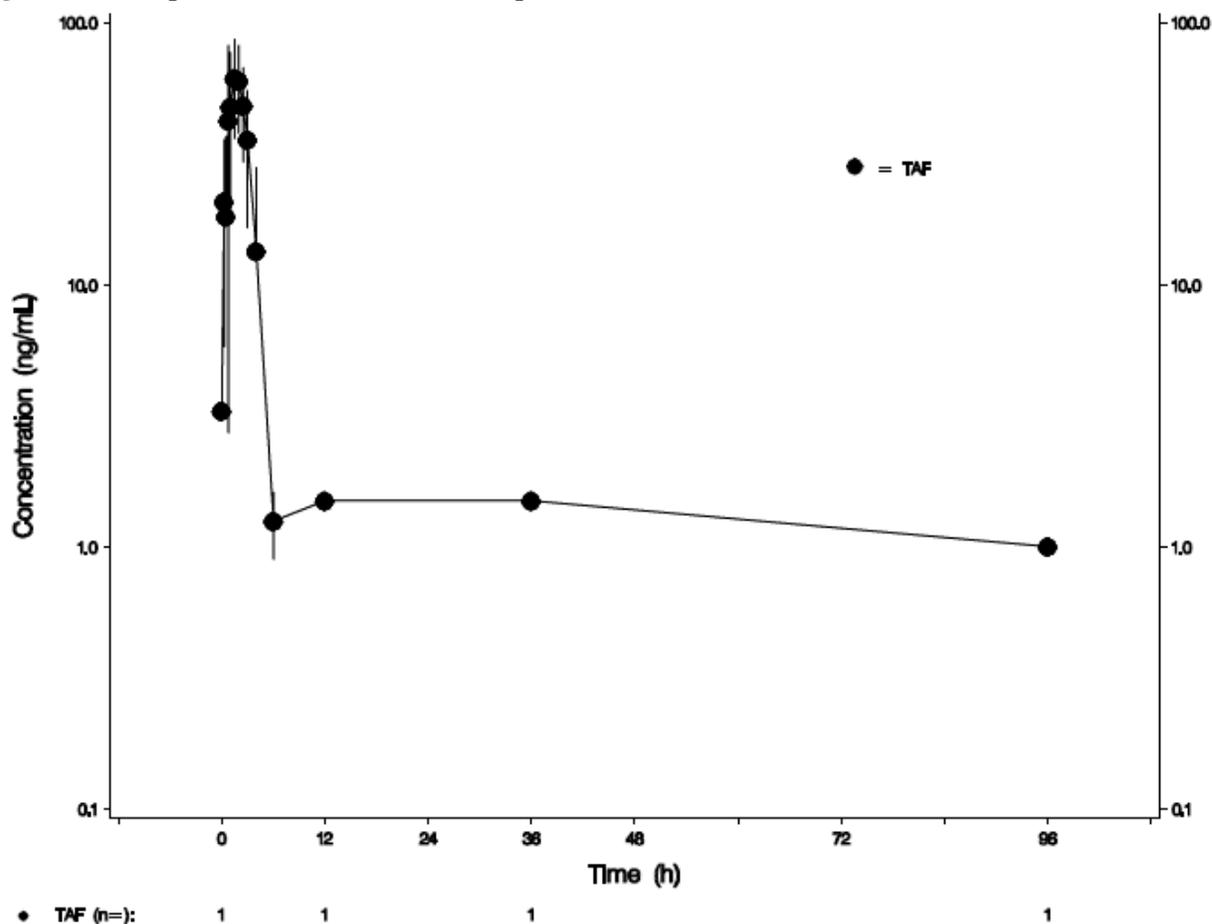
Characteristic	TAF (N = 8)
Sex (n, %)	
Male	8 (100.0)
Female	0
Age at baseline (years)	
Mean (SD)	29 (9.2)
Median (Q1, Q3)	29 (22, 36)
Min, Max	19, 45
Race (n, %)	
White	7 (87.5)
Other	1 (12.5)
Ethnicity	
Hispanic/Latino	4 (50.0)
Non-Hispanic/Latino	4 (50.0)
Weight (kg)	
Mean (SD)	80.3 (9.16)
Median (Q1, Q3)	80.3 (71.9, 87.8)
Min, Max	69.5, 93.3
Height (cm)	
Mean (SD)	176.1 (3.43)
Median (Q1, Q3)	176.7 (173.8, 178.3)
Min, Max	170.6, 181.0
Body mass index (kg/m²)	
Mean (SD)	25.9 (2.70)
Median (Q1, Q3)	25.9 (23.4, 28.3)
Min, Max	22.6, 29.3
Estimated glomerular filtration rate by Cockcroft-Gault (mL/min)	
Mean (SD)	127.2 (36.22)
Median (Q1, Q3)	117.5 (100.6, 147.7)
Min, Max	87.7, 198.2

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Pharmacokinetics

The mean blood-to-plasma ratio of [^{14}C]-radioactivity increased from 0.6 at 0.25 hours postdose to 2.4 at 216 hours postdose, suggesting slower clearance from blood cells relative to plasma. In plasma, TAF was quantifiable for 6 hours (Figure 9, Table 15), while TFV was quantifiable for 96 hours (Figure 10, Table 16). Mean \pm SD cumulative urinary, fecal, and combined urinary plus fecal recovery of total [^{14}C]-radioactivity was $36.2\% \pm 5.62\%$ (n=8), $47.2\% \pm 4.62\%$ (n=7 due to one subject with insufficient stool samples), and $84.4\% \pm 2.45\%$, respectively.

Figure 9. TAF plasma concentration-time profile.



- Values below the lower limit of quantitation (BLQ) were treated as 0 for summary statistics and missing for log-normalized data.
- Values where no sample was available (NS) were treated as missing for summary statistics and log-normalized data.
- Values presented as mean \pm standard deviation.

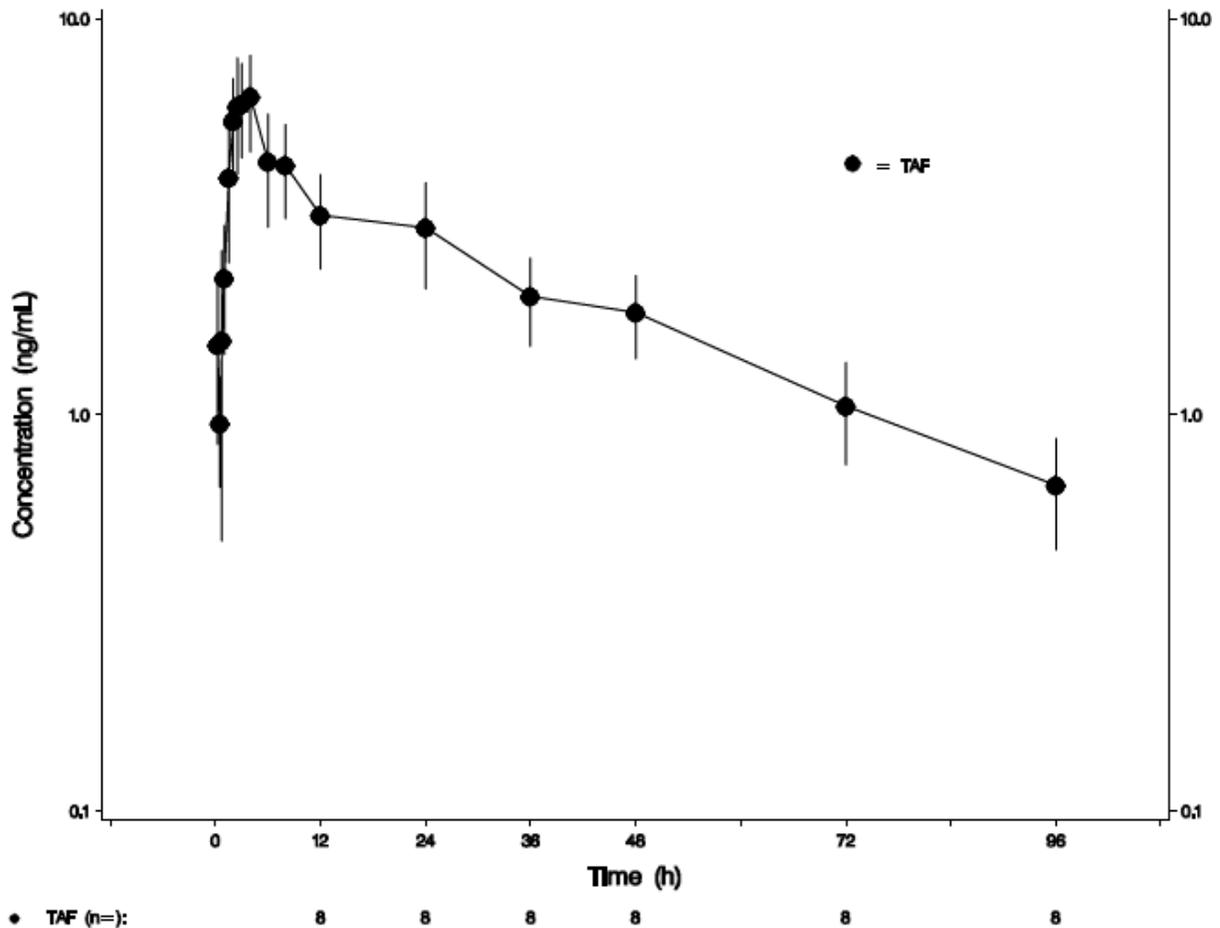
CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 15. TAF plasma PK parameters.

PK Parameter	Mean (%CV)
	(N = 8)
C_{max} (ng/mL)	78.1 (34.6)
AUC_{last} (ng•h/mL)	157.3 (23.1)
AUC_{inf} (ng•h/mL)	161.8 (22.4)
T_{max} (h) ^a	2.00 (1.50, 2.76)
$T_{1/2}$ (h) ^a	0.51 (0.45, 0.62)

a Median (Q1, Q3)

Figure 10. TFV plasma concentration-time profile.



- a Values below the lower limit of quantitation (BLQ) were treated as 0 for summary statistics and missing for log-normalized data.
- b Values where no sample was available (NS) were treated as missing for summary statistics and log-normalized data.
- c Values presented as mean ± standard deviation.

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Table 16. TFV plasma PK parameters.

PK Parameter	Mean (%CV)
	(N = 8)
C_{\max} (ng/mL)	7.2 (16.3)
AUC_{last} (ng•h/mL)	192.9 (24.0)
AUC_{inf} (ng•h/mL) ^a	224.6 (24.6)
T_{\max} (h) ^a	3.25 (2.25, 4.00)
$T_{1/2}$ (h) ^a	32.37 (31.11, 36.19)

a Median (Q1, Q3)

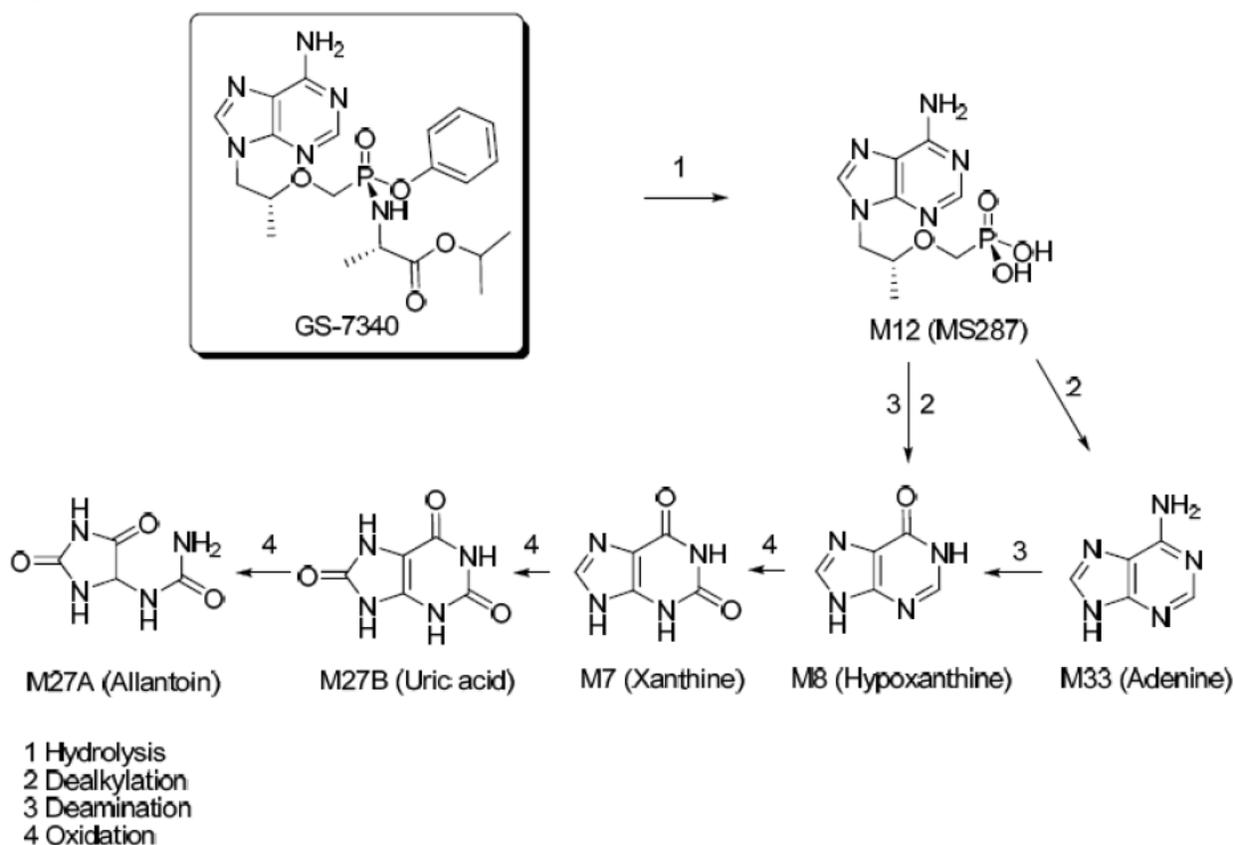
Plasma samples were pooled across subjects and/or time for analysis of [¹⁴C]-TAF and metabolites. At the first maximal plasma concentration ~2 hours postdose, TAF was the predominant species (72.6% of total radioactivity quantified). At the second maximal plasma concentration ~24-48 hours postdose, the predominant species was uric acid (97.6% of total quantified radioactivity). Plasma radioactivity AUC over 96 hours contributed by uric acid, TAF, and TFV were 73.9%, 1.8%, and 1.5% of the total, respectively.

Urine samples were pooled across timepoints by subject and analyzed for [¹⁴C]-TAF and metabolites. Mean ± SD total radioactive dose quantified was 25.8% ± 5.50%, of which TFV, uric acid, and TAF comprised 22.2%, 1.93%, and 1.41% of the total radioactive dose, respectively. Thus TFV represents 86% of the radioactivity recovered in urine.

Fecal samples were pooled across timepoints by subject and analyzed for [¹⁴C]-TAF and metabolites. Mean ± SD total radioactive dose quantified was 31.7% ± 10.5%, with 31.4% of the radioactive dose quantified as TFV. Thus TFV represents 99% of the radioactivity recovered in feces. Other metabolites were detected in trace amounts. TAF was not detected.

The tentative TAF biotransformation pathway involves conversion to TFV followed by further metabolism via the purine catabolic pathway (Figure 11).

Figure 11. Tentative TAF biotransformation pathway.



Note: M12 = TFV.

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

Safety

There were no deaths, SAEs, or discontinuations due to an AE. One subject reported arthralgia that was considered related to study drug.

DISCUSSION

In this study, the elimination pathway of TAF was sufficiently characterized and metabolites identified. Radioactivity percent recovery was acceptable as it was >80%.³

LABEL RECOMMENDATIONS

The label text derived from this study, found in section 12.3, is acceptable: “ (b) (4)

[Redacted text block]

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

(b) (4)

”

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

3.1.3 GS-US-292-0102 - Phase 2 study of E/C/F/TAF versus E/C/F/TDF in HIV-infected, treatment naïve adults: intensive PK substudy

ADMINISTRATIVE	
Study Period	12/28/2011-03/07/2014
Link	\\cdsesub1\evsprod\nda207561\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5351-stud-rep-contr\gs-us-292-0102\report-body.pdf

STUDY DESIGN	
<p>Randomized, double-blind, active- and placebo-controlled</p> <p>Arm 1: E/C/F/TAF + placebo E/C/F/TDF for 48 weeks (N=100)</p> <p>Arm 2: E/C/F/TDF + placebo E/C/F/TAF for 48 weeks (N=50)</p> <p>After 48 weeks, subjects had the option to continue receiving E/C/F/TAF in an open-label extension study. In addition, virologically suppressed subjects who were actively participating in a Gilead-sponsored study of DRV+COBI plus TVD or F/TAF (Study GS-US-299-0102) and who had reached at least the Week 48 visit were also eligible to receive E/C/F/TAF in extension phase.</p> <p>A PK substudy was conducted in a target of 24 subjects at weeks 4 or 8.</p>	
Population	HIV infected, treatment naïve adults
Study Rationale	Safety and efficacy of E/C/F/TAF
Treatments	<p>E/C/F/TAF (150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF) tablets taken daily with food.</p> <p>Lot numbers for the 48 week study: CP1105B1, CP1105B2, CP1201B1, and CP1203B1R.</p> <p>Lot numbers for the open label extension: CP1208B1, CP1305B1, and CP1311B1.</p> <p>E/C/F/TDF (150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF) tablets taken daily with food.</p> <p>Lot numbers: BK1005B1, BK1104B1, and BK1201B1.</p> <p>E/C/F/TAF placebo.</p> <p>Lot numbers: CP1107B1 and CP1107B2.</p> <p>E/C/F/TDF placebo.</p> <p>Lot numbers: BK1004B1, BK1105B1, and BK1202B1.</p>
Dose Selection Rationale	Same doses used in phase 3

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN (CONTINUED)																																	
Interfering Substances Excluded	Immunosuppressants, chemotherapeutics, medications contraindicated for use with FTC or TDF, and the following:																																
	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;">Drug Class</th> <th style="width: 50%;">Agents Disallowed^a</th> </tr> </thead> <tbody> <tr> <td>Alpha Adrenergic Receptor Antagonists</td> <td>Alfuzosin</td> </tr> <tr> <td>Analeptics</td> <td>Modafenil</td> </tr> <tr> <td>Antibacterials</td> <td>Telithromycin</td> </tr> <tr> <td>Anticonvulsants</td> <td>Phenobarbital, Phenytoin, Carbamazepine, or Oxcarbazepine</td> </tr> <tr> <td>Antifungals</td> <td>Vonconazole</td> </tr> <tr> <td>Antihistamines</td> <td>Astemizole or Terfenadine</td> </tr> <tr> <td>Antimycobacterials</td> <td>Rifampin, Rifapentine, or Rifabutin</td> </tr> <tr> <td>Calcium Channel Blockers</td> <td>Bepidil</td> </tr> <tr> <td>Ergot Derivatives</td> <td>Ergotamine, Ergonovine, Dihydroergotamine, Methylergonovine, Ergometrine</td> </tr> <tr> <td>GI Motility Agents</td> <td>Cisapride</td> </tr> <tr> <td>Herbal Supplements</td> <td>St. John's Wort or Echinacea</td> </tr> <tr> <td>HMG-CoA Reductase Inhibitors</td> <td>Simvastatin, Lovastatin, or Cerivastatin</td> </tr> <tr> <td>Neuroleptics</td> <td>Pimozide</td> </tr> <tr> <td>Sedatives/Hypnotics</td> <td>Midazolam or Triazolam, with the exception of one-time use for procedures</td> </tr> <tr> <td>Systemic Corticosteroids, with the exception of short-term (< 1 week) use of prednisone as a steroid burst</td> <td>All agents, including dexamethasone</td> </tr> </tbody> </table>	Drug Class	Agents Disallowed ^a	Alpha Adrenergic Receptor Antagonists	Alfuzosin	Analeptics	Modafenil	Antibacterials	Telithromycin	Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, or Oxcarbazepine	Antifungals	Vonconazole	Antihistamines	Astemizole or Terfenadine	Antimycobacterials	Rifampin, Rifapentine, or Rifabutin	Calcium Channel Blockers	Bepidil	Ergot Derivatives	Ergotamine, Ergonovine, Dihydroergotamine, Methylergonovine, Ergometrine	GI Motility Agents	Cisapride	Herbal Supplements	St. John's Wort or Echinacea	HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin, or Cerivastatin	Neuroleptics	Pimozide	Sedatives/Hypnotics	Midazolam or Triazolam, with the exception of one-time use for procedures	Systemic Corticosteroids, with the exception of short-term (< 1 week) use of prednisone as a steroid burst	All agents, including dexamethasone
	Drug Class	Agents Disallowed ^a																															
	Alpha Adrenergic Receptor Antagonists	Alfuzosin																															
	Analeptics	Modafenil																															
	Antibacterials	Telithromycin																															
	Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, or Oxcarbazepine																															
	Antifungals	Vonconazole																															
	Antihistamines	Astemizole or Terfenadine																															
	Antimycobacterials	Rifampin, Rifapentine, or Rifabutin																															
	Calcium Channel Blockers	Bepidil																															
	Ergot Derivatives	Ergotamine, Ergonovine, Dihydroergotamine, Methylergonovine, Ergometrine																															
	GI Motility Agents	Cisapride																															
	Herbal Supplements	St. John's Wort or Echinacea																															
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin, or Cerivastatin																																
Neuroleptics	Pimozide																																
Sedatives/Hypnotics	Midazolam or Triazolam, with the exception of one-time use for procedures																																
Systemic Corticosteroids, with the exception of short-term (< 1 week) use of prednisone as a steroid burst	All agents, including dexamethasone																																
<small>^a Administration of any of the above medications was discontinued at least 30 days prior to the baseline (Day 1) visit and for the duration of the study.</small>																																	
Analytes	E/C/F/TAF arm: EVG, COBI, FTC, TAF, TFV, TFV-DP E/C/F/TDF arm: TFV, TFV-DP																																
Sampling Times	All analytes except TFV-DP: Predose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, and 24 hours postdose TFV-DP: predose, and 1, 2, 6, 12, and 24 hours postdose																																

STUDY CONDUCT

Bioanalytical methods

Bioanalytical methods for quantification of EVG, COBI, FTC, TAF, and TFV in plasma were acceptable. TFV-DP method validation and sample analysis reports were not provided.

Protocol deviations

There were no relevant protocol deviations reported for subjects in the E/C/F/TAF intensive PK substudy.

STUDY RESULTS

Study population

Twenty seven subjects completed the PK substudy (Table 17).

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 17. Demographics.

Characteristic	E/C/F/TAF arm (n=19)	E/C/F/TDF arm (n=8)	Total (n=27)
Age	33 (21-52)	42 (28-48)	36 (21-52)
Male	19 (100)	8 (100)	27 (100)
Race			
White	14 (74)	8 (100)	22 (81)
Black	4 (21)		4 (15)
Asian	1 (5)		1 (4)
Hispanic	8 (42)	3 (38)	11 (41)
BMI (kg/m ²)	26 (20-35)	24 (19-28)	26 (19-35)
CrCl (mL/min)	120 (74-247)	135 (95-151)	121 (74-247)

Table prepared by reviewer. Values are median (range) or N(%).

Pharmacokinetics

PK parameters are shown below (Table 18, Table 19, Table 20, Table 22). Compared to the E/C/F/TDF arm, TFV AUC was decreased 91% in the E/C/F/TAF arm (Table 21) and TFV-DP AUC was increased 5.4-fold (Table 22).

Table 18. EVG, COBI, and FTC PK parameters.

	AUC _{tau} (ng·h/mL) Mean (%CV)	C _{max} (ng/mL) Mean (%CV)	C _{tau} (ng/mL) Mean (%CV)	T _{max} (h) Median (Q1, Q3)	t _{1/2} (h) Median (Q1, Q3)
EVG	22,797.0 (34.7)	2113.1 (33.7)	287.3 (61.7)	3.92 (2.00, 4.00)	6.59 (6.18, 7.63)
COBI	9459.1 (33.9)	1450.3 (28.4)	20.6 (85.2)	3.00 (2.00, 3.98)	3.00 (2.81, 3.36)
FTC	11,714.1 (16.6)	2056.3 (20.2)	95.2 (46.7)	1.50 (1.08, 2.00)	6.41 (5.82, 6.97)

Table 19. TAF PK parameters.

	AUC _{last} (ng·h/mL) Mean (%CV) N = 19	C _{max} (ng/mL) Mean (%CV) N = 19	T _{max} (h) Median (Q1, Q3) N = 19	t _{1/2} (h) Median (Q1, Q3) N = 19
TAF	227.5 (47.3)	232.8 (64.6)	1.00 (0.75, 1.50)	0.47 (0.37, 0.87)

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Table 20. TFV PK parameters.

Parameter	Units	E/C/F/TAF (N = 19) ^b	STB (N = 7)
AUC _{tau}	ng•h/mL	326.2 (14.8)	3795.2 (21.9)
C _{max}	ng/mL	18.2 (12.4)	440.6 (27.7)
C _{tau}	ng/mL	11.4 (17.9)	82.8 (26.6)
T _{max} ^a	h	3.00 (1.50, 3.98)	1.50 (0.80, 1.53)
t _{1/2} ^a	h	37.81 (33.02, 45.72)	14.02 (12.06, 17.43)

a Values are listed as mean (%CV) except T_{max} and t_{1/2}, which are listed as median (Q1, Q3)

b For t_{1/2} calculation, n = 15 in the E/C/F/TAF group

Table 21. Statistical comparison of TFV PK parameters.

TFV PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 19)	STB (N = 9)		
AUC _{tau} (ng•h/mL)	322.96	3727.03	8.67	(7.53, 9.98)
C _{tau} (ng/mL)	11.27	80.19	14.05	(11.62, 16.99)
C _{max} (ng/mL)	18.07	426.69	4.23	(3.53, 5.08)

GLSM = geometric least-squares mean

Table 22. TFV-DP PK parameters.

TFV-DP PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 10)	STB (N = 5)		
AUC _{tau} (µM•h)	11.51	2.16	531.83	(295.55, 957.00)

CV% for mean AUC in the E/C/F/TAF and STB arms were 42% and 83%, respectively.

Safety

Common AEs included the following:

- E/C/F/TAF group — nausea (22.3%, 25 subjects); diarrhea (17.0%, 19 subjects); upper respiratory tract infection and fatigue (both 16.1%, 18 subjects); and depression (10.7%, 12 subjects)
- STB group — upper respiratory tract infection (20.7%, 12 subjects); diarrhea (15.5%, 9 subjects); back pain and headache (both 13.8%, 8 subjects); nausea (12.1%, 7 subjects); and cough (10.3%, 6 subjects)

There were no deaths in the study. Overall AEs are summarized below (Table 23).

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 23. Overall summary of AEs.

	E/C/F/TAF (N=112)	STB (N=58)
Subjects Experiencing Any Treatment-Emergent Adverse Event	107 (95.5%)	57 (98.3%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	72 (64.3%)	29 (50.0%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	13 (11.6%)	3 (5.2%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	43 (38.4%)	19 (32.8%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event	9 (8.0%)	1 (1.7%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	1 (0.9%)	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	12 (10.7%)	3 (5.2%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	4 (3.6%)	0

DISCUSSION

This is the only E/C/F/TAF study where multiple dose PK for all analytes in HIV-infected subjects were measured. Although females were eligible for inclusion in the study, the PK substudy only included males (5% of the overall study participants were female).

One deficiency is that the TFV-DP bioanalytical methods were not adequately described. TFV-DP bioanalytical methods were better described for study GS-US-120-0104, where it was clear that the method was not fully validated methods.

LABELING RECOMMENDATIONS

(b) (4)
[REDACTED]
in section 12.3 of the E/C/F/TAF label, we propose including the PK parameters from the E/C/F/TAF arm of this study.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

3.1.4 *GS-US-292-0103 – Single and multiple dose PK of E/C/F/TAF vs single agents in healthy volunteers*

ADMINISTRATIVE	
Study Period	10/5/11-11/21/11
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\gs-us-292-0103\

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN			
Single-center, randomized, open-label, multiple-dose, multiple-cohort, 2-period, crossover study in healthy volunteers.			
Cohort 1			
<u>Treatment A</u> : STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/GS-7340 10 mg			
<u>Treatment B</u> : EVG 150 mg + COBI 150 mg			
Cohort 2			
<u>Treatment A</u> : STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/GS-7340 10 mg			
<u>Treatment C</u> : FTC 200 mg + GS-7340 25 mg			
Each treatment was administered orally once daily, in the morning, with food, for 12 days. Within each cohort, subjects were randomized in a 1:1 ratio to receive treatments in Sequence I or Sequence II, as follows:			
	Period 1	Period 2	
Cohort 1	Days 1-12	Days 13-24	Day 34
Sequence I	A	B	Follow-up
Sequence II	B	A	
Cohort 2			
Sequence I	A	C	
Sequence II	C	A	
Study Rationale	Characterize the single and multiple dose PK of the E/C/F/TAF FDC relative to single agents		
Dose Selection Rationale	This study evaluated the FDC doses used in phase III. Due to a drug-drug interaction between TAF and COBI, the TAF dose is 10 mg when combined with COBI in the FDC versus 25 mg when not combined with COBI.		
Formulation batch #	EVG: AJ0802D1-A; COBI: BB1004B1-A; FTC: 02177AF; TAF: CM1102B1		
Interfering Substances Excluded	All except vitamins, acetaminophen, ibuprofen, and/or hormonal contraceptives		
Sampling Times	<ul style="list-style-type: none"> Day 1 (Cohort 2 only): 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose Day 12: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, and 24 hours postdose Day 13 (Cohort 2 only): 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose Day 24: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, and 48 hours postdose 		

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STUDY CONDUCT

Bioanalytical methods

Bioanalytical methods were acceptable (Table 24).

Table 24. Bioanalytical methods.

Analyte	Method #	Matrix	Method validation or sample analysis deficiencies
EVG	60-0949	Plasma	None
COBI			
FTC	42-0831		
TAF	60-1115		
TFV	42-0831, 60-1116		

Table prepared by reviewer.

Protocol deviations

None reported.

STUDY RESULTS

Study population

34 subjects were randomized; 1 subject withdrew consent during the study. 34 subjects were included in the safety analysis and 33 in the PK analysis (Table 25).

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 25. Subject demographics.

	Cohort 1 (N=14)	Cohort 2 (N=20)	Total (N=34)
Age at Day -1 (Years)			
Mean (SD)	29 (10.1)	34 (7.7)	32 (9.0)
Median	26	36	34
Min, Max	18, 42	20, 45	18, 45
Sex, n (%)			
Male	10 (71.4%)	14 (70.0%)	24 (70.6%)
Female	4 (28.6%)	6 (30.0%)	10 (29.4%)
Race			
Black or African-American	6 (42.9%)	8 (40.0%)	14 (41.2%)
White	8 (57.1%)	12 (60.0%)	20 (58.8%)
Ethnicity, n (%)			
Hispanic/Latino	6 (42.9%)	7 (35.0%)	13 (38.2%)
Non-Hispanic/Latino	8 (57.1%)	13 (65.0%)	21 (61.8%)
Weight (kg)			
Mean (SD)	73.8 (7.92)	75.6 (14.23)	74.9 (11.92)
Median	75.1	78.5	76.0
Min, Max	58.5, 83.6	46.6, 103.5	46.6, 103.5
BMI (kg/m ²)			
Mean (SD)	25.1 (2.82)	25.3 (3.49)	25.2 (3.19)
Median	24.4	25.7	25.5
Min, Max	20.8, 29.4	18.9, 30.4	18.9, 30.4
eGFR _{CG} (mL/min)			
Mean (SD)	123.8 (19.13)	129.1 (25.63)	126.9 (23.01)
Median	122.1	129.1	125.8
Min, Max	93.5, 153.5	95.7, 208.7	93.5, 208.7

BMI = body mass index; eGFR_{CG} = estimated glomerular filtration rate calculated using the Cockcroft-Gault method

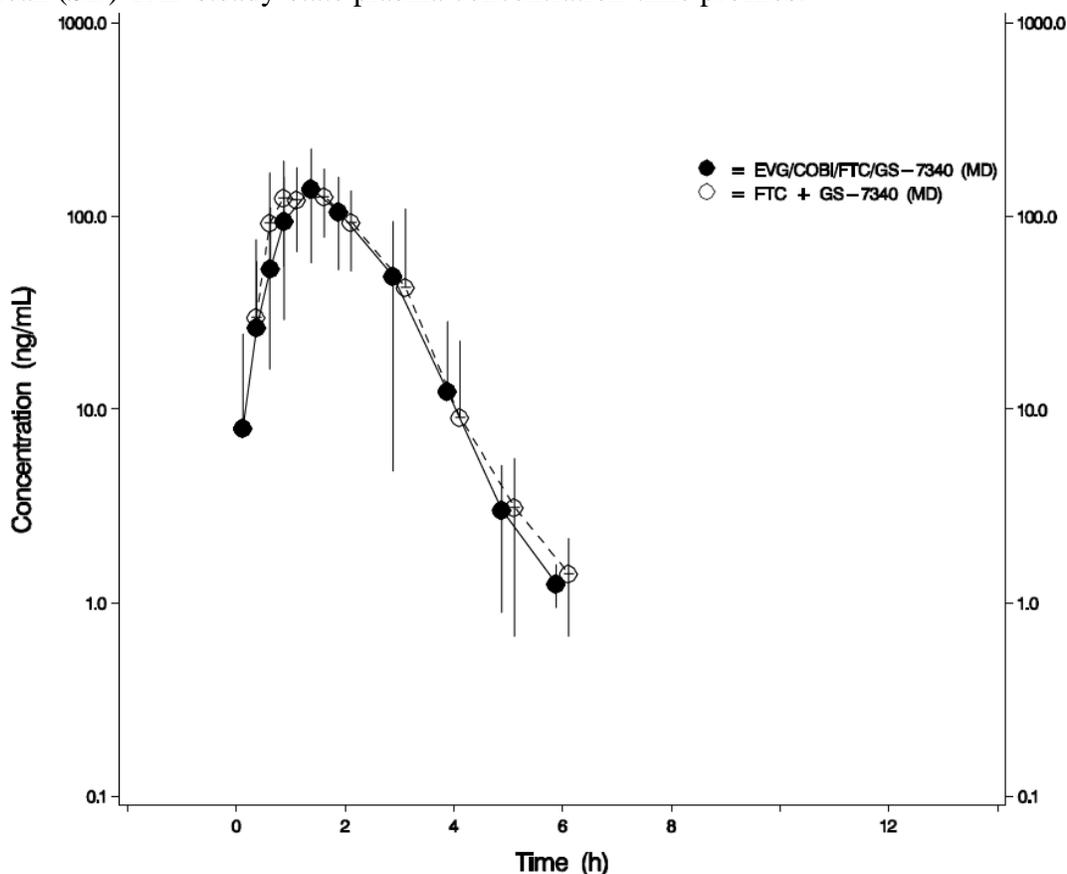
Pharmacokinetics

TAF

After administration of the E/C/F/TAF FDC or TAF single agent, TAF single- and multiple-dose PK was similar (Figure 12, Table 26, Table 27, Table 28). After multiple dosing, there was no accumulation of TAF.

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Figure 12. Mean (SD) TAF steady-state plasma concentration-time profiles.



● = EVG/COBI/FTC/GS-7340 (MD) (n=): 19 19 7
 ○ = FTC + GS-7340 (MD) (n=): 19 19 8

Table 26. Single-dose TAF PK parameters.

GS-7340 PK Parameter	EVG/COBI/FTC/GS-7340 10 mg (Treatment A) (N = 10)	FTC + GS-7340 25 mg (Treatment C) (N = 9)
AUC _{last} (ng•h/mL)	244.8 (17.2)	235.7 (29.2)
AUC _{inf} (ng•h/mL)	246.2 (17.2)	237.0 (28.9)
%AUC _{exp}	0.6 (42.2)	0.6 (45.6)
C _{max} (ng/mL)	167.2 (38.6)	158.8 (28.2)
T _{max} (h)	1.00 (1.00, 2.00)	1.00 (0.50, 1.00)
t _{1/2} (h)	0.47 (0.43, 0.59)	0.47 (0.42, 0.53)

Data are presented as mean (%CV), except T_{max} and t_{1/2} which are presented as median (Q1, Q3). C_{tau} was below the limit of quantitation for all samples.

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Table 27. Multiple-dose TAF PK parameters.

GS-7340 PK Parameter	Cohort 1	Cohort 2	
	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 14)	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 19)	FTC + GS-7340 25 mg Treatment C (N = 19)
AUC _{last} (ng•h/mL)	245.4 (33.9)	250.2 (24.7)	278.2 (28.8)
C _{max} (ng/mL)	169.8 (28.3)	176.9 (35.1)	179.5 (33.9)
T _{max} (h)	1.50 (1.00, 2.00)	1.50 (1.50, 2.00)	1.00 (0.75, 1.50)
t _{1/2} (h)	0.49 (0.44, 0.61)	0.57 (0.41, 0.63)	0.48 (0.44, 0.64)

Data are presented as mean (%CV), except T_{max} and t_{1/2} which are presented as median (Q1, Q3). AUC_{last} is presented rather than AUC_{tau} because GS-7340 plasma concentrations are below the limit of quantitation (BLQ) by approximately 5 hours postdose, and this parameter provides a more appropriate measure of exposure. C_{tau} was BLQ for all subjects.

Table 28. Comparison of TAF steady-state PK parameters between E/C/F/TAF and TAF single agent.

GS-7340 PK Parameter	Geometric Least-Squares Mean		Geometric Least-Squares Means Ratio (%) (90% CI)
	Test EVG/COBI/FTC/GS-7340 10 mg (N = 19)	Reference FTC + GS-7340 25 mg (N = 19)	
AUC _{last} (ng•h/mL)	243.66	266.53	91.42 (84.12, 99.35)
C _{max} (ng/mL)	167.09	169.33	98.68 (84.57, 115.13)

TFV

Compared to TFV single agent, TFV AUC in the E/C/F/TAF group was somewhat increased, with 90% CIs slightly above 125% (Figure 13, Table 29, Table 30, Table 31). The large variability in the F/TAF concentration-time profile at the two hour timepoint was due to one subject with a greatly elevated C_{max} of ~80 ng/mL (Figure 13).

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Figure 13. Mean (SD) TFV plasma steady-state concentration-time profiles.

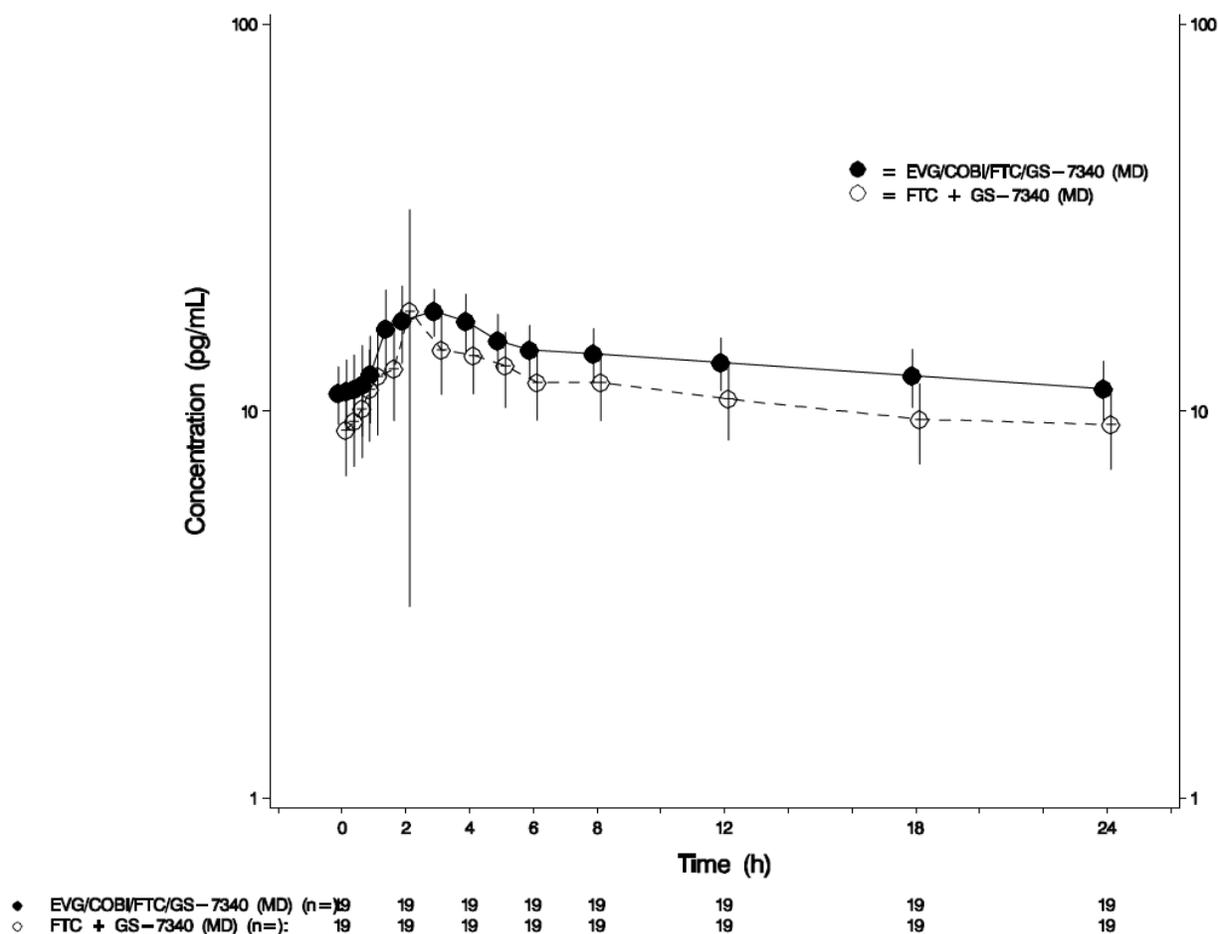


Table 29. TFV single dose PK parameters.

TFV PK Parameter	EVG/COBI/FTC/GS-7340 10 mg (Treatment A) (N = 10)	FTC + GS-7340 25 mg (Treatment C) (N = 9)
AUC _{last} (ng•h/mL)	97.4 (16.1)	99.4 (14.8)
AUC _{inf} (ng•h/mL)	317.0 (27.2)	233.5 (19.7)
AUC _{exp} (%)	66.7 (17.6)	57.0 (7.0)
C _{max} (ng/mL)	8.7 (13.2)	8.6 (20.4)
T _{max} (h)	2.00 (1.50, 3.00)	2.00 (1.00, 2.00)

Data are presented as mean (%CV) except T_{max} which is presented as median (Q1, Q3).

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Table 30. TFV multiple dose PK parameters.

TFV PK Parameter	Cohort 1	Cohort 2	
	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 14)	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 19)	FTC + GS-7340 25 mg Treatment C (N = 19)
AUC _{tau} (ng•h/mL)	329.5 (15.2)	324.2 (15.4)	265.9 (22.2)
C _{max} (ng/mL)	19.2 (15.7)	19.6 (13.9)	19.2 (76.0)
C _{tau} (ng/mL)	11.2 (16.6)	11.4 (17.8)	9.2 (23.5)
T _{max} (h)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)
t _{1/2} (h) ^a	41.13 (37.56, 51.69)	46.46 (35.25, 53.83)	41.02 (39.00, 51.73)

Data are presented as mean (%CV), except T_{max} and t_{1/2} which are presented as median (Q1, Q3)

a For t_{1/2} n = 18 in EVG/COBI/FTC/GS-7340 (Cohort 2) and n = 16 in FTC + GS-7340

Table 31. Comparison of TFV steady-state PK parameters between E/C/F/TAF and TFV single agent.

TFV PK Parameter	Geometric Least-Squares Mean		Geometric Least-Squares Means Ratio (%) (90% CI)
	Test EVG/COBI/FTC/GS-7340 10 mg (N = 19)	Reference FTC + GS-7340 25 mg (N = 19)	
AUC _{tau} (ng•h/mL)	320.54	259.28	123.63 (116.97, 130.67)
C _{max} (ng/mL)	19.35	16.95	114.16 (97.52, 133.64)
C _{tau} (ng/mL)	11.22	8.95	125.37 (117.72, 133.51)

EVG

After administration of the E/C/F/TAF FDC or EVG single agent, EVG multiple-dose PK was similar, with 90% CIs within 80-125% (Figure 14, Table 32, Table 33).

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Figure 14. Mean (SD) EVG steady-state plasma concentration-time profiles.

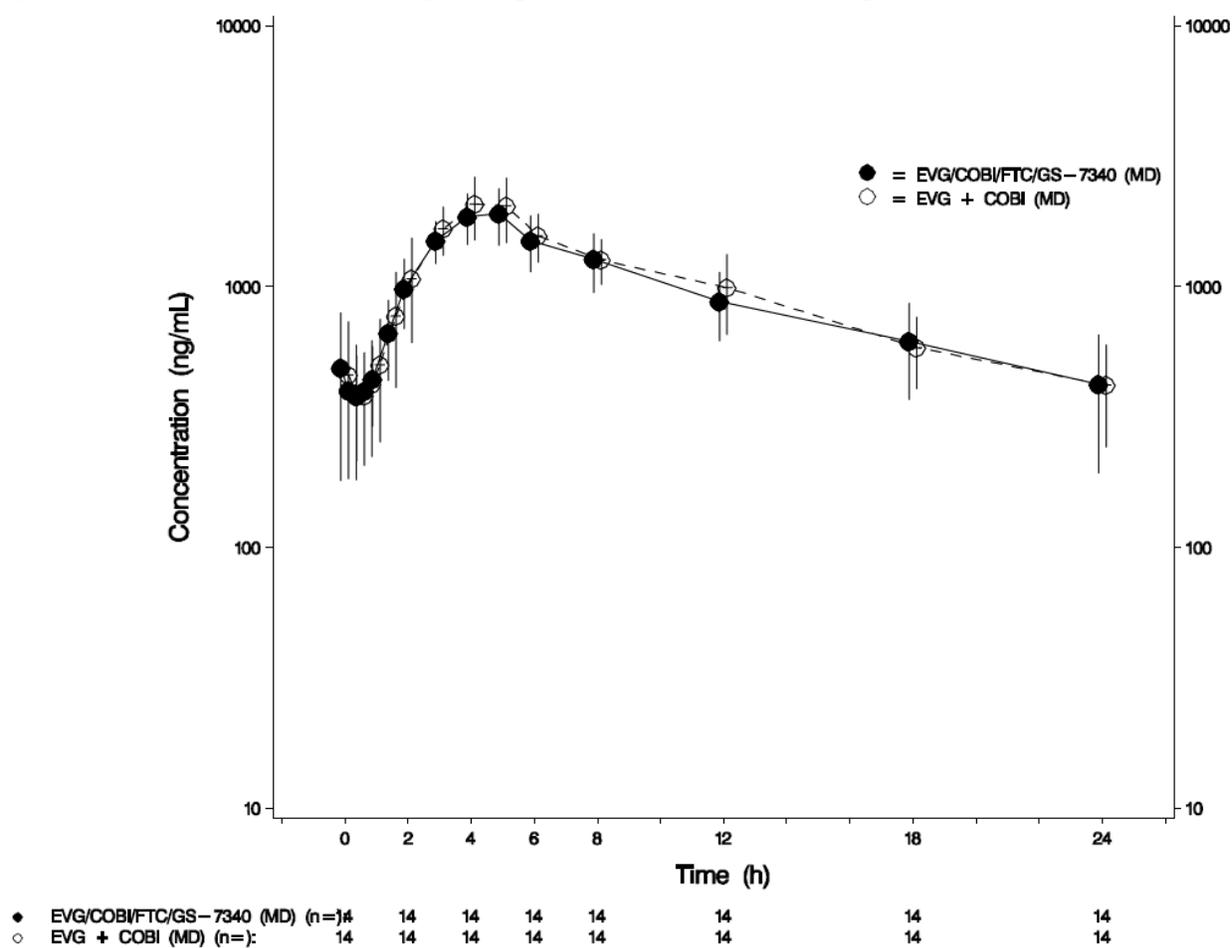


Table 32. EVG multiple-dose PK parameters.

EVG PK Parameter	Cohort 2	Cohort 1	
	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 19)	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 14)	EVG + COBI Treatment B (N = 14)
AUC _{tau} (ng•h/mL)	23651.0 (33.5)	22067.1 (26.3)	23099.2 (22.7)
C _{max} (ng/mL)	2238.8 (30.2)	1943.5 (23.9)	2161.0 (27.0)
C _{tau} (ng/mL)	470.4 (44.0)	422.2 (54.4)	418.6 (42.2)
T _{max} (h)	5.00 (4.00, 5.00)	5.00 (4.00, 5.00)	4.03 (4.00, 5.00)
t _{1/2} (h)	9.79 (7.42, 11.82)	9.98 (8.47, 11.02)	9.94 (8.59, 11.05)

Data are presented as mean (%CV), except T_{max} and t_{1/2} which are presented as median (Q1, Q3)

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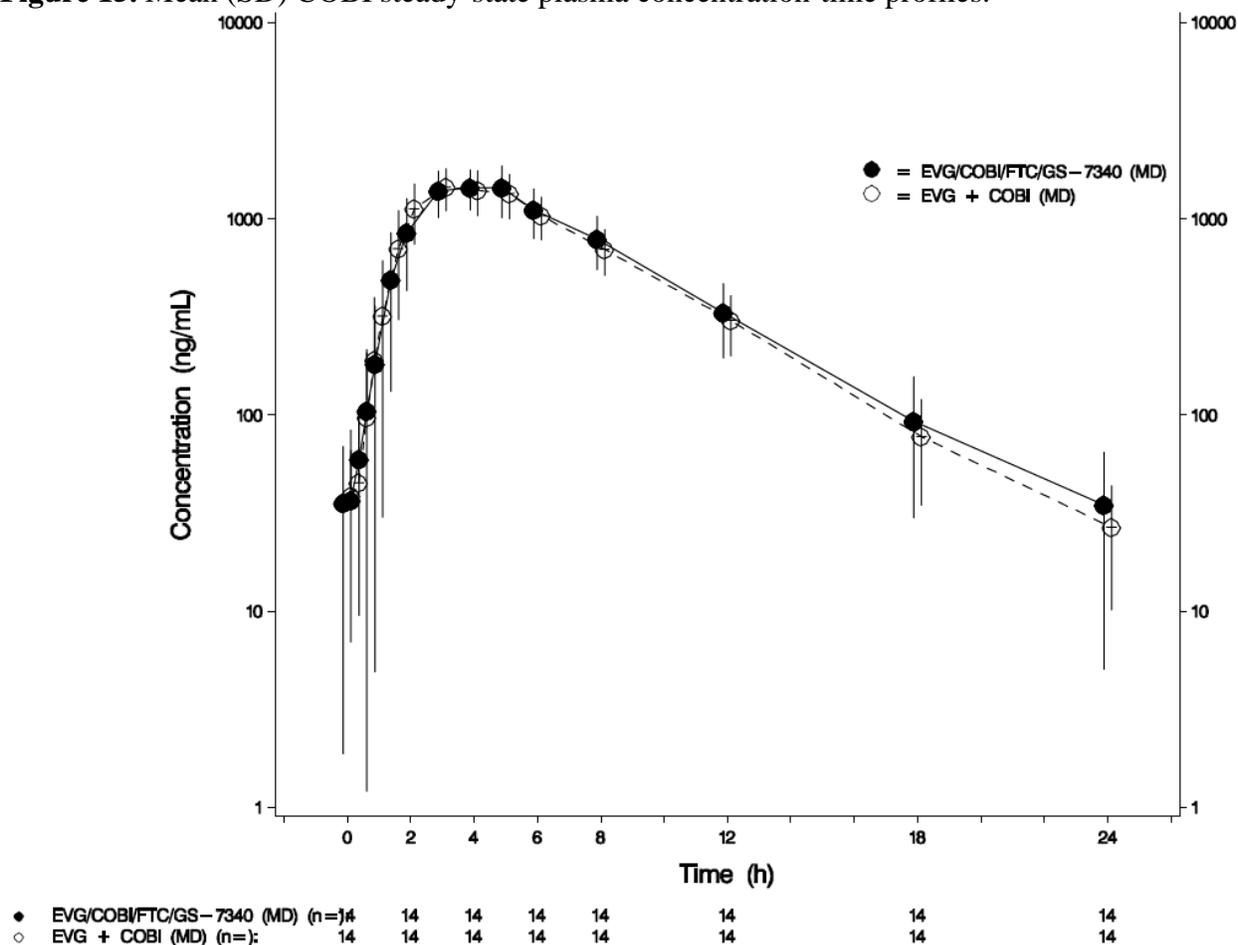
Table 33. Comparison of EVG steady-state PK parameters between E/C/F/TAF and EVG single agent.

EVG PK Parameter	Geometric Least-Squares Mean		Geometric Least-Squares Means Ratio (%) (90% CI)
	Test EVG/COBI/FTC/GS-7340 (N = 14)	Reference EVG + COBI (N = 14)	
AUC _{tau} (ng•h/mL)	21426.41	22583.98	94.87 (91.51, 98.36)
C _{max} (ng/mL)	1891.43	2094.17	90.32 (85.07, 95.89)
C _{tau} (ng/mL)	377.82	386.21	97.83 (88.39, 108.27)

COBI

After administration of the E/C/F/TAF FDC or COBI single agent, COBI multiple-dose PK was similar, with only the 90% CI for C_{tau} being slightly above 125% (Figure 15, Table 34, Table 35).

Figure 15. Mean (SD) COBI steady-state plasma concentration-time profiles.



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Table 34. COBI multiple dose PK parameters.

COBI PK Parameter	Cohort 2	Cohort 1	
	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 19)	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 14)	EVG + COBI Treatment B (N = 14)
AUC _{tau} (ng•h/mL)	10273.5 (21.7)	11209.8 (27.4)	10931.2 (25.5)
C _{max} (ng/mL)	1503.5 (19.6)	1560.7 (26.1)	1489.4 (23.2)
C _{tau} (ng/mL)	30.7 (63.0)	34.6 (85.5)	26.7 (62.1)
T _{max} (h)	4.00 (3.00, 5.00)	3.50 (3.00, 5.00)	3.00 (3.00, 4.00)
t _{1/2} (h)	3.34 (2.91, 3.77)	3.41 (2.88, 3.59)	3.27 (3.06, 3.66)

Data are presented as mean (%CV), except T_{max} and t_{1/2} which are presented as median (Q1, Q3)

Table 35. Comparison of COBI steady-state PK parameters between E/C/F/TAF and COBI single agent.

COBI PK Parameter	Geometric Least-Squares Mean		Geometric Least-Squares Means Ratio (%) (90% CI)
	Test EVG/COBI/FTC/GS-7340 (N = 14)	Reference EVG + COBI (N = 14)	
AUC _{tau} (ng•h/mL)	10815.14	10602.88	102.00 (98.10, 106.06)
C _{max} (ng/mL)	1508.41	1449.45	104.07 (99.41, 108.94)
C _{tau} (ng/mL)	26.05	22.37	116.43 (102.05, 132.83)

FTC

After administration of the E/C/F/TAF FDC or FTCsingle agent, FTC multiple-dose PK was similar, with only the 90% CI for C_{tau} being slightly above 125% (Figure 16, Table 36, Table 37).

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Figure 16. Mean (SD) FTC steady-state plasma concentration-time profiles.

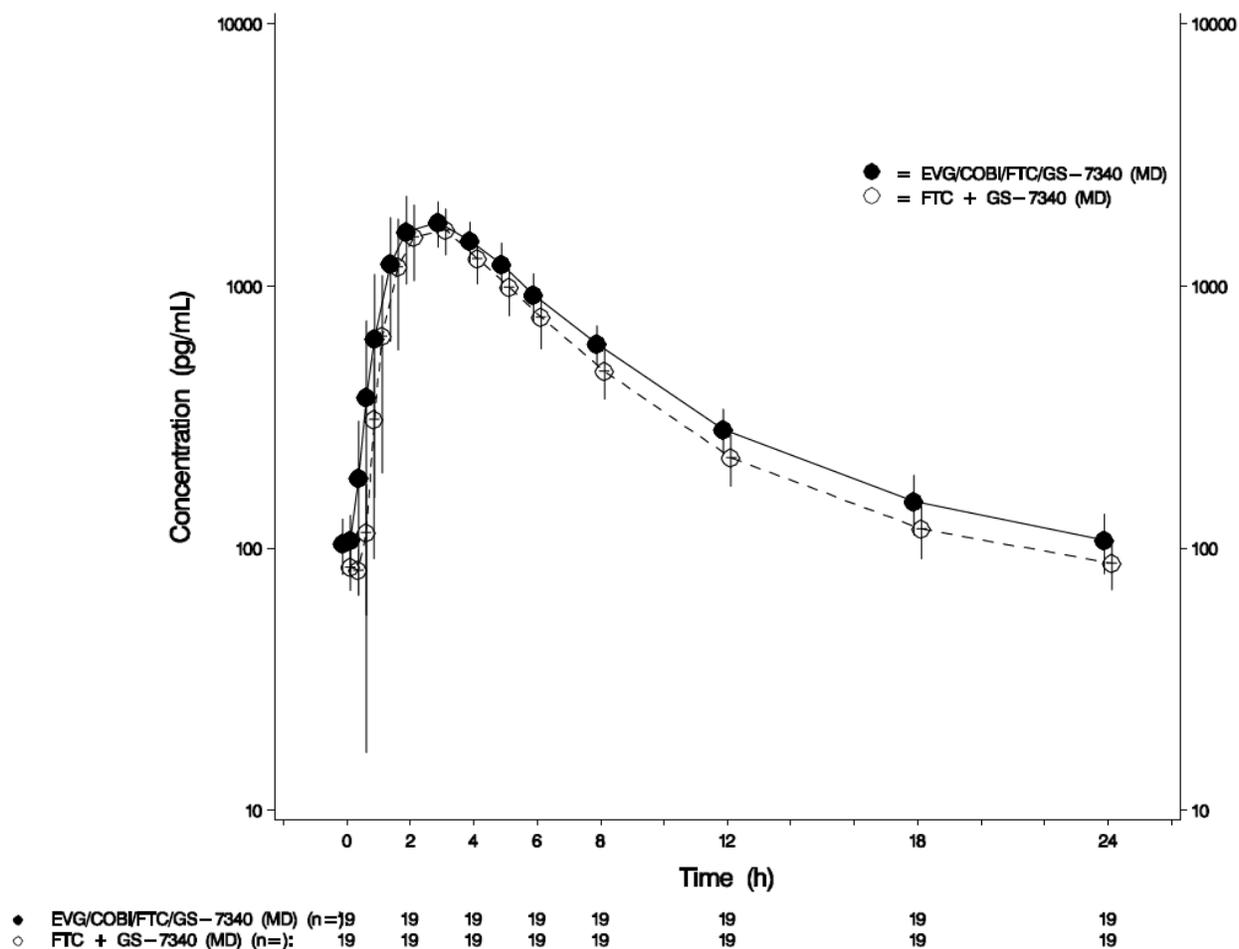


Table 36. Steady-state FTC PK parameters.

FTC PK Parameter	Cohort 1		Cohort 2
	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 14)	EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 19)	FTC + GS-7340 25 mg Treatment C (N = 19)
AUC _{tau} (ng•h/mL)	12302.0 (16.6)	12352.6 (13.5)	10520.9 (13.8)
C _{max} (ng/mL)	1948.8 (20.4)	1947.0 (21.2)	1788.8 (19.2)
C _{tau} (ng/mL)	103.4 (24.3)	107.4 (25.8)	87.5 (20.6)
T _{max} (h)	2.00 (2.00, 3.00)	3.00 (2.00, 3.00)	2.00 (2.00, 3.00)
t _{1/2} (h)	10.83 (8.59, 17.89)	10.02 (8.78, 18.49)	16.02 (8.62, 24.34)

Data are presented as mean (%CV), except T_{max} and t_{1/2} which are presented as median (Q1, Q3)

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Table 37. Comparison of FTC steady-state PK parameters between E/C/F/TAF and FTC single agent.

FTC PK Parameter	Geometric Least-Squares Mean		Geometric Least-Squares Means Ratio (%) (90% CI)
	Test EVG/COBI/FTC/GS-7340 10 mg Treatment A (N = 19)	Reference FTC + GS-7340 25 mg Treatment C (N = 19)	
AUC _{tau} (ng•h/mL)	12255.60	10423.78	117.57 (113.72, 121.55)
C _{max} (ng/mL)	1915.19	1757.17	108.99 (102.81, 115.55)
C _{tau} (ng/mL)	103.88	85.67	121.26 (114.66, 128.24)

Antiviral activity

At Week 24, 91.3% of subjects (21 of 23) in the Week 24 full analysis set had virologic success (FDA snapshot algorithm, HIV-1 RNA < 50 copies/mL) (Table 38).

Table 38. Week 24 antiviral activity.

HIV-1 RNA Category ^a	E/C/F/TAF (N = 23)
Virologic Success at Week 24 ^b	
HIV-1 RNA < 50 copies/mL	21 (91.3%)
Virologic Failure at Week 24 ^b	2 (8.7%)
HIV-1 RNA ≥ 50 copies/mL	2 (8.7%)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL ^c	0
Added New ARV	0
No Virologic Data in Week 24 Window ^b	0
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^c	0
Missing Data during Window but on Study Drug	0

a The Week 24 FAS included subjects in the FAS who were enrolled by 11 February 2014.

b The Week 24 window was between Days 140 and 195 (inclusive).

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

Safety

AEs considered related to study drug included one subject who received EVG/c and reported pruritus, and one subject who received F/TAF and reported dermatitis. There were no SAEs. No subject prematurely discontinued due to an AE.

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CONCLUSIONS

Comparing the components of the E/C/F/TAF FDC and their corresponding single agents, there were no clinically-relevant differences in exposures.

LABEL RECOMMENDATIONS

No labeling is derived from this study.

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3.1.5 GS-US-292-0106 – Multiple dose PK of E/C/F/TAF in HIV-infected adolescents [Interim report]

ADMINISTRATIVE	
Study Period	5/6/2013-8/22/2014
Study report link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-292-0106
Response to Information Request for additional PK analysis	\\CDSESUB1\evsprod\NDA207561\0016\m1\us\111-info-amendment

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN	
Open-label study.	
<p>QD = once daily; F/U = follow-up</p> <p>^a Screening for Part B commenced after the PK data from Part A confirmed the adolescent dose of E/C/F/TAF.</p>	
<p>The objective of Part A was evaluation of steady-state E/C/F/TAF intensive PK at week 4. The objectives of Part B were safety, tolerability, and antiviral activity through Week 48.</p>	
Population	<input type="checkbox"/> Healthy Volunteers <input checked="" type="checkbox"/> Patients
Study Rationale	E/C/F/TAF PK, safety, tolerability, and antiviral activity (through Week 48)
Treatments	E/C/F/TAF (150/150/200/10 mg) daily
Dose Selection Rationale	Same as adult dose studied in phase 3
Administration	<input type="checkbox"/> Fasted <input checked="" type="checkbox"/> Fed
Formulation	Fixed dose combination tablet, Lot numbers: CP1205B1, CP1303B1, CP1308B1, CP1310B1, CP1311B1, and CP1313B1
Sampling Times	<p><u>Intensive PK</u> All subjects in Part A: Week 4 blood samples were collected predose (0 hours), 5 minutes postdose, and 0.25, 0.5, 1, 1.5, 2, 4, 5, 8, and 24 hours postdose</p> <p><u>Single PK sample</u> All subjects: single sample at weeks 4 (Part B only), 8, 12, 16, 32, and 40</p> <p><u>Trough PK sample</u> All subjects: trough (20-24 hour postdose) collected at weeks 1, 2, 24, and 48</p>

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STUDY DESIGN (CONTINUED)		
Interfering Substances Excluded	Drug Class	Agents Disallowed^a
	Alpha Adrenergic Receptor Antagonists	Alfuzosin
	Analeptics	Modafinil
	Antibacterials	Telithromycin
	Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
	Antifungals	Voriconazole
	Antihistamines	Astemizole, Terfenadine
	Antimycobacterials	Rifampin, Rifapentine, Rifabutin
	Endothelin Receptor Antagonists	Bosentan
	Calcium Channel Blockers	Bepridil
	Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylegonovine Ergometrine
	GI Motility Agents	Cisapride
	Herbal Supplements	St John's Wort, Echinacea
	HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin, Cerivastatin
	Neuroleptics	Pimozide
	Sedatives/Hypnotics	Midazolam, Triazolam
	Systemic ^b Glucocorticoids with the exception of short-term (≤ 1 week) use of prednisone as a steroid burst	All agents, including dexamethasone
<p>a Administration of any of the above medications must have been discontinued at least 21 days prior to the baseline/Day 1 visit and for the duration of the study.</p> <p>b Systemic use was defined as intravenously or orally administered corticosteroid.</p>		

STUDY CONDUCT

Bioanalytical methods

Method validation and sample analysis were acceptable for EVG, FTC, TAF, and TFV (Table 39). During sample analysis of COBI, consistent interference was observed in the blank, extracted blank, and carryover blanks. This interference is estimated to result in a bias in sample concentration of 16-29% for samples <10 ng/mL, 7-16% at concentrations of 10-25 ng/mL, and minimal bias at concentrations >25 ng/mL (Table 40). The COBI calibration range for method 60-1343 is 5-2500 ng/mL. Samples <10 ng/mL comprised 31/210 (15%) adolescent non-BQL intensive PK samples. As the interference is only significant at low concentrations, this issue is not expected to significantly affect estimation of COBI C_{max} or AUC. As a result, the COBI sample concentrations and PK analyses were accepted as reported.

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Table 39. Bioanalytical methods.

Analyte	Method	Deficiencies
EVG	60-1343	None
COBI	60-1343	Interference during sample analysis
FTC	42-0831	None
TAF	60-1115	None
TFV	60-1368, 42-0831	None

Table prepared by reviewer.

Table 40. Effect of interference on COBI sample concentrations.

Calibration sample (ng/mL)	Peak area			Subtract interfering peak with area of 2900			% Difference in instrument response (analyte/IS)
	analyte	IS	analyte/IS	analyte	IS	analyte/IS	
5	9851	155742	0.063	6951	155742	0.045	29%
10	18654	155207	0.120	15754	155207	0.102	16%
25	42503	156712	0.271	39603	156712	0.253	7%
75	111274	145093	0.767	108374	145093	0.747	3%
250	396003	161284	2.455	393103	161284	2.437	1%
750							<1%
2250							
2500							

Table prepared by reviewer.

Protocol deviations

Five important protocol deviations were reported. Two involved overdose of study drug for two subjects in part B, which does not affect the PK results as PK was assessed in Part A. The other three deviations involved week 1 and week 2 laboratory samples, which did not affect the PK analysis as it was conducted at week 4.

STUDY RESULTS ()

Study population

The PK substudy is complete. Part B is ongoing. 48 subjects were enrolled; 47 subjects are still in the study and one subject has completed the study (Table 41).

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Table 41. Subject demographics in the PK substudy.

	E/C/F/TAF (n=24)
Age (years)	15 (12-17)
Male sex	13 (54.2%)
Race	
Asian	4 (16.7%)
Black	20 (83.3%)
Hispanic ethnicity	0
Baseline weight (kg)	51 (35-80)
Baseline BMI (kg/m ²)	19 (16-27)

Table prepared by reviewer. Values are median (range) or N (%).

Concomitant medications

The list of concomitant medications reported for subjects in the study did not include any CYP3A inducers. Only one subject was taking a concomitant oral CYP3A inhibitor during the study (isoniazid). As isoniazid is a much weaker CYP3A inhibitor compared to COBI, there is no impact on the study.

Pharmacokinetics

The PK of E/C/F/TAF in adolescents was compared to a pooled intensive PK dataset from study GS-US-292-0102 in HIV-infected adults and study GS-US-292-0103 in healthy adults. Compared to adults, several analytes had reduced exposure (90% CIs outside of 80-125%) in adolescents, including EVG (C_{trough}), TAF, and COBI (Table 42). While EVG C_{trough} was decreased compared to adults, all subjects exceeded the target for antiviral efficacy (protein-adjusted IC_{95} of 45 ng/mL, Figure 17). As EVG C_{trough} appeared to differ between HIV-infected and HIV-uninfected adults, we asked the sponsor to limit the statistical PK comparison to adolescents versus HIV-infected adults. In this analysis, compared to adults, EVG C_{trough} was similar though with wide confidence intervals, while TAF and COBI exposures remained decreased (Table 43).

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Table 42. PK comparison of adolescents versus adults (HIV-infected plus HIV-uninfected).

PK Parameter	GLSMs		GLSM Ratio (%)	90% CI
	GS-US-292-0106 (Test) (N = 24)	GS-US-292-0102, GS-US-292-0103 (Reference) (N = 52)		
EVG				
AUC _{tau} (ng•h/mL)	23128.88	21865.51	105.78	94.66, 118.21
C _{max} (ng/mL)	2186.24	2023.29	108.05	97.87, 119.30
C _{trough} (ng/mL)	234.44	338.24	69.31	52.79, 91.01
TAF				
AUC _{last} (ng•h/mL)	159.50	225.53	70.72	56.12, 89.11
C _{max} (ng/mL)	135.19	173.97	77.71	59.88, 100.85
TFV				
AUC _{tau} (ng•h/mL) ^a	282.64	322.64	87.60	81.23, 94.47
C _{max} (ng/mL)	17.18	18.78	91.50	83.93, 99.75
C _{trough} (ng/mL)	9.73	11.20	86.94	79.73, 94.81
COBI				
AUC _{tau} (ng•h/mL) ^a	7762.56	9832.00	78.95	68.68, 90.75
C _{max} (ng/mL)	1144.60	1456.27	78.60	69.71, 88.62
C _{trough} (ng/mL) ^{b,c}	13.42	22.21	60.41	39.13, 93.26
FTC				
AUC _{tau} (ng•h/mL)	14,007.48	11,964.30	117.08	106.68, 128.49
C _{max} (ng/mL)	2209.14	1947.42	113.44	103.49, 124.35
C _{trough} (ng/mL) ^a	94.98	97.42	97.49	83.42, 113.94

GLSM = geometric least-squares mean

a N = 23 for the Test group

b N = 15 for the Test group

c N = 51 for the Reference group

Figure 17. EVG C_{trough} by population.

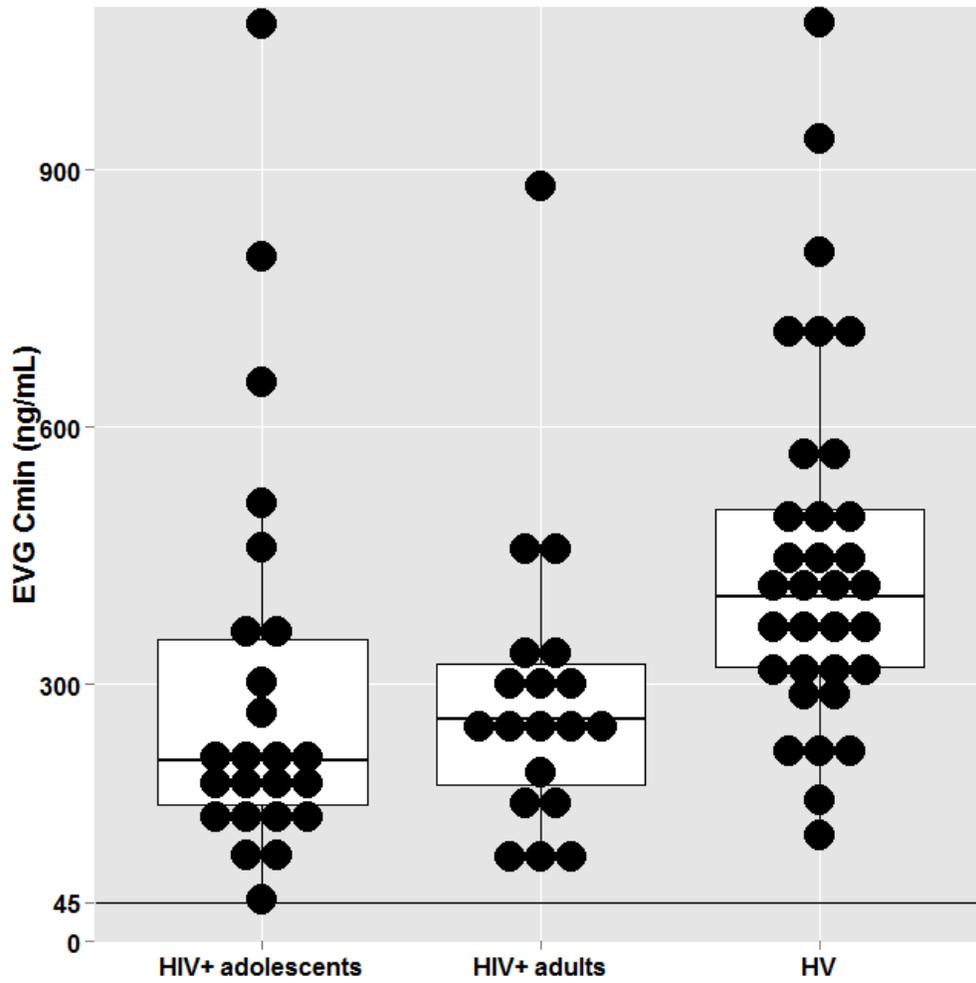


Figure prepared by reviewer. HV=healthy volunteers.

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Table 43. PK comparison of adolescents versus HIV-infected adults.

PK Parameter	GLSMs		GLSM Ratio (%)	90% CI
	Test (Study GS-US-292-0106) (N = 24)	Reference (Historical Control) (N = 19)		
EVG				
AUC _{tau} (ng•h/mL)	23128.88	21553.74	107.31	91.55, 125.78
C _{max} (ng/mL)	2186.24	1997.55	109.45	93.88, 127.59
C _{trough} (ng/mL)	234.44	247.71	94.64	68.45, 130.86
TAF				
AUC _{last}	159.50	206.19	77.35	58.60, 102.12
C _{max}	135.19	191.23	70.69	49.94, 100.07
TFV				
AUC _{tau} (ng•h/mL)	282.64	322.96	87.52	80.22, 95.47
C _{max} (ng/mL)	17.18	18.07	95.13	86.55, 104.55
C _{trough} (ng/mL)	9.73	11.27	86.38	77.96, 95.70
COBI				
AUC _{tau} (ng•h/mL)	7762.56	8975.72	86.48	72.36, 103.36
C _{max} (ng/mL)	1144.60	1400.19	81.75	70.44, 94.86
C _{trough} (ng/mL)	13.42	17.01	78.87	48.20, 129.06
FTC				
AUC _{tau} (ng•h/mL)	14,007.48	11576.55	121.00	108.92, 134.42
C _{max} (ng/mL)	2209.14	2014.35	109.67	97.81, 122.97
C _{trough} (ng/mL)	94.98	89.11	106.58	87.89, 129.25

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Safety

A number of study drug-related AEs were reported (Table 44). One subject had a study-drug related SAE (visual impairment and intermediate uveitis). No AEs led to study discontinuation and there were no deaths.

Table 44. Study drug-related AEs.

Adverse Event by System Organ Class and Preferred Term ^{a,b}	E/C/F/TAF (N = 48)
Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug	18 (37.5%)
Eye disorders	1 (2.1%)
Intermediate uveitis	1 (2.1%)
Visual impairment	1 (2.1%)
Gastrointestinal disorders	17 (35.4%)
Nausea	10 (20.8%)
Abdominal pain	6 (12.5%)
Vomiting	5 (10.4%)
Abdominal pain upper	3 (6.3%)
Diarrhoea	3 (6.3%)
Dyspepsia	1 (2.1%)
Flatulence	1 (2.1%)
General disorders and administration site conditions	1 (2.1%)
Fatigue	1 (2.1%)
Infections and infestations	1 (2.1%)
Chorioretinitis	1 (2.1%)
Metabolism and nutrition disorders	2 (4.2%)
Decreased appetite	1 (2.1%)
Increased appetite	1 (2.1%)
Nervous system disorders	7 (14.6%)
Somnolence	3 (6.3%)
Dizziness	2 (4.2%)
Headache	2 (4.2%)
Lethargy	1 (2.1%)

a Adverse events were coded using MedDRA 17.0.

b Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively. System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies.

DISCUSSION

Compared to adults administered E/C/F/TAF, adolescent exposures were decreased for EVG C_{trough} , TAF, and COBI. Though EVG C_{trough} was decreased compared to adults, all adolescents had values above the target for antiviral efficacy. TAF has flat exposure-response relationships for efficacy and safety, thus 30% reduced exposures are acceptable. COBI exposures are of secondary importance, as the purpose of COBI is to increase the exposures of EVG and TAF. In conclusion, while E/C/F/TAF exposures were decreased in adolescents compared to adults, exposures were overall acceptable.

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LABEL RECOMMENDATIONS

Label section 12.3 does not include PK parameters of E/C/F/TAF in adolescents, though the following statement is made: “ (b) (4)

We recommend the following: “Exposures of tenofovir alafenamide achieved in 24 pediatric subjects aged 12 to < 18 years who received [TRADENAME] in Study 106 were decreased compared to exposures achieved in treatment-naïve adults following administration of [TRADENAME], but were deemed acceptable based on exposure-response relationships.”

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3.2 Intrinsic factors

3.2.1 *GS-US-120-0108 – PK of TAF in subjects with severe renal impairment*

ADMINISTRATIVE	
Study Period	5/7/2012-8/20/2012
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-120-0108\report-body-revised.pdf

STUDY DESIGN	
Open-label, parallel, single-dose study.	
<p style="text-align: center;"> -28 Days Day 0 Day 1 Day 7 Day 14: Follow-up Screening Single Dose Discharge </p> <p style="text-align: center;">Days 1-7: X*</p>	
<div style="display: flex; align-items: center; margin-bottom: 5px;"> <div style="width: 20px; height: 10px; background-color: #808080; margin-right: 5px;"></div> Clinic Confinement </div> <div style="display: flex; align-items: center; margin-bottom: 5px;"> X Urine Collection </div> <div style="display: flex; align-items: center;"> * Intensive PK Sampling </div>	
Population	HIV- and HBV-negative subjects with severe renal impairment (Cockcroft-Gault CrCL ≥ 15 mL/min to ≤ 29 mL/min) and matched subjects with normal renal function (Cockcroft-Gault CrCL ≥ 90 mL/min)
Study Rationale	Determine the impact of severe renal impairment on the PK of TAF
Treatments	Single TAF 25 mg dose (tablet, lot numbers: CM1102B1, CM1202B1, and CM1102B1-A) taken orally within 5 minutes of consuming a standardized meal
Dose Selection Rationale	TAF 25 mg produces equivalent exposures to TAF 10 mg administered as part of E/C/F/TAF
Interfering Substances Excluded	Severe renal impairment: <ul style="list-style-type: none"> • Treatment with probenecid, chronic high-dose NSAIDs, or nephrotoxic drugs within 28 days of study entry • All concomitant medications including herbals must have been approved by the medical monitor prior to enrollment

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	Control group: any prescription, herbal, or over the counter medications within 28 days of starting the study unless approved by the medical monitor
Sampling Times	Plasma: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours postdose Urine collection intervals: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, and 120-144 hours after dosing
Analytes	TAF and TFV
PK Analysis	Noncompartmental

STUDY CONDUCT

Bioanalytical methods

Bioanalytical methods were acceptable (Table 45).

Table 45. Bioanalytical methods.

Analyte	Matrix	Validation method #	Deficiencies
TAF	plasma	60-1115	None
TFV	plasma	60-1116	
TAF	urine	60-1220	
TFV	urine	60-1220	

Table prepared by reviewer.

Concomitant medications

During the study, one subject in the severe renal impairment group (1225-1009) used the concomitant Pgp inhibitor nifedipine. This was not discussed in the study report. TAF AUC in this subject was below the median for the severe renal impairment group, while TFV AUC was the second highest in the group. Removing this subject from the TFV dataset changed the geometric mean for AUC_{inf} from 1902.6 ng*h/mL to 1819.6 ng*h/mL, a 4% difference. Due to this small change, the subject was not excluded from the analysis.

Protocol deviations

Compared to the matched subject with severe renal impairment, one healthy subject was enrolled even though BMI exceeded the protocol-specified limit of +15%.

STUDY RESULTS

Study population

14 subjects with severe renal impairment and 13 matched controls were enrolled, dosed, and completed study drug. Demographic characteristics were well matched between groups (Table 46).

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Table 46. Demographics.

Characteristic	Severe Renal Impairment (N=14)	Normal Renal Function (N=13)
Age at Day 1 (years)		
Mean (SD)	65 (8.3)	63 (6.4)
Median (Min, Max)	66 (46, 73)	64 (53, 74)
Sex (n, %)		
Male	6 (42.9)	6 (46.2)
Female	8 (57.1)	7 (53.8)
Race (n, %)		
African-American	3 (21.4)	1 (7.7)
White	11 (78.6)	12 (92.3)
Ethnicity (n, %)		
Hispanic/Latino	2 (14.3)	3 (23.1)
Nonhispanic/Latino	12 (85.7)	10 (76.9)
Weight (kg)		
Mean (SD)	72.9 (13.60)	82.3 (11.65)
Median (Min, Max)	74.7 (56.4, 99.0)	82.6 (64.2, 99.5)
Height (cm)		
Mean (SD)	165.8 (13.05)	172.4 (11.46)
Median (Min, Max)	163.1 (146.0, 188.6)	170.0 (157.0, 190.0)
Body Mass Index (kg/m²)		
Mean (SD)	26.3 (3.40)	27.7 (3.94)
Median (Min, Max)	26.1 (21.3, 31.1)	27.0 (20.5, 34.8)
eGFR by Cockcroft-Gault (mL/min)		
Mean (SD)	24.0 (5.37)	103.2 (16.33)
Median (Min, Max)	25.5 (13.1, 32.6)	94.2 (84.3, 140.2)
eGFR by MDRD (mL/min/1.73 m²)		
Mean (SD)	21.8 (7.06)	94.2 (15.22)
Median (Min, Max)	23.4 (12.2, 32.6)	94.5 (67.4, 114.5)
eGFR by CKDepi (mL/min/1.73 m²)		
Mean (SD)	20.3 (6.76)	89.9 (12.44)
Median (Min, Max)	21.7 (10.7, 30.0)	92.6 (67.5, 115.2)

eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease

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Pharmacokinetics

Relative to healthy controls, subjects with severe renal impairment had TAF AUC increased 92% and C_{max} increased 80% (Table 47, Table 48); renal clearance was reduced 88% (Table 49). Relative to healthy controls, subjects with severe renal impairment had TFV AUC increased 5.7-fold (Table 50, Table 51); renal clearance was reduced 75% (Table 52).

Table 47. TAF plasma PK.

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)

Table 48. Statistical comparison of TAF plasma PK.

GLS Mean Ratio % (90% CI) Severe Renal Impairment (Test) Versus Normal Renal Function (Reference)	
PK Parameter	TAF
AUC _{inf} (ng.h/mL)	191.89 (137.81, 267.18)
AUC _{last} (ng.h/mL)	192.26 (137.81, 268.21)
C _{max} (ng/mL)	179.43 (123.73, 260.20)

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

Table 49. TAF Urine PK.

Mean (%CV)	Severe Renal Impairment (n=14)	Normal Renal Function (n=13)
TAF		
CL _{renal} (mL/min)	4.2 (77.6)	35.8 (51.7)
Percent of dose recovered in urine (%)	0.47 (95.6)	2.00 (34.6)
Ae (ng)	117,230.4 (95.6)	500,408.6 (34.6)

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Table 50. TFV plasma PK.

Mean (%CV)	Severe Renal Impairment (n=14)	Normal Renal Function (n=13)
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)

Table 51. Statistical comparison of TFV plasma PK.

GLSM Ratio % (90% CI) Severe Renal Impairment (Test) versus Normal Renal Function (Reference)	
PK Parameter	TFV
AUC _{inf} (ng.h/mL)	573.76 (457.21, 720.01)
AUC _{last} (ng.h/mL)	545.91 (442.82, 672.99)
C _{max} (ng/mL)	279.31 (231.48, 337.02)

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

Table 52. TFV urine PK.

Mean (%CV)	Severe Renal Impairment (n=14)	Normal Renal Function (n=13)
TFV		
CL _{renal} (mL/min)	51.4 (40.1)	209.4 (24.6)
Percent of dose recovered in urine (%)	30.12 (24.6)	24.17 (23.3)
Ae (ng)	4,548,490 (24.6)	3,650,168 (23.3)

Safety

AEs were reported by >40% of subjects in both groups (Table 53). There were no AEs causing discontinuation, deaths, or SAEs during the study.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 53. Adverse events.

Adverse Events by System Organ Class and Preferred Term	Severe Renal Impairment (N=14)	Normal Renal Function (N=13)
	n (%)	n (%)
Any Treatment-Emergent Adverse Event	6 (42.9)	7 (53.8)
Gastrointestinal Disorders	1 (7.1)	2 (15.4)
Diarrhea	1 (7.1)	1 (7.7)
Flatulence	0	1 (7.7)
Musculoskeletal and Connective Tissue Disorders	3 (21.4)	2 (15.4)
Arthralgia	2 (14.3)	1 (7.7)
Back Pain	1 (7.1)	0
Muscle Spasms	0	1 (7.7)
Nervous System Disorders	1 (7.1)	5 (38.5)
Headache	0	4 (30.8)
Dizziness Postural	1 (7.1)	0
Somnolence	0	1 (7.7)
Vascular Disorders	1 (7.1)	0
Phlebitis	1 (7.1)	0

DISCUSSION AND LABEL RECOMMENDATIONS

The only potential deficiency in this study was that subjects taking medication that interact with TAF (such as Pgp inhibitors and inducers) were not specifically excluded. One subject in the severe renal impairment group was taking a Pgp inhibitor. The subject was not excluded from the PK analysis because with and without the subject included, there was no effect on TAF or TFV PK for the group.

The following statement in the label section 12.3 relates to this study: “ (b) (4)

[Redacted text block]

This statement is potentially misleading (b) (4)
 [Redacted text block]. We
 recommend the following edits:

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

(b) (4)



CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

3.2.2 GS-US-120-0114 - TAF PK in HIV-uninfected subjects with mild to moderate hepatic impairment

ADMINISTRATIVE	
Study Period	6/5/13-8/5/13
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-120-0114

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN	
2-cohort, open-label, multi-center, single-dose, parallel-group study	
<p>Cohort 1:</p> <p>Group 1: Subjects with mild hepatic impairment (Child-Pugh-Turcotte [CPT] Class A score of 5-6) (n = 10)</p> <p>Group 2: Subjects with normal hepatic function (n = 10)</p> <p>Cohort 2:</p> <p>Group 1: Subjects with moderate hepatic impairment (CPT Class B score of 7–9) (n = 10)</p> <p>Group 2: Subjects with normal hepatic function (n = 10)</p>	
Population	Subjects with hepatic impairment were HIV and HBV uninfected. Each subject in the mild or moderate impairment group was matched for age (± 10 years), gender, and BMI ($\pm 20\%$) with a healthy subject.
Study Rationale	Determine the effect of mild and moderate hepatic impairment on the PK of TAF
Treatments	All subjects received a single TAF 25 mg dose
Dose Selection Rationale	TAF 25 mg is bioequivalent to TAF 10 mg coadministered with cobicistat 150 mg, which are the TAF and cobicistat doses in the E/C/F/TAF fixed dose combination tablet.
Administration	<input checked="" type="checkbox"/> Fasted <input type="checkbox"/> Fed
Formulation	Tablet (lot number CM1208B1)
Interfering Substances Excluded	<p>Subjects with hepatic impairment</p> <ul style="list-style-type: none"> • Inhibitors and inducers of Pgp • Competitors of renal excretion or other compounds known to alter the PK of TFV • Nephrotoxic drugs • Any antiretrovirals except for study drug <p>Healthy controls</p> <ul style="list-style-type: none"> • No medications allowed except vitamins, acetaminophen/ibuprofen, and hormonal contraception, or other medications approved by the Medical Monitor
Sampling Times	<p>Plasma: On Day 1, intensive PK sampling occurred predose and at 5 minutes and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, 36, 48, 60, 72, 96, 120, and 144 hours postdose.</p> <p>Protein binding: TAF and TFV percent protein binding in plasma was determined at 1 and 4 hours postdose and 2 and 24 hours postdose, respectively.</p> <p>Urine: predose and at postdose intervals between 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, 36 to 48 hours, 48 to 60 hours, 60 to 72 hours, and 72 to 96 hours.</p>

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY CONDUCT

Bioanalysis

Bioanalytical methods were acceptable according (Table 54).

Table 54. Bioanalytical methods.

Analyte	Matrix	Method type	Method report #	Method validation or sample analysis deficiencies
TAF	Plasma	LC/MS/MS	60-1115	None
TFV			60-1352	
TAF		Ultrafiltration	60N-1334	
TFV		Equilibrium dialysis		

Table prepared by reviewer.

Protocol violations

There were no significant protocol deviations.

STUDY RESULTS

Study population

All 40 enrolled subjects received a single dose of TAF 25 mg and completed the study. Subjects with hepatic impairment were demographically well-matched with healthy volunteers (Table 55).

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Table 55. Subject demographics.

Characteristic	Mild Hepatic Impairment Group (CPT Score 5-6) Cohort 1 (N = 10)	Moderate Hepatic Impairment Group (CPT Score 7-9) Cohort 2 (N = 10)	Matched Normal Hepatic Function Group		
			Cohort 1 (N = 10)	Cohort 2 (N = 10)	Total (N = 20)
Sex (n, %)					
Male	5 (50.0)	7 (70.0)	5 (50.0)	7 (70.0)	12 (60.0)
Female	5 (50.0)	3 (30.0)	5 (50.0)	3 (30.0)	8 (40.0)
Age (years)					
Mean (SD)	58 (3.7)	54 (5.2)	56 (4.9)	54 (6.4)	55 (5.6)
Median	58	55	55	53	54
Min, Max	51, 63	46, 64	49, 67	46, 65	46, 67
Race (n, %)					
White	7 (70.0)	9 (90.0)	5 (50.0)	8 (80.0)	13 (65.0)
Black	2 (20.0)	1 (10.0)	2 (20.0)	2 (20.0)	4 (20.0)
Asian	1 (10.0)	0	0	0	0
American Indian or Alaska Native	0	0	2 (20.0)	0	2 (10.0)
Other	0	0	1 (10.0)	0	1 (5.0)
Weight (kg)					
Mean (SD)	77.2 (10.76)	85.6 (14.47)	79.5 (16.13)	86.5 (15.08)	83.0 (15.62)
Median	75.0	88.1	73.9	83.4	79.1
Min, Max	66.0, 98.6	65.0, 112.6	63.3, 111.9	66.7, 108.0	63.3, 111.9
BMI (kg/m ²)					
Mean (SD)	26.7 (2.95)	28.1 (3.48)	28.3 (2.91)	28.5 (3.44)	28.4 (3.11)
Median	26.4	27.8	28.1	29.0	28.8
Min, Max	23.0, 32.0	21.1, 32.9	24.9, 32.8	20.7, 33.6	20.7, 33.6
eGFR _{CG} (mL/min)					
Mean (SD)	107.5 (29.08)	114.9 (27.99)	99.8 (19.32)	105.9 (19.06)	102.9 (18.94)
Median	112.9	125.0	99.0	98.6	98.8
Min, Max	61.9, 154.4	65.1, 157.9	75.4, 131.6	81.7, 135.2	75.4, 135.2

eGFR_{CG} = eGFR by Cockcroft-Gault Formula
 Source: Section 15.1, Table 2; Appendix 16.2, Listing 2

Source: sponsor's analysis.

Pharmacokinetics

TAF and TFV AUC were <13% in mild and moderate hepatic impairment and variability was generally higher in hepatic impairment; C_{max} was similarly affected in all cases (Table 56). All subjects were included in the PK analyses. TAF and TFV protein binding were not significantly altered by mild to moderate hepatic impairment (Table 57). There were no apparent graphical relationships between TAF and TFV AUC and C_{max} and CPT score.

As there were no PK difference between normal and hepatically impaired subjects, urine samples were not analyzed.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 56. Summary of TAF and TFV percent change in AUC in hepatic impairment relative to controls.

	TAF	TFV
Hepatic impairment	AUC _{inf} % change (90% CI) relative to controls	AUC _{inf} % change (90% CI) relative to controls
Mild	↓8 (-34, +29)	-11 (33, 18)
Moderate	↑13 (-13, +45)	-3 (-23, 23)

Table prepared by reviewer.

Table 57. TAF and TFV protein binding.

Hepatic impairment	TAF unbound fraction (%)		TFV unbound fraction (%)	
	1 h postdose	4 h postdose	2 h postdose	24 h postdose
Mild	17 (8-25)	19 (8-32)	~100	
Moderate	20 (13-26)	21 (20-27)		
Controls	16 (9-24)	17 (12-30)		

Table prepared by reviewer. Values are median (range).

Safety

All AEs considered possibly related to study drug were classified by the investigator as mild in severity. The most common AEs reported were vomiting, headache, and somnolence. No SAEs or deaths occurred during this study, and no subject discontinued the study due to an AE.

DISCUSSION

The list of excluded medications did not account for all pathways potentially affecting disposition of TAF (Pgp, BCRP, OATP1B1, OATP1B3) and TFV (OAT1, OAT3, and MRP4). However, known inhibitors of these transporters involved in the disposition of TAF and TFV were not among the concomitant medications used by subjects in the study and thus concomitant medications likely had no effect on study results.

CONCLUSIONS

We agree with the proposed E/C/F/TAF labeling recommendations for subjects with hepatic impairment:

- no dose adjustment in CPT A and B
- not recommended for CPT C

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

3.2.3 GS-US-292-0108 – Single and multiple dose PK of E/C/F/TAF in healthy Japanese and Caucasian subjects

ADMINISTRATIVE	
Study Period	10/8/2012-12/6/2012
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-292-0108

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN	
<div style="text-align: right; margin-bottom: 10px;"><i>Follow-Up</i></div> <div style="display: flex; justify-content: space-between; margin-bottom: 10px;"> Day -28 -1 1 4 8 10 18 19 23 29 </div> <p style="margin-top: 20px;"> Single Dose + Intensive Plasma & Urine PK ◆ </p> <p> Multiple Dose Administration ◆◆◆◆◆◆◆◆◆◆ </p> <p> Intensive Plasma & Urine PK X </p> <p> Complete Safety Assessments (PE, ECG, labs, vitals, & weight) ● </p> <p> Clinic Confinement ▬ </p>	
Population	Healthy Volunteers
Study Rationale	Evaluate the single and multiple dose PK of E/C/F/TAF FDC in healthy Japanese and Caucasian subjects
Treatments	Single dose of E/C/F/TAF (150/150/200/10 mg) on day 1 with a meal and once-daily dosing on days 8-19 with a meal
Dose Selection Rationale	The dose used in this study is the same as used in phase 3
Formulation	FDC, lot numbers: CP1201B1
Interfering Substances Excluded	Alcohol, nicotine, medications (prescription, OTC, herbal)
Sampling Times	<p><u>Plasma</u> Days 1 and 19: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 12, 18, 24, 36, 48, and 72 hours postdose. Additional troughs: predose on Days 13, 15, and 17</p> <p><u>Urine</u> Days 1 and 19: prior to dosing and 0-6, 6-12, 12-24, 24-48, 48-72, and 72-96 hours after dosing.</p>

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY CONDUCT

Bioanalytical methods

Bioanalytical methods were acceptable (Table 58).

Table 58. Bioanalytical methods.

Analyte	Matrix	Method report #	Sample analysis report #	Deficiencies
EVG	Plasma	60-0949	60-12103A	None
COBI		60-0949	60-12103A	
FTC		42-0831	60-12103B	
TAF		60-1115	60-12103C	
TFV		42-0831, 60-1116	60-12103D	

Table prepared by reviewer.

Protocol deviations

None reported.

STUDY RESULTS

Study population

Seventeen of 20 subjects enrolled completed the study (Table 59). Subject demographics were similar (Table 60).

Table 59. Subject disposition.

Subject Disposition	Caucasian (N=10)	Japanese (N=10)	Total (N=20)
	n (%)	n (%)	n (%)
Enrolled	10 (100.0)	10 (100.0)	20 (100.0)
Completed Study	8 (80.0)	9 (90.0)	17 (85.0)
Discontinued Study Drug Prematurely	2 (20.0)	1 (10.0)	3 (15.0)
Adverse Event	1 (10.0)	0	1 (5.0)
Consent Withdrawal	1 (10.0)	1 (10.0)	2 (10.0)

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 60. Subject demographics.

Characteristic	Caucasian (N=10)	Japanese (N=10)
Sex (n, %)		
Male	5 (50.0)	6 (60.0)
Female	5 (50.0)	4 (40.0)
Age (years)		
Mean (SD)	36 (10.8)	40 (9.7)
Median	36	42
Min, Max	23, 51	26, 51
Weight (kg)		
Mean (SD)	72.4 (15.72)	67.3 (7.04)
Median	71.4	69.5
Min, Max	48.1, 106.4	51.0, 75.0
Height (cm)		
Mean (SD)	172.1 (8.11)	168.4 (8.73)
Median	171.8	169.7
Min, Max	158.2, 186.7	153.1, 182.3
Body Mass Index (kg/m²)		
Mean (SD)	24.2 (2.79)	23.7 (2.31)
Median	23.7	23.8
Min, Max	19.8, 29.6	20.6, 28.2
Estimated Glomerular Filtration Rate by Cockcroft-Gault (CG) Formula (mL/min)		
Mean (SD)	119.2 (40.66)	112.1 (17.94)
Median	113.5	110.6
Min, Max	79.3, 217.2	79.9, 144.6

Pharmacokinetics

After a single dose, the components of E/C/F/TAF generally had increased exposures (C_{max} being most sensitive), with 90% CIs of TAF and TFV not including zero (Table 61, Table 62, Table 64, Table 66, Table 68, Table 70). After multiple dosing, all components of E/C/F/TAF had decreased exposures (C_{min} being most sensitive), with 90% CIs of COBI, FTC, and TFV not including zero (Table 61, Table 63, Table 65, Table 67, Table 69, Table 71). After a single dose, one Caucasian subject had an EVG C_{min} below the its protein-adjusted IC₉₅ value for inhibition of HIV-1 virus [45 ng/mL]; no subjects had an EVG C_{min} below the IC₉₅ after multiple dosing.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 61. PK summary.

	Relative percent exposure change (90% CI) in Japanese versus Caucasians on the most sensitive PK parameter	
Analyte	Single dose	Multiple dose
EVG	AUC -17 (-38, +11)	C _{min} -35 (-59, +2)
COBI	C _{max} +25 (-12, +77)	C _{min} -32 (-52, -4)
FTC	C _{max} +12 (-6, +32)	C _{min} -24 (-42, -1)
TAF	C _{max} +44 (+10, +89)	AUC -12 (-33, +17)
TFV	C _{max} +64 (+12, +142)	C _{min} -23 (-37, -7)

Table prepared by reviewer.

Table 62. Single dose EVG PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=10)	Caucasian (n=10)	GLSMR (90% CI)
EVG AUC _{inf} (ng·h/mL)	24237.95	28506.47	85.03 (64.76, 111.63)
EVG AUC _{last} (ng·h/mL)	22923.30	27572.43	83.14 (62.14, 111.24)
EVG C _{max} (ng/mL)	2119.70	2289.51	92.58 (71.41, 120.03)

Table 63. Multiple dose EVG PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=9)	Caucasian (n=8)	GLSMR (90% CI)
EVG AUC _{tau} (ng·h/mL)	29403.89	34440.44	85.38 (64.45, 113.09)
EVG C _{tau} (ng/mL)	328.52	505.50	64.99 (41.43, 101.95)
EVG C _{max} (ng/mL)	2822.34	3541.15	79.70 (60.58, 104.85)

Table 64. Single dose COBI PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=10)	Caucasian (n=10)	GLSMR (90% CI)
COBI AUC _{inf} (ng·h/mL)	5890.37	4832.34	121.89 (81.29, 182.79)
COBI AUC _{last} (ng·h/mL)	5837.73	4757.88	122.70 (81.43, 184.87)
COBI C _{max} (ng/mL)	904.91	726.16	124.62 (87.95, 176.56)

Table 65. Multiple dose COBI PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=9)	Caucasian (n=8)	GLSMR (90% CI)
COBI AUC _{tau} (ng·h/mL)	8095.36	9530.54	84.94 (58.33, 123.68)
COBI C _{tau} (ng/mL)	17.29	25.61	67.53 (47.70, 95.60)
COBI C _{max} (ng/mL)	1278.20	1338.81	95.47 (69.22, 131.67)

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 66. Single dose FTC PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=10)	Caucasian (n=10)	GLSMR (90% CI)
FTC AUC _{inf} (ng·h/mL)	11931.25	12470.87	95.67 (84.67, 108.10)
FTC AUC _{last} (ng·h/mL)	11704.70	12088.48	96.83 (85.30, 109.91)
FTC C _{max} (ng/mL)	2600.66	2331.51	111.54 (94.39, 131.82)

Table 67. Multiple dose FTC PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=9)	Caucasian (n=8)	GLSMR (90% CI)
FTC AUC _{tau} (ng·h/mL)	13054.23	14491.43	90.08 (76.80, 105.66)
FTC C _{tau} (ng/mL)	72.54	95.82	75.71 (57.90, 99.00)
FTC C _{max} (ng/mL)	2926.67	2712.32	107.90 (95.19, 122.31)

Table 68. Single dose TAF PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=10)	Caucasian (n=10)	GLSMR (90% CI)
TAF AUC _{inf} (ng·h/mL)	236.51	225.02	105.11 (83.87, 131.72)
TAF AUC _{last} (ng·h/mL)	235.14	222.78	105.55 (84.12, 132.43)
TAF C _{max} (ng/mL)	346.87	240.75	144.08 (109.82, 189.04)

Table 69. Multiple dose TAF PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=9)	Caucasian (n=8)	GLSMR (90% CI)
TAF AUC _{last} (ng·h/mL)	245.76	277.90	88.43 (67.00, 116.73)
TAF C _{max} (ng/mL)	312.11	287.87	108.42 (77.27, 152.14)

Table 70. Single dose TFV PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=10)	Caucasian (n=10)	GLSMR (90% CI)
TFV AUC _{inf} (ng·h/mL)	333.06 ^a	333.25	99.95 (86.15, 115.95)
TFV AUC _{last} (ng·h/mL)	214.35	223.98	95.70 (84.75, 108.07)
TFV C _{max} (ng/mL)	17.59	10.71	164.26 (111.70, 241.57)

a n=9 for AUC_{inf}

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Table 71. Multiple dose TFV PK.

Geometric Least Squares Mean PK Parameter	Japanese (n=9)	Caucasian (n=8)	GLSMR (90% CI)
TFV AUC _{tau} (ng·h/mL)	328.32	392.78	83.59 (68.06, 102.66)
TFV C _{tau} (ng/mL)	11.00	14.37	76.53 (62.87, 93.15)
TFV C _{max} (ng/mL)	23.51	22.29	105.47 (83.13, 133.83)

Safety

The most common TEAEs considered related to study drug included nausea (40% of Caucasians, 10% of Japanese) and vomiting (30% of Caucasians, 10% of Japanese; Table 72). One subject who received a single dose of study drug discontinued due to TEAEs (headache, urticaria, and pruritus considered related to study drug). There were no SAEs or deaths during the study.

Table 72. Subjects with vomiting AEs.

Subject ID	Race	Gender	Onset date	Resolution date
4925-1002	Caucasian	Male	1	2
4925-1009	Caucasian	Female	11	11
4925-1009	Caucasian	Female	15	15
4925-1010	Caucasian	Female	1	1
4925-1010	Caucasian	Female	8	8
4925-1018	Japanese	Female	1	1
4925-1018	Japanese	Female	13	14

Table prepared by reviewer.

DISCUSSION

Several subjects vomited on day 1, when single dose PK was assessed. All subjects that vomited had day 1 EVG C_{max} values above or near the median for their race group, suggesting that absorption of study drugs was unaffected by vomiting. No subjects vomited on more than two days, or on day 19 when steady-state PK was assessed; thus steady-state PK parameters were likely unaffected by vomiting.

After multiple doses, exposures were generally decreased in healthy Japanese subjects relative to healthy Caucasians. The mean 35% reduction in EVG C_{min} is not of concern as all Japanese subjects had EVG C_{min} values above the protein-adjusted IC₉₅ value. The mean 32% reduction in COBI C_{min} is not of concern because COBI inhibition of midazolam clearance was similar at COBI doses of 50, 100, and 200 mg (with corresponding midazolam clearance percent inhibition of -88, -93, and -95%, respectively).⁴ The mean 32% reduction in FTC C_{min} is not of concern as FTC anti-HIV activity was on the flat portion of the dose-response curve at doses of 100, 200, and 400 mg daily.⁴ The mean 12% reduction in TAF AUC and mean 23% reduction in TFV C_{min} are not of concern because no exposure-response relationships for efficacy were identified for TAF or TFV.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

LABEL RECOMMENDATIONS

We agree with the following statement in section 12.3 of the E/C/F/TAF label: “No dose adjustment is recommended based on race.”

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

3.2.4 GS-US-292-0112 – Phase 3 study in HIV-infected subjects with mild to moderate renal impairment: Intensive E/C/F/TAF PK substudy [Interim week 24 report]

ADMINISTRATIVE	
Study Period	3/27/2013-9/9/2014
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-292-0112\report-body.pdf

STUDY DESIGN	
Open-label, multicenter study. Subjects were enrolled in cohort 1 if on ART and virologically suppressed, or cohort 2 if ART naïve.	
<p style="text-align: center;"> Screening^a ≤ 30 days prior to Baseline </p> <p style="text-align: center;"> Baseline (Day 1)^b Week 12 IDMC^a Week 24 Primary Endpoint Week 96^c </p> <p style="text-align: center;"> Cohort 1: Switch, eGFR_{CG} 30-69 mL/min E/C/F/TAF QD Cohort 2: ART-naïve, eGFR_{CG} 30-69 mL/min E/C/F/TAF QD </p> <p style="text-align: center;"> 30-Day F/U </p> <p style="text-align: center;"> Total n = 260 PK/PD substudy n = 30 (6 with eGFR_{CG} 30 to 49 mL/min) </p>	
<p>F/U = follow-up; IDMC = independent data monitoring committee; QD = once daily</p> <p>a. Subjects were screened within 30 days before the baseline/Day 1 visit to determine eligibility for participation in the study.</p> <p>b. Following the baseline visit, subjects returned for study visits at Weeks 1, 2, 4, 8, 12, 16, and 24, and then every 12 weeks through Week 96.</p> <p>c. Subjects who complete the study through Week 96 and do not wish to continue to receive study drug will be required to return to the clinic 30 days after the completion of study drug for the 30-Day Follow-up visit. See Section 7.2 for a Sweden-specific protocol addendum.</p>	
Population	HIV-infected subjects with mild to moderate renal impairment (eGFR Cockcroft-Gault of 30-69 mL/min, inclusive)
Study Rationale	Safety, intensive PK substudy
Treatments	E/C/F/TAF (150/150/200/10 mg) FDC orally once daily with food for 96 weeks
Dose Selection Rationale	Same dose as used in pivotal trials
Formulation	FDC tablet. Lot numbers: CP1204B1, CP1208B1, CP1303B1, CP1307B1, CP1310B1, CP1311B1, CP1313B1, and CP1314B1

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

STUDY DESIGN (CONTINUED)		
Interfering Substances Excluded	Drug Class	Agents Disallowed^a
	Alpha Adrenergic Receptor Antagonists	Alfuzosin
	Analeptics	Modafinil
	Antibacterials	Telithromycin
	Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
	Antifungals	Voriconazole
	Antihistamines	Astemizole, Terfenadine
	Antimycobacterials	Rifampin, Rifapentine, Rifabutin
	Calcium Channel Blockers	Bepidil
	Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylergonovine Ergometrine
	GI Motility Agents	Cisapride
	Herbal/Natural Supplements	St. John's Wort, Echinacea
	HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin, Cerivastatin
	Neuroleptics	Pimozide
	Sedatives/Hypnotics	Midazolam, Triazolam
	Systemic Corticosteroids with the exception of short-term (≤ 1 week) use of prednisone	All agents, including dexamethasone
<p>^a Administration of any of the above medications must have been discontinued at least 21 days prior to the baseline/Day 1 visit and for the duration of the study.</p>		
Sampling Times	<p>The intensive PK/PD substudy visit occurred at the week 2, 4, or 8 visit. Iohexol clearance was measured at the intensive PK visit and at a week 24 visit.</p> <p>Plasma samples for measurement of E/C/F/TAF PK were collected prior to dosing and at 5 minutes, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours post-dose.</p> <p>PBMC samples for measurement of TFV-DP concentrations were collected predose and 2, 4, and 8 hours postdose.</p> <p>Iohexol clearance (PD measure of actual GFR) was measured in intensive PK participants. Iohexol 1500 mg was administered as an IV bolus over 1-2 min. Plasma samples for measurement of iohexol were collected at 0, 5 min, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours postdose.</p>	

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STUDY CONDUCT

Bioanalytical methods

There were several deficiencies in bioanalytical methods (Table 73).

Table 73. Bioanalytical methods.

Analyte	Method	Matrix	Deficiencies
Iohexol	2100-775	plasma	<ul style="list-style-type: none"> Interference only assessed with TAF (and not other components of E/C/F/TAF) Method was validated using d₅-iohexol, while d₁₀-iohexol was used for sample analysis
TAF	60-1115		Interference seen in analyte blanks (blank + internal standard and extracted blank) with a peak area up to 25% of the LLOQ peak area
TFV	60-1368		None
FTC	42-0831		None
EVG	60-1343		Not analyzed within the combination (E/C/F/TAF) frozen duration of stability
COBI	60-1343		Not analyzed within the combination (E/C/F/TAF) frozen duration of stability

Table prepared by reviewer.

Protocol deviations

Nine subjects participating in the PK substudy had protocol deviations (Table 74). One subject received a prohibited concomitant medication (etravirine) with the potential to affect the PK results. However, use of etravirine occurred on week 36 while the PK substudy occurred on week 2, 4, or 8; thus this deviation did not affect the PK results.

Table 74. Protocol deviations affecting subjects in the PK substudy.

Subject ID	Protocol deviation
1598-8002	Inclusion/exclusion criteria - plasma HIV RNA
1950-8058	Inclusion/exclusion criteria - HCV RNA
1950-8230	Procedural – missed Cystatin C assessment
2106-8016	Inclusion/exclusion criteria – history of prostate cancer
2704-8045	Received prohibited concomitant medications – Etravirine and lamivudine for three days
5120-8064	Inclusion/exclusion criteria - plasma HIV RNA
5120-8073	Inclusion/exclusion criteria - plasma HIV RNA
5120-8202	Inclusion/exclusion criteria – initial serum creatinine values not within 25% of each other
5122-8191	Procedural deviation – woman of childbearing potential not on contraception

Table prepared by reviewer.

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STUDY RESULTS

Study population

246 treatment-experienced subjects were enrolled in cohort 1 and six treatment-naïve subjects were enrolled in cohort 2. Thirty-three subjects were enrolled in the PK/PD substudy. Demographics in the PK/PD substudy were comparable across eGFR_{CG} categories with the exception of race, where whites were overrepresented in the eGFR_{CG}≥50 mL/min group and Asians were overrepresented in the eGFR_{CG}<50mL/min group (Table 75).

Table 75. Demographics.

Characteristic	eGFR _{CG} <50 mL/min (n=10)	eGFR _{CG} ≥50 mL/min (n=23)	Total (n=33)
Age	53.5 (39-77)	57 (43-73)	57 (39-77)
Male	7 (70%)	21 (91%)	28 (85%)
Race			
White	3 (30%)	15 (65%)	18 (55%)
Black	2 (20%)	5 (22%)	7 (21%)
Asian	4 (40%)	2 (9%)	6 (18%)
American Indian or Alaska Native	1 (10%)	1 (4%)	1 (3%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	1 (3%)
Hispanic ethnicity	2 (20%)	3 (13%)	5 (15%)
eGFR _{CG} (mL/min)	44 (33-50)	60 (52-89)	58 (33-89)
BMI (mg/m ²)	23 (17-26)	25 (16-32)	24 (16-32)

Table prepared by reviewer. Values are median (range) or N (%).

Pharmacodynamics

Baseline versus week 2/4/8 or week 24 actual GFR (aGFR), as measured by iohexol clearance, was unchanged across eGFR_{CG} categories, indicating no effect of E/C/F/TAF treatment on renal function (Table 76).

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Table 76. Baseline versus week 2/4/8 or week 24 visit aGFR values.

Comparison	aGFR (GLSM)				GLSM Ratio (%)	90% CI
	n	Test Treatment	n	Reference Treatment		
Subjects with eGFR_{CG} < 50 mL/min at Baseline						
Week 2/4/8 aGFR vs Baseline aGFR (mL/min)	10	43.28	10	46.57	92.93	(84.16,102.61)
Week 24 aGFR vs Baseline aGFR (mL/min)	9	44.31	10	46.57	95.15	(85.84,105.47)
Subjects with eGFR_{CG} ≥ 50 mL/min at Baseline						
Week 2/4/8 aGFR vs Baseline aGFR (mL/min)	22	63.93	22	62.80	101.80	(95.32,108.72)
Week 24 aGFR vs Baseline aGFR (mL/min)	21	66.60	22	62.80	106.06	(99.19,113.39)

GLSM = geometric least-squares mean

Pharmacokinetics

With the exception of COBI C_{min}, which was highly variable, in all cases exposures were increased in the eGFR_{CG}<50 mL/min group relative to the eGFR_{CG}≥50 mL/min group (Table 77, Table 78, Table 79, Table 80). Similarly, compared to HIV-infected subjects with normal renal function, exposures were generally increased in both eGFR_{CG} groups; in particular, in subjects with eGFR_{CG}<50 mL/min, FTC and TFV AUC were increased >2-fold (Table 81, Table 82).

Table 77. TAF PK by eGFR group.

TAF PK Parameter	AUC _{last}		C _{max}	
Mean (%CV)	N	(ng*h/mL)	N	(ng/mL)
eGFR _{CG} <50 mL/min (Excluding Subject 1598-8021) ^a	7	340.5 (60.1)	7	308.9 (82.2)
eGFR _{CG} ≥ 50 mL/min	22	226.7 (44.1)	22	251.3 (62.9)

a Subject 1598-8021 was excluded for sensitivity analysis as TAF PK parameter estimates are unreliable due to an unusual PK profile.

Table 78. TFV PK by eGFR group.

TFV PK Parameter	AUC _{tau}		C _{max}		C _{tau}	
Mean (%CV)	N	(ng*h/mL)	N	(ng/mL)	N	(ng/mL)
eGFR _{CG} <50 mL/min	8	680.4 (28.7)	8	36.1 (27.9)	7	21.7 (27.8)
eGFR _{CG} ≥ 50 mL/min	21	504.0 (29.1)	22	26.9 (24.7)	18	18.2 (31.9)

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Table 79. FTC PK by eGFR group.

FTC PK Parameter	AUC _{tau}		C _{max}		C _{tau}	
	N	(ng*h/mL)	N	(ng/mL)	N	(ng/mL)
eGFR _{CG} <50 mL/min	8	25,139.5 (21.8)	8	3042.5 (13.4)	7	203.3 (17.7)
eGFR _{CG} ≥ 50 mL/min	21	19,379.7 (23.1)	22	2500.9 (26.9)	19	190.8 (38.9)

Table 80. EVG and COBI PK by eGFR group.

PK Parameter	EVG AUC _{tau}		COBI AUC _{tau}		EVG C _{max}		COBI C _{max}		EVG C _{tau}		COBI C _{tau}	
	N	(ng*h/mL)	N	(ng*h/mL)	N	(ng/mL)	N	(ng/mL)	N	(ng/mL)	N	(ng/mL)
Mean (%CV)												
eGFR _{CG} < 50 mL/min	8	28,705.8 (38.3)	8	11,316.8 (48.8)	8	2677.5 (32.1)	8	1385.0 (23.8)	7	425.3 (82.7)	6	33.9 (88.2)
eGFR _{CG} ≥ 50 mL/min	20	26,468.4 (29.6)	21	9393.7 (43.1)	22	2291.4 (30.9)	22	1256.6 (34.7)	19	331.7 (72.1)	19	39.7 (108.8)

Table 81. Summary of PK of E/C/F/TAF in HIV-infected subjects with normal renal function relative to renally impaired subjects in the current study.

Analyte	PK parameter	Normal renal function*	Current study eGFR _{CG} ≥30- <50 mL/min	Current study eGFR _{CG} ≥50-69 mL/min
EVG	C _{min} (ng/mL)	287 (62)	425 (83)	332 (72)
COBI	AUC _{tau} (ng*h/mL)	9459 (34)	11,317 (49)	9394 (43)
FTC	AUC _{tau} (ng*h/mL)	11,714 (17)	25,140 (22)	19380 (23)
TAF	AUC _{last} (ng*h/mL)	228 (47)	341 (60)	227 (44)
TFV	AUC _{tau} (ng*h/mL)	326 (15)	680 (29)	504 (29)

Table prepared by reviewer. *Data from Phase 2 study GS-US-292-0102 (n=19). Values are mean (CV%).

Table 82. Percent changes in PK parameters of E/C/F/TAF in renally impaired subjects in the current study compared to HIV-infected subjects with normal renal function.

Analyte	PK parameter	Current study eGFR _{CG} ≥30- <50 mL/min	Current study eGFR _{CG} ≥50-69 mL/min
EVG	C _{min} (ng/mL)	↑48	↑16
COBI	AUC _{tau} (ng*h/mL)	↑20	↓1
FTC	AUC _{tau} (ng*h/mL)	↑115	↑65
TAF	AUC _{last} (ng*h/mL)	↑50	↔
TFV	AUC _{tau} (ng*h/mL)	↑109	↑55

Table prepared by reviewer. Values are percent change (parameter mean in renally impaired group/parameter mean in normal renal function group*100) relative to subjects with normal renal function (Phase 2 study GS-US-292-0102, n=19).

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Safety

As of the 24 week data cut date, 16/248 (6.5%) subjects enrolled discontinued treatment; 8 (3.2%) discontinued due to an AE. One subject discontinued due to an AE considered related to study drug. 26 subjects (10.7%) reported at least one SAE; all were considered unrelated to study drug. No deaths have been reported.

DISCUSSION

There were minor bioanalytical issues with all analytes except FTC and TFV. These issues do not impact interpretation of the study results because FTC and TFV are the analytes of primary interest due to their being mainly renally excreted.

This study was not designed with PK as the primary endpoint. A better design to assess the impact of renal function on PK would have included an arm of matched HIV-infected subjects without renal impairment to reduce the impact of potentially confounding demographic variables and to avoid cross-study comparisons.

Baseline eGFR as measured by creatinine using the Cockcroft-Gault equation versus Cystatin C using the CKD-Epi equation differed significantly (Table 83).⁵ This difference was hypothesized to be due to inhibition of tubular secretion of creatinine in patients taking cobicistat or ritonavir, resulting in artificially high creatinine values and thus lower eGFR_{CG} values. However, this hypothesis was not supported, as the discrepancy between mean eGFR measured by creatinine versus Cystatin C was present for subjects on COBI or RTV at baseline versus those not on COBI/RTV (Table 83).⁵ In addition, in the PK substudy, baseline eGFR was closer to aGFR for creatinine versus Cystatin C (Table 84). Thus the use of creatinine and the Cockcroft-Gault equation used to determine baseline renal function for enrollment was considered acceptable.

Table 83. Baseline eGFR as measured by creatinine versus Cystatin C (n=248).⁵

	Cockcroft-Gault	CKD-Epi, Creatinine	CKD-Epi, Cystatin C
Mean eGFR (SD)	54.8 (11.6)	54.7 (14.4)	70.5 (21.1)
Baseline COBI/RTV ¹	54.9 (11.3)	55.3 (14.0)	70.4 (19.8)
No baseline COBI/RTV	54.6 (11.9)	54.1 (14.8)	70.6 (22.3)

Baseline COBI/RTV (n=115); No baseline COBI/RTV (n=133).

Table 84. Baseline iohexol aGFR versus creatinine and Cystatin eGFR.⁵

	Mean (SD)	Median (Q1, Q3)
Iohexol GFR	60.1 (19.1)	59.6 (46.2, 71.4)
eGFR		
Cockcroft-Gault	56.7 (11.8)	57.6 (48.3, 64.4)
CKD-Epi, Creatinine	57.8 (17.0)	54.7 (48.3, 65.0)
CKD-Epi, CysC	69.7 (21.0)	72.6 (56.6, 79.9)

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TFV and FTC AUC were increased >2-fold in subjects with eGFR<50 mL/min. The increase in TFV is not of concern as its exposures are reduced ~90% from administration of TAF versus TDF. In its US prescribing information, FTC is dosed 200 mg QD in subjects with CrCL \geq 50 mL/min and 200 mg every 48 hours in subjects with CrCL of 30-49 mL/min. This dose adjustment appears to be based on a single dose FTC PK study in which AUC in subjects with CrCL of 30-49 mL/min versus >80 mL/min was increased 2.15-fold (Table 85, Table 86).⁶

Table 85. Single dose FTC PK by renal impairment group in study FTC-107.⁶

Study Group (CL _{cr})	Statistic	C _{max} (μg/mL)	t _{max} (hr)	AUC _{0-t} (μg·h/mL)	AUC _{0-∞} (μg·h/mL)	t _{1/2} (hr)	CL/F (mL/min)
I (n=6) > 80 mL/min	Mean	2.20	1.84	11.38	11.78	14.19	302
	%CV	29	51	26	25	24	31
II (n=6) 50-80 mL/min	Mean	3.78	1.75	19.39	19.86	11.50	168
	%CV	23	43	6	6	9	6
III (n=6) 30-49 mL/min	Mean	3.18	1.67	24.44	25.08	15.51	138
	%CV	17	45	22	23	7	21
IV (n=5) < 30 mL/min	Mean	2.84	2.10	32.32	33.73	16.40	99
	%CV	24	64	6	6	5	6
V (n=5) Functional anephric Requiring hemodialysis	Mean	2.83	2.80	46.81	53.22	23.00	64
	%CV	17	45	18	19	8	19

Table 86. Statistical comparison of single dose FTC PK by renal impairment group in study FTC-107.⁶

PK Parameter	Statistic	Group II vs. Group I	Group III vs. Group I	Group IV vs. Group I	Group V vs. Group I
AUC _{0-∞} (hr·μg/mL)	*GLSM Ratio	1.73	2.15	2.95	4.59
	90% CI	1.44, 2.09	1.79, 2.59	2.43, 3.58	3.78, 5.57
C _{max} (μg/mL)	*GLSM Ratio	1.76	1.49	1.32	1.33
	90% CI	1.36, 2.27	1.16, 1.93	1.01, 1.73	1.02, 1.74
t _{max} (hr)	*GLSM Ratio	0.95	0.91	1.14	1.52
	90% CI	0.41, 1.50	0.36, 1.45	0.57, 1.72	0.92, 2.10
t _{1/2} (hr)	*GLSM Ratio	0.83	1.12	1.18	1.66
	90% CI	0.73, 0.94	0.98, 1.27	1.03, 1.35	1.44, 1.90
CL/F (mL/min)	*GLSM Ratio	0.58	0.47	0.34	0.22
	90% CI	0.48, 0.69	0.39, 0.56	0.28, 0.41	0.18, 0.26

LABEL RECOMMENDATIONS

The sponsor's label proposes that E/C/F/TAF FDC can be administered without dose adjustment to subjects with CrCL \geq 30 mL/min. Unless safety is deemed adequately established in subjects with CrCL of 30-49 mL/min in the Clinical review, based on FTC PK in this study and on the FTC US prescribing information, we disagree and propose not to recommend administration of E/C/F/TAF to subjects with CrCL<50 mL/min.

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3.3 Extrinsic factors

3.3.1 *GS-US-216-0137 – Drug-drug interaction study of EVG/COBI and carbamazepine in healthy subjects*

ADMINISTRATIVE	
Study Period	1/9/14-3/10/14
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-216-0137

ENZYME AND TRANSPORTER INTERACTIONS

The major interactions expected in the study are via CYP3A, as all study drugs are CYP3A substrates, COBI is a CYP3A inhibitor, and CBZ is a CYP3A inducer (Table 87).

Carbamazepine has an initial half-life of 25-65 h, decreasing to 12-17 h upon repeated doses. Carbamazepine-10,11-epoxide (CBZE) is a CYP3A-mediated metabolite of CBZ with equipotent anticonvulsant activity in animals.

Table 87. Disposition and drug interaction profile of study drugs.

Drug	Elimination	Substrate	Inhibitor	Inducer
EVG	Hepatobiliary excretion (95% of dose recovered in feces)	CYP3A (major) UGT1A1/3 (minor)		
COBI	Hepatobiliary excretion (COBI followed by its metabolites)	CYP3A (major) CYP2D6 (minor)	CYP3A CYP2D6 P-gp BCRP OATP1B1 OATP1B3	
CBZ	Metabolism (3% excreted unchanged in urine)	CYP3A (major) CYP2C8 (minor) UGT2B7 (minor)	CYP2C19	CYP3A4 CYP2B6 CYP1A2 CYP2C9 UGT

Table prepared by reviewer. *Sources: US prescribing information, UW Drug interaction database, Stribild Clin Pharm NDA review.

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STUDY CONDUCT

Bioanalytical methods

Validation and sample analysis methods were acceptable (Table 88).

Table 88. Bioanalytical methods.

Analyte	Method #	Calibration range
EVG	60-1343	20-10000 ng/mL
COBI		5-2500 ng/mL
CBZ	42-1371	20-20000 ng/mL
CBZE		5-5000 ng/mL

Table prepared by reviewer.

Protocol deviations

None reported.

STUDY RESULTS

Study population

14 subjects received at least one dose of study medication and 12 completed the study (Table 89). One subject discontinued due to an AE and one withdrew consent.

Table 89. Demographics.

Characteristic	All subjects (n=14)*
Age (years)	40 (22-55)
Female sex	2 (14%)
Race	
White	9 (64%)
Black	5 (36%)
Hispanic ethnicity	4 (29%)
BMI (kg/m ²)	25.6 (21.4-28.9)

Table prepared by reviewer. *Values are median (range) or n (%)

Pharmacokinetics

Steady-state EVG exposures were reduced when coadministered with COBI+CBZ (Table 90). Median half-life was reduced from 11 h to 3 h when coadministered with COBI+CBZ. All PK parameters decreased in each subject.

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Table 90. EVG PK.

PK Parameter (Test/Reference)	Test		Reference		GLSM Ratio (%)	90% CI
	N	GLSM	N	GLSM		
Analyte: EVG						
EVG+COBI+CBZ (Test) vs. EVG+COBI (Reference)						
AUC _{tau} ^a (h•ng/mL)	12	8012.62	14	26,097.94	30.70	(28.23,33.39)
C _{max} (ng/mL)	12	1104.65	14	2016.86	54.77	(48.92,61.32)
C _{tau} ^b (ng/mL)	12	15.70	14	525.41	2.99	(2.25,3.97)

GLSMs were obtained using a mixed-effects model. The model included treatment as a fixed effect and subject as a random effect.

a AUC_{tau} is AUC₀₋₂₄ for EVG.

b EVG C_{tau} was BLQ (< 20.0 ng/mL) in 8 of 12 subjects following administration of EVG+COBI+CBZ. C_{tau} values of EVG that were BLQ were treated as LLQ/2 = 10 ng/mL.

Source: sponsor's analysis.

Steady-state COBI exposures were reduced when coadministered with EVG+CBZ (Table 91). Median half-life was reduced from 3.8 h to 3.1 h when coadministered with EVG+CBZ. All PK parameters decreased in each subject.

Table 91. COBI PK.

PK Parameter (Test/Reference)	Test		Reference		GLSM Ratio (%)	90% CI
	N	GLSM	N	GLSM		
Analyte: COBI						
EVG+COBI+CBZ (Test) vs. EVG+COBI (Reference)						
AUC _{tau} ^a (h•ng/mL)	12	1685.72	14	10,421.85	16.17	(14.33,18.26)
C _{max} (ng/mL)	12	385.34	14	1365.56	28.22	(24.40,32.63)
C _{tau} ^b (ng/mL)	12	3.54	14	36.16	9.78	(6.76,14.17)

GLSMs were obtained using a mixed-effects model. The model included treatment as a fixed effect and subject as a random effect.

a AUC_{tau} is AUC₀₋₂₄ for COBI.

b COBI C_{tau} was BLQ (< 5.0 ng/mL) in 8 of 12 subjects following administration of EVG+COBI+CBZ. C_{tau} values of COBI that were BLQ were treated as LLQ/2 = 2.5 ng/mL.

Source: sponsor's analysis.

Steady-state CBZ exposures were increased when coadministered with EVG+COBI (Table 92). All PK parameters increased in each subject.

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Table 92. CBZ PK.

PK Parameter (Test/Reference)	Test		Reference		GLSM Ratio (%)	90% CI
	N	GLSM	N	GLSM		
Analyte: CBZ						
EVG+COBI+CBZ (Test) vs. CBZ (Reference)						
AUC _{tau} ^a (h•ng/mL)	12	99,291.69	14	69,249.04	143.38	(135.55,151.67)
C _{max} (ng/mL)	12	9174.92	14	6542.07	140.24	(132.22,148.75)
C _{tau} (ng/mL)	12	7897.77	14	5217.48	151.37	(141.47,161.97)

GLSMs were obtained using a mixed-effects model. The model included treatment as a fixed effect and subject as a random effect.

^a AUC_{tau} is AUC₀₋₁₂ for CBZ.

Source: sponsor's analysis.

Steady-state CBZE exposures were decreased when CBZ was coadministered with EVG+COBI (Table 93). All PK parameters decreased in each subject.

Table 93. CBZE PK.

PK Parameter (Test/Reference)	Test		Reference		GLSM Ratio (%)	90% CI
	N	GLSM	N	GLSM		
Analyte: CBZE						
EVG+COBI+CBZ (Test) vs. CBZ (Reference)						
AUC _{tau} ^a (h•ng/mL)	12	5784.84	14	8937.32	64.73	(63.05,66.45)
C _{max} (ng/mL)	12	611.60	14	832.39	73.47	(69.56,77.61)
C _{tau} (ng/mL)	12	415.32	14	701.75	59.18	(57.09,61.35)

GLSMs were obtained using a mixed-effects model. The model included treatment as a fixed effect and subject as a random effect.

^a AUC_{tau} is AUC₀₋₁₂ for CBZE.

Source: sponsor's analysis.

No subjects were excluded from the PK analyses.

Safety

One subject discontinued the study on day 34 due to hepatic enzyme elevation. The subject had no symptoms associated with liver injury. The AE was resolved by day 49.

No deaths or SAEs were reported during the study.

LABEL RECOMMENDATIONS

Discussion

With half-lives of 11 h and 3 h for EVG and COBI, respectively, the 10 day dosing regimen was sufficient to reach steady-state. Similarly, 18 days of CBZ dosing was sufficient to reach steady-state.

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The effect of COBI on EVG, CBZ, and CBZE PK were consistent with COBI being a known CYP3A inhibition. The effect of CBZ on COBI and EVG PK were consistent CBZ being a known CYP3A inducer.

When coadministered with COBI+CBZ, mean EVG C_{tau} was below its protein-adjusted IC_{95} value for inhibition of HIV-1 virus [45 ng/mL], the parameter most associated with antiviral activity.⁷ Adult therapeutic levels of CBZ are 4-12 $\mu\text{g/mL}$. Per the CBZ label, when given with CYP3A inhibitors, close monitoring of CBZ levels is recommended and dose adjustment may be required.⁸ COBI concentrations were also affected by CBZ, which in turn affects TAF and TFV concentrations through effects on Pgp. Due to reduced EVG C_{min} (below its target concentration) and reduced COBI exposures (and likely but unconfirmed reduced TAF and TFV exposures), we agree with the sponsor's recommendation to contraindicate the use of E/C/F/TAF with CBZ.

Conclusions and label recommendations

We agree with the proposal in section 4 of the E/C/F/TAF label to contraindicate the use of E/C/F/TAF with CBZ.

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3.3.2 GS-US-292-0110 – Effect of food on the PK of TAF and TFV in healthy subjects administered E/C/F/TAF

ADMINISTRATIVE	
Study Period	8/12/2013-9/30/2013
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-292-0110\report-body.pdf

STUDY DESIGN			
Randomized, 3-period, cross-over study. Subjects received a dose of E/C/F/TAF FDC on days 1, 8, and 15, and were randomized to one of six treatment sequences. Each sequence included the following three treatments: fasted (treatment A), light/low-fat meal (treatment B), and high calorie/high-fat meal (treatment C).			
Treatment Sequence	Day 1	Day 8	Day 15
I	A	B	C
II	A	C	B
III	B	A	C
IV	B	C	A
V	C	A	B
VI	C	B	A
<p>The study treatments were as follows:</p> <p><u>Treatment A (Reference Therapy):</u> E/C/F/TAF STR, administered orally under fasted conditions.</p> <p><u>Treatment B (Test Product):</u> E/C/F/TAF STR, administered orally under fed (approximately 400 kcal, approximately 20% fat) conditions.</p> <p><u>Treatment C (Test Product):</u> E/C/F/TAF STR, administered orally under fed (approximately 800 kcal, approximately 50% fat) conditions.</p>			
Population	Healthy adults		
Study Rationale	Effect of food on the PK of TAF and TFV		
Treatments	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg FDC tablet (lot # CP1209B1)		
Dose Selection Rationale	Same product as administered in the pivotal studies		
Interfering Substances Excluded	Prescription, over the counter, or herbal medications taken within 28 days of study drug dosing with the exception of vitamins, acetaminophen/ibuprofen, and hormonal contraceptives.		
Analytes	TAF, TFV		
Sampling Times	Plasma: 5 and 15 minutes; 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, 24 and 48 hours postdose on days 1, 8, and 15		
PK Analysis	Noncompartmental		

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STUDY CONDUCT

Bioanalytical methods

Table 94. Bioanalytical methods.

Analyte	Matrix	Validation method #	Deficiencies
TAF	plasma	60-1115	Interference seen in analyte blank and extracted blank with peak area of up to 25% of LLOQ (1 ng/mL)
TFV	plasma	60-1116	none

Table prepared by reviewer.

Protocol deviations

No important deviations reported.

STUDY RESULTS

Study population

43 subjects were enrolled; the population included a relatively large fraction of blacks and Hispanics (Table 95).

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Table 95. Demographics.

Characteristic ^a	Total (N = 43)
Sex (n, %)	
Male	30 (69.8)
Female	13 (30.2)
Age (years)	
Mean (SD)	33 (7.9)
Median	34
Min, Max	21, 45
Race (n, %)	
American Indian or Alaska Native	1 (2.3)
Black or African American	19 (44.2)
Native Hawaiian or Other Pacific Islander	1 (2.3)
White	22 (51.2)
Ethnicity (n, %)	
Hispanic/Latino	22 (51.2)
Non-Hispanic/Latino	21 (48.8)
Weight (kg)	
Mean (SD)	75.9 (11.23)
Median	78.1
Min, Max	57.5, 99.3
Height (cm)	
Mean (SD)	173.9 (7.80)
Median	175.0
Min, Max	159.0, 193.5
Body Mass Index (kg/m ²)	
Mean (SD)	25.1 (2.84)
Median	25.3
Min, Max	19.4, 29.9
Estimated Creatinine Clearance by Cockcroft-Gault (CG) Formula (mL/min)	
Mean (SD)	113.6 (21.59)
Median	111.6
Min, Max	80.1, 165.5

Pharmacokinetics

Relative to the fasted condition, TAF AUC_{inf} was increased 15% and 18% with a light meal and high calorie meal, respectively; TAF C_{max} was decreased 32% and 37%, respectively (Table 96, Table 97). Relative to the fasted condition, TFV AUC_{inf} was increased 14% and 13% with a

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light meal and high calorie meal, respectively, while TFV AUC_{last} was unchanged in both fed conditions; TFV C_{max} was decreased 16% in both fed conditions (Table 98, Table 99).

Table 96. TAF PK by meal condition.

TAF PK Parameter (N = 42)	E/C/F/TAF Light/LF Meal	E/C/F/TAF HC/HF Meal	E/C/F/TAF Fasted
AUC _{inf} (ng•h/mL)	252.2 (32.3)	254.5 (29.6)	223.9 (44.9)
AUC _{last} (ng•h/mL)	250.3 (32.7)	251.4 (30.4)	222.5 (45.2)
C _{max} (ng/mL)	219.5 (43.7)	210.7 (47.0)	329.1 (47.0)
T _{max} (h)	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	0.50 (0.50, 0.75)
T _½ (h)	0.39 (0.37, 0.45)	0.50 (0.40, 0.56)	0.42 (0.34, 0.47)
V _z /F (L)	26.5 (43.4)	33.2 (61.9)	30.3 (33.1)
CL/F (L/h)	44.4 (37.2)	43.0 (33.7)	51.5 (35.3)

HC/HF = high-calorie, high-fat; LF = low-fat

Data are presented as mean (%CV), except for T_{max} and T_½, which are presented as median (Q1, Q3).

Table 97. Statistical comparison of TAF PK by meal condition.

Treatment Condition (N = 42)	TAF PK Parameter		
	AUC _{inf} (ng•h/mL)	AUC _{last} (ng•h/mL)	C _{max} (ng/mL)
Test Treatment: Light/LF Meal GLSM	238.94	236.73	200.65
Test Treatment: HC/HF Meal GLSM	243.71	240.22	186.36
Reference Treatment: Fasted GLSM	207.37	205.94	294.90
Light/LF Meal vs. Fasted GLSM ratio (90% CI), %	115.22 (107.14, 123.91)	114.95 (106.82, 123.69)	68.04 (58.96, 78.52)
HC/HF Meal vs. Fasted GLSM ratio (90% CI), %	117.53 (109.28, 126.39)	116.65 (108.40, 125.52)	63.20 (54.76, 72.93)
HC/HF Meal vs. Light/LF Meal GLSM ratio (90% CI), %	102.00 (94.85, 109.69)	101.48 (94.30, 109.20)	92.88 (80.49, 107.18)

CI = confidence interval, GLSM = geometric least-squares mean, HC/HF = high-calorie/high-fat; LF = low-fat

GLSMs were obtained using a mixed-effects model.

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Table 98. TFV PK by meal condition.

TFV PK Parameter (N = 42)	E/C/F/TAF Light/LF Meal	E/C/F/TAF HC/HF Meal	E/C/F/TAF Fasted
AUC _{inf} (ng•h/mL)	322.7 (20.3)	319.5 (19.2)	285.4 (22.3)
AUC _{last} (ng•h/mL)	180.6 (17.8)	180.2 (16.1)	179.0 (19.6)
C _{max} (ng/mL)	12.9 (38.3)	13.1 (44.1)	15.3 (36.5)
T _{max} (h)	1.50 (1.00, 2.00)	1.50 (0.75, 3.00)	0.75 (0.50, 1.00)
T _½ (h)	43.14 (36.27, 47.99)	40.14 (36.77, 47.31)	34.70 (31.99, 38.43)
Vz/F (L)	1190.2 (22.5)	1174.7 (20.7)	1128.0 (25.0)
CL/F (L/h)	19.5 (21.6)	19.6 (20.4)	22.3 (23.9)

HC/HF = high-calorie, high-fat; LF = low-fat

Data are presented as mean (%CV), except for T_{max} and T_½, which are presented as median (Q1, Q3).

Table 99. Statistical comparison of TFV PK by meal condition.

Treatment Condition (N = 42)	TFV PK Parameter		
	AUC _{inf} (ng•h/mL)	AUC _{last} (ng•h/mL)	C _{max} (ng/mL)
Test Treatment: Light/LF Meal GLSM	316.09	177.76	12.06
Test Treatment: HC/HF Meal GLSM	313.69	177.76	12.01
Reference Treatment: Fasted GLSM	278.40	175.33	14.34
Light/LF Meal vs. Fasted GLSM ratio (90% CI), %	113.54 (108.23, 119.11)	101.38 (97.77, 105.13)	84.11 (75.71, 93.45)
HC/HF Meal vs. Fasted GLSM ratio (90% CI), %	112.68 (107.40, 118.21)	101.39 (97.77, 105.13)	83.76 (75.39, 93.05)
HC/HF Meal vs. Light/LF Meal GLSM ratio (90% CI), %	99.24 (94.60, 104.11)	100.00 (96.44, 103.70)	99.58 (89.63, 110.63)

CI = confidence interval, GLSM = geometric least-squares mean, HC/HF = high-calorie/high-fat; LF = low-fat
GLSMs were obtained using a mixed-effects model.

Safety

One subject discontinued the study early due to physician discretion after one dose of study drug. No AEs considered related to study drug were reported. No subjects discontinued due to an AE, and there were no SAEs or deaths.

DISCUSSION AND LABEL RECOMMENDATIONS

One deficiency was interference in quantification of TAF noted in the analyte blank and extracted blank (up to 25% of peak area of the LLOQ [1 ng/mL]). This was unlikely to affect calculation of TAF AUC or C_{max}; TAF C_{min} is not measurable 24 h postdose. Thus the analysis was considered acceptable with an LLOQ of 1 ng/mL.

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TFV-DP was measured as a secondary endpoint in a subset of 10 subjects, with one 2 hour postdose sample per subject. This data was not reviewed as there was insufficient data to draw any conclusions regarding food effect.

In subjects administered E/C/F/TAF or its components as single agents with food in cross-over study 292-0103, PK was comparable for the components of E/C/F/TAF versus single agents, suggesting no formulation-related difference in food effect for E/C/F/TAF versus single agents.

Given the lack of known TAF and TFV exposure-response relationships in subjects administered E/C/F/TAF, the TAF and TFV exposure changes observed when given with meals are not considered to be clinically significant. EVG and COBI are recommended to be administered with food, while FTC and TDF may be taken without regard to food. We agree with the recommendation in the E/C/F/TAF label which recommends administration with food.

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3.3.3 GS-US-292-1316 - Drug-drug interaction study of E/C/F/TAF and sertraline in healthy subjects

ADMINISTRATIVE	
Study Period	2/28/2014-3/28/2014
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-292-1316

STUDY DESIGN																	
Open-label, 3-period, drug interaction study.																	
Day -28	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Day 21 (± 2 days)
Screening ^a	◆	● A	● B	● B	● B	● B	● B	● B	● B	● B	● B	● B	● B	● B	● C	■	Follow-up Telephone Contact
		↔ PK												↔ PK			
Clinic Check-in = ◆; Study Drug Dosing = ●; Clinic Discharge = ■; Clinic Confinement = a Screening procedures occurred within 28 days prior to scheduled first dose. A Treatment A: SER 50-mg tablet, single dose B Treatment B: E/C/F/TAF 150/150/200/10-mg tablet, single dose, administered daily for 12 days C Treatment C: SER 50-mg tablet, single dose plus E/C/F/TAF 150/150/200/10-mg tablet, single dose All treatments administered orally in the morning with food.																	
Population				Healthy adults													
Study Rationale				Drug interaction evaluation between E/C/F/TAF and sertraline													
Treatments				E/C/F/TAF 150/150/200/10 mg tablet (lot number: CP1310B1) Sertraline 50 mg tablet (lot number: V130262)													
Dose Selection Rationale				Phase 3 dose of E/C/F/TAF, approved sertraline dose													
Interfering Substances Excluded				Any prescription, OTC, or herbal products within 28 days of study drug dosing with the exception of vitamins, acetaminophen, ibuprofen, and/or hormonal contraceptives.													
Sampling Times				Days 1, 13, and 14 at the following time points: 0 (predose), 5 minutes, 15 minutes, and 0.5, 0.75, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 8, 12, 16, and 24 hours postdose.													
Analytes				EVG, COBI, FTC, TAF, TFV, and SER													

STUDY CONDUCT

Bioanalytical methods

Bioanalytical methods were acceptable (Table 100).

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Table 100. Bioanalytical methods.

Analyte	Method	Deficiencies
EVG	60-1343	None
COBI	60-1343	None
FTC	42--0831	None
TAF	60-1115	None
TFV	60-1368	In an interference test, at the low TFV QC, the addition of TAF resulted in 4-fold increased TFV concentrations. This was attributed to TFV-related impurities in the TAF reference materials.
Sertraline	42-1402	None

Protocol deviations

None reported.

STUDY RESULTS

Study population

20 subjects received at least one dose; one subject withdrew consent during the last treatment period. Demographics are summarized in Table 101.

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Table 101. Demographics.

Characteristic ^a	All Subjects (N = 20)
Age	
Mean (SD)	35 (8.1)
Median	36
Min, Max	23, 44
Sex	
Male	12 (60.0%)
Female	8 (40.0%)
Race	
Black	2 (10.0%)
White	18 (90.0%)
Ethnicity	
Hispanic or Latino	18 (90.0%)
Not Hispanic or Latino	2 (10.0%)
Weight (kg)	
Mean (SD)	74.4 (12.91)
Median	72.9
Min, Max	55.3, 110.0
Height (cm)	
Mean (SD)	168.2 (8.75)
Median	167.3
Min, Max	157.0, 190.5
Body Mass Index (kg/m²)	
Mean (SD)	26.1 (2.47)
Median	26.4
Min, Max	20.8, 30.3
eGFR (mL/min)	
Mean (SD)	129.1 (29.23)
Median	129.1
Min, Max	82.3, 186.2

Pharmacokinetics

Percent changes in PK parameters of each analyte in the E/C/F/TAF + sertraline (test) period compared to the E/C/F/TAF (reference) period are summarized in Table 102. Percent changes were <16% for each analyte/parameter.

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Table 102. Percent change (90% CI) in PK parameters for the E/C/F/TAF + sertraline (test) period (n=19) relative to the E/C/F/TAF (reference) period (n=19).

Analyte	AUCtau (ng*h/mL)	Cmax (ng/mL)	Cmin (ng/mL)
EVG	↓6 (-11, -2)	↓2 (-18, -7)	↓1 (-7, +5)
COBI	0 (-3, +3)	↑6 (+1, +10)	↓13 (-21, -5)
FTC	↓16 (-19, -12)	↓10 (-18, -2)	↓6 (-10, -1)
TAF	↓4 (-11, +3)*	0 (-14, +16)	Not detectable
TFV	↑2 (0, +4)	↑10 (0, +21)	↑1 (-1, +3)
Sertraline	↑9 (-10, +32)	↓7 (-23, +13)	↑14 (-6, +38)

Table prepared by reviewer. *AUClast.

Safety

No deaths or SAEs were reported. AEs are summarized in Table 103.

Table 103. Summary of AEs.

Subjects Experiencing any	SER (N = 20)	E/C/F/TAF (N = 20)	E/C/F/TAF+SER (N = 19)
Treatment- emergent AE	2 (10.0%)	3 (15.0%)	6 (31.6%)
Grade 3 or 4 AE	0	0	0
Treatment AE Related to Study Drug	1 (5.0%)	1 (5.0%)	5 (26.3%)
SAEs	0	0	0
AE Leading to Permanent Study Drug Discontinuation	0	0	0

DISCUSSION AND LABEL RECOMMENDATIONS

Concentration-time profiles and PK parameters for each analyte were measured with adequate precision (data not shown). No individual subjects had a large drug interaction (spaghetti plots not shown).

We agree with the proposed E/C/F/TAF labeling in that no dose adjustment of E/C/F/TAF or sertraline is recommended when these two products are coadministered.

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3.3.4 GS-US-311-0101 – Drug-drug interaction study of TAF and COBI in healthy subjects

ADMINISTRATIVE	
Study Period	6/6/2011-8/31/2011
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-0101

NOTES

This study had several cohorts evaluating drug interactions between F/TAF and ARVs. As E/C/F/TAF is a complete ARV regimen, this review is only of the TAF ± COBI arm (cohort 4).

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STUDY DESIGN					
Open-label, cross-over study.					
<div style="border: 1px solid black; padding: 10px; margin: 0 auto; width: 80%;"> <p style="text-align: center; margin: 0;">Cohorts 2 and 4</p> <div style="display: flex; justify-content: space-between; margin: 0;"> Screening Day -28 0 1 12 13 22 23 Follow-up </div> <div style="text-align: center; margin: 10px 0;"> </div> <div style="margin-top: 10px;"> <p>Daily Study Drug Administration </p> <p>Clinic Confinement </p> <p>Intensive PK Samples X</p> </div> </div>					
Cohort 4	<table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; text-align: center; padding: 2px;">Day 1 to 12</th> <th style="width: 50%; text-align: center; padding: 2px;">Day 13 to 22</th> </tr> <tr> <td style="padding: 2px;">Treatment G: Oral tablet containing single-agent GS-7340 8 mg once daily in the morning, fed</td> <td style="padding: 2px;">Treatment H: Oral tablet containing single-agent GS-7340 8 mg plus COBI 150-mg oral tablet once daily in the morning, fed</td> </tr> </table>	Day 1 to 12	Day 13 to 22	Treatment G: Oral tablet containing single-agent GS-7340 8 mg once daily in the morning, fed	Treatment H: Oral tablet containing single-agent GS-7340 8 mg plus COBI 150-mg oral tablet once daily in the morning, fed
Day 1 to 12	Day 13 to 22				
Treatment G: Oral tablet containing single-agent GS-7340 8 mg once daily in the morning, fed	Treatment H: Oral tablet containing single-agent GS-7340 8 mg plus COBI 150-mg oral tablet once daily in the morning, fed				
Population	Healthy adults aged 18-45 years				
Study Rationale	Evaluation of drug interaction TAF and COBI				
Treatments	TAF 8 mg tablet (Lot CM1002B1) COBI 150 mg tablet (Lot BB1004B1-A)				
Dose Selection Rationale	TAF 8 mg was associated with antiviral activity in a monotherapy study but TAF 25 mg was chosen for evaluation in phase 2 and phase 3 studies. COBI 150 mg was incorporated in E/C/F/TAF				
Interfering Substances Excluded	Any prescription, OTC, or herbal products within 28 days of study drug dosing with the exception of vitamins, acetaminophen, ibuprofen, and/or hormonal contraceptives.				
Sampling Times	Days 1 and 13: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, and 5 hours postdose. Days 12 and 22: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours postdose.				
Analytes	TAF, TFV, COBI				

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STUDY CONDUCT

Bioanalytical methods

TAF, TFV, and COBI bioanalytical methods were acceptable.

Protocol deviations

None reported.

STUDY RESULTS

Study population

Demographics for cohort 4 are included in Table 104.

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Table 104. Demographics.

Characteristic	Cohort 1 Sequence AB (n=12)	Cohort 2 Sequence CD (n=12)	Cohort 3 Sequence EF (n=14)	Cohort 4 Sequence GH (n=12)	Total (N=50)
Sex, n (%)					
Male	6 (50.0)	6 (50.0)	9 (64.3)	8 (66.7)	29 (58.0)
Female	6 (50.0)	6 (50.0)	5 (35.7)	4 (33.3)	21 (42.0)
Age (years)					
Mean (SD)	33 (6.2)	37 (6.5)	37 (5.9)	33 (8.8)	35 (6.9)
Median	34	37	38	34	36
Min, Max	24, 44	21, 44	26, 45	22, 44	21, 45
Race, n (%)					
White	8 (66.7)	11 (91.7)	12 (85.7)	9 (75.0)	40 (80.0)
Black	4 (33.3)	1 (8.3)	2 (14.3)	3 (25.0)	10 (20.0)
Asian	0	0	0	0	0
Other	0	0	0	0	0
Height (cm)					
N	12	12	14	12	50
Mean (SD)	166.8 (9.24)	167.1 (7.99)	169.2 (9.07)	171.3 (7.85)	168.6 (8.51)
Median	167.5	164.8	165.0	171.5	167.5
Min, Max	151.0, 183.0	156.0, 179.0	160.0, 188.0	161.0, 187.5	151.0, 188.0
Body Mass Index (kg/m²)					
N	12	12	14	12	50
Mean (SD)	25.8 (2.94)	26.4 (2.89)	27.0 (1.98)	26.6 (2.68)	26.5 (2.58)
Median	26.9	27.2	27.7	27.1	27.2
Min, Max	20.4, 29.2	20.5, 29.3	23.2, 29.6	22.3, 31.0	20.4, 31.0
Weight (kg)					
N	12	12	14	12	50
Mean (SD)	72.2 (11.83)	73.7 (10.52)	77.5 (8.79)	78.2 (12.02)	75.5 (10.75)
Median	77.2	74.4	75.9	76.4	75.9
Min, Max	46.5, 85.0	50.6, 89.8	63.1, 92.0	63.3, 108.8	46.5, 108.8
eGFR by Cockcroft-Gault (mL/min)					
N	12	12	14	12	50
Mean (SD)	129.4 (16.71)	137.4 (26.43)	130.1 (21.16)	126.6 (13.75)	130.8 (19.91)
Median	128.9	133.9	126.1	126.3	128.6
Min, Max	102.2, 170.0	87.2, 190.7	102.0, 165.8	93.3, 144.6	87.2, 190.7

SD = standard deviation

Treatment A = FTC/GS-7340 FDC (200/40 mg); Treatment B = FTC/GS-7340 FDC (200/40 mg) + EFV (600 mg);
 Treatment C = FTC/GS-7340 FDC (200/25 mg); Treatment D = FTC/GS-7340 FDC (200/25 mg) + DRV/co (800/150 mg);
 Treatment E = DRV/co (800/150 mg); Treatment F = FTC/GS-7340 FDC (200/25 mg) + DRV/co (800/150 mg);
 Treatment G = GS-7340 (8 mg); Treatment H = GS-7340 (8 mg) + COBI (150 mg).

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Pharmacokinetics

TAF exposures were increased ~2.5-fold and TFV exposures were increased ~3.3-fold when coadministered with COBI (Table 105, Table 106). COBI PK was only measured when coadministered with TAF.

Table 105. Statistical comparison of TAF exposures.

GS-7340 PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
GS-7340 8 mg + COBI (Test) vs GS-7340 8 mg (Reference), (N = 12)				
AUC _{last} (ng·h/mL)	200.95	75.81	265.06	(229.00, 306.80)
C _{max} (ng/mL)	173.43	61.21	283.31	(219.65, 365.43)

Table 106. Statistical comparison of TFV exposures.

TFV PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
GS-7340 8 mg + COBI (Test) vs GS-7340 8 mg (Reference), (N = 12)				
AUC _{tau} (ng·h/mL)	280.26	84.70	330.88	(310.20, 352.93)
C _{max} (ng/mL)	18.87	5.65	334.09	(301.98, 369.62)
C _{tau} (ng/mL)	9.96	2.97	334.86	(312.43, 358.91)

Safety

There were no deaths or SAEs in the study. There were no AEs leading to study drug discontinuation for treatments G or H. Four AEs were reported for treatment G and three for treatment H.

DISCUSSION AND LABEL RECOMMENDATIONS

TAF, TFV, and COBI concentration-time profiles and PK parameters were estimated with adequate precision (data not shown). When coadministered with COBI, there were no subjects in cohort 4 with a TAF or TFV exposure change that was very different from the mean increase of ~2.5-3-fold (data not shown). Due to the ~2.5-fold TAF exposure increase when coadministered with COBI 150 mg, the E/C/F/TAF product studied in phase 2 and phase 3 contained 10 mg TAF, which corresponds to exposures of single agent TAF 25 mg. Exposures corresponding to single agent TAF 25 mg was chosen for commercialization based on antiviral activity demonstrated in monotherapy study GS-US-120-0104.

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4 In vitro studies

4.1 Protein binding

4.1.1 60N-1334 – Ex vivo protein binding of TAF and TFV in human plasma samples from study GS-US-120-0114

ADMINISTRATIVE	
Report date	1/27/2014
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-120-0114-(b)(4)-60-1344.pdf

Methods

TAF protein binding was determined for 78 plasma samples collected from 39 subjects at 1 and 4 h post-dose. TAF protein binding was determined by ultrafiltration at 37°C. Plasma samples were equilibrated at 37°C for ~15 minutes prior to centrifugation for ~20 minutes at 37°C to generate the ultrafiltrate. TAF concentrations in ultrafiltrate samples (post-filtration) were determined by an LC-MS/MS method. Plasma sample concentrations (pre-filtration) were obtained from (b)(4) Study 60-1344A. TAF percent unbound was calculated based on ultrafiltrate (post-filtration) and plasma (pre-filtration) sample concentrations according to percent unbound = $100 * C_{\text{blood}} / C_{\text{plasma}}$.

TFV protein binding was determined for 72 human plasma samples collected from 39 subjects at 2 and 24 h post-dose. TFV protein binding was determined at 37°C for 3 hours by an equilibrium dialysis method. Equilibrium dialysis was carried out in singlet using a plasma volume of 0.7-1 mL, which was first spiked with ~50 ng/mL [¹⁴C]TFV at final concentration, and dialyzed against an equal volume of 0.133M potassium phosphate buffer (pH 7.4). Radioactivity in post-dialysis plasma and buffer samples was determined by LSC and was used for the TFV percent unbound calculation (percent unbound = $100 * C_{\text{ultrafiltrate}} / C_{\text{plasma}}$).

Results

For samples from normal subjects matched to mildly and moderately impaired patients, TAF mean ± SD percent unbound was $17.4 \pm 4.6\%$ and $15.2 \pm 3.3\%$, respectively. The range of TAF percent unbound was 9.2-30.3% for normal subjects matched to mildly impaired patients and 9.7-21.7% for normal subjects matched to moderately impaired patients.

For samples from normal subjects matched to mildly and moderately impaired patients, the mean ± SD TFV percent unbound was $100.9 \pm 2.3\%$ and $100.1 \pm 1.3\%$, respectively. For samples from mildly and moderately hepatic impaired patients, the mean ± SD TFV percent unbound was $101.4 \pm 1.2\%$ and $102.2 \pm 1.9\%$, respectively. TFV percent recovery was >80% in most subjects.

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Label recommendations

We agree with the following E/C/F/TAF label statement (section 12.3) derived from this study:

[REDACTED] ” (b) (4)

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

4.2 Drug metabolizing enzymes

4.2.1 *Substrate*

4.2.1.1 AD-120-2004 - Human cytochrome P450 metabolic reaction phenotyping of TAF

ADMINISTRATIVE	
Report date	3/4/2011
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomaat\5322-rep-hep-metab-interact-stud\ad-120-2004

Methods

Test compounds (TAF or CYP positive control substrate) at a concentration of 5µM were incubated with bacterially expressed human CYP450 enzyme preparations (BactosomesTM) at the following final CYP450 concentrations: CYP1A2 100 pmol/mL, CYP2C8 50 pmol/mL, CYP2C9 25 pmol/mL, CYP2C19 100 pmol/mL, CYP2D6 50 pmol/mL or CYP3A4 25 pmol/mL. Pre-incubations at 37°C were done prior to the addition of NADPH (final concentration = 1 mM) to initiate the reaction. Incubations were also performed using control Bactosomes (no CYP450 enzymes present) to reveal any nonenzymatic degradation. Compounds known to be metabolized selectively by each CYP450 enzyme were used as positive control substrates. Each compound was incubated individually for 0, 5, 15, 30, and 45 min with each enzyme. Samples were analyzed by LC/MS/MS.

Results

Metabolism of TAF was not detected by CYP1A2, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 (less than 10% loss of substrate over the course of the incubation). Metabolism of TAF was detectable with CYP3A4 (26.6% of the positive control).

Label recommendations

We agree with the following E/C/F/TAF label statement (section 12.3) derived from this study:

[REDACTED] (b) (4)

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

4.2.1.2 AD-120-2031 - Effect of inhibitors of CatA, CES1, and CYP3A4 on TAF metabolism in human hepatocytes

ADMINISTRATIVE	
Report date	6/19/2013
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2031

Introduction

TAF has been shown to be cleaved by cathepsin A (CatA) in PBMCs and other lymphatic tissues.^{9,10} This study evaluated metabolism of TAF by CatA, carboxylesterase 1 (CES1), and CYP3A in human hepatocytes.

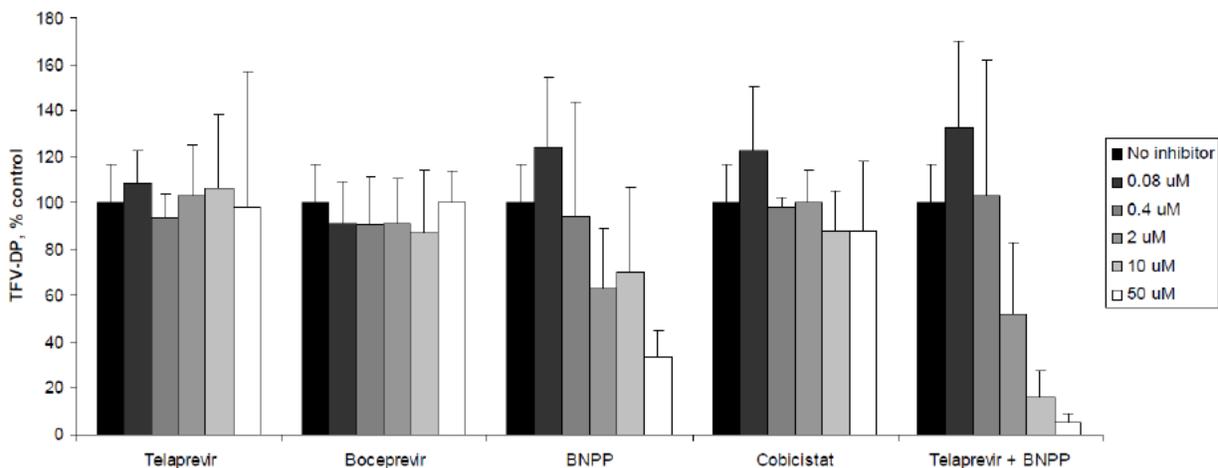
Methods

Primary human hepatocytes from three donors were incubated (duplicate wells) for 24 hours with 0.5 μ M TAF alone (control) and with varying concentrations (0, 0.08, 0.4, 2, 10, and 50 μ M) of the inhibitor(s) (test condition). Inhibitors included telaprevir and boceprevir (CatA inhibitors), bis(p-nitrophenyl)phosphate (BNPP) (CES1 inhibitor), and COBI (CYP3A inhibitor). Harvested cells were stored overnight at -20 $^{\circ}$ C to facilitate nucleotide extraction. Intracellular TFV-DP was quantified by LC/MS/MS as a measure of TAF metabolism.

Results

TFV-DP concentrations were not affected by incubation with telaprevir, boceprevir, or COBI. Incubation of BNPP resulted in an apparent concentration-dependent reduction in TFV-DP concentrations. Compared to BNPP alone, telaprevir plus BNPP resulted in a greater reduction in TFV-DP concentrations (Figure 18).

Figure 18. Intracellular formation of TFV-DP following continuous incubation of primary human hepatocytes with 0.5 μ M TAF in the presence of inhibitors of CatA, CES1, and CYP3A4.



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Conclusion

Coadministration of TAF with or CatA or CYP3A inhibitors are unlikely to affect conversion to the active TFV-DP; CES1 inhibitors may have an effect.

Label recommendations

We agree with the following E/C/F/TAF label statement (section 12.3) derived from this study: “In vitro studies have shown that tenofovir alafenamide is metabolized to tenofovir (b) (4) by cathepsin A in peripheral blood mononuclear cells (PBMCs) (b) (4) and macrophages; and by carboxylesterase-1 in hepatocytes.”

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4.2.2 Inhibition

4.2.2.1 AD-120-2003 - Human cytochrome P450 inhibition potential of TAF

ADMINISTRATIVE	
Report date	3/4/2011
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2003

Methods

Test compounds at concentrations up to 25 μM were incubated with human liver microsomes and NADPH in the presence and absence of individual probe substrates. Substrate concentrations were equal to or less than their respective K_m values. Probe substrate metabolites (acetaminophen, 4-hydroxybupropion, 6 α -hydroxypaclitaxel, 4-hydroxytolbutamide, 4'-hydroxymephenytoin, dextropran, 1'-hydroxymidazolam, and 6 β -Hydroxytestosterone) were measured by LC/MS/MS. IC_{50} values were calculated where possible.

Results

TAF did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6; TAF inhibited CYP3A (Table 107).

Table 107. Effects of TAF and Positive Control Inhibitors on the Activities of Major Human Cytochromes P450.

Enzyme	Activity	Calculated IC_{50} (μM)	
		Control Inhibitor ^a	GS-7340
CYP1A2	Phenacetin O-deethylase	0.05	>25
CYP2B6	Bupropion 4-hydroxylase	0.72	> 25
CYP2C8	Paclitaxel 6 α -hydroxylase	0.34	> 25
CYP2C9	Tolbutamide 4-hydroxylase	0.64	>25
CYP2C19	S Mephenytoin 4'-hydroxylase	7.65	>25
CYP2D6	Dextromethorphan O-demethylase	0.05	>25
CYP3A	Midazolam 1'-hydroxylase	0.03	7.6
	Testosterone 6 β -hydroxylase	0.11	7.4

a Control Inhibitors: CYP1A2, α -Naphthoflavone (0–3 μM); CYP2B6, Ticlopidine (0-10 μM); CYP2C8 Montelukast (0–3 μM); CYP2C9, Sulfaphenazole (0–10 μM); CYP2C19, Tranylcypromine (0–50 μM); CYP2D6, Quinidine (0–3 μM); CYP3A, Ketoconazole (0–3 μM).

Discussion

With the exception of tranylcypromine for inhibition of CYP2C19, the control inhibitors used were recommended in FDA guidance.¹¹

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The sponsor classified TAF as a weak CYP3A inhibitor. As E/C/F/TAF contains COBI, a strong CYP3A inhibitor, TAF is not expected to result in additional CYP3A inhibition.

Label recommendations

Section 7.2 of the E/C/F/TAF label describes the potential for E/C/F/TAF to affect other drugs. We agree with the decision to only describe the effects of COBI on enzymes and transporters in this section.

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4.2.2.2 AD-120-2040 - Human CYP mechanism-based inhibition of TAF

ADMINISTRATIVE	
Report date	8/5/2014
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2040

Methods

TAF 50 μ M was pre-incubated with human liver microsomes at 37°C for 30 minutes with or without 1 mM NADPH (CYP cofactor). Enzyme substrate was then added. Enzyme specific metabolites were quantified by LC/MS/MS, except resorufin was quantified fluorometrically. Mechanism-based inhibition was calculated as percent change in the ratio of the metabolite peak area ratio (PAR) values obtained after pre-incubations performed in the absence and presence of NADPH cofactor, and corrected for the change in activity when incubated with DMSO vehicle instead of TAF or positive control inhibitor.

$$Ratio = \frac{PAR_{NADPH+}}{PAR_{NADPH-}} \bullet \frac{PAR_{DMSO,NADPH-}}{PAR_{DMSO,NADPH+}}$$

$$\%Change = (1 - Ratio) \bullet 100\%$$

Results

Compared to positive controls, TAF shows no potential for mechanism-based inhibition of CYP enzymes (Table 108).

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Table 108. %Change Values for Time- and Cofactor-Dependent Inhibition of Major Human Hepatic Microsomal CYP Enzymes by TAF.

CYP Enzyme	Probe Activity	Calculated %Change	
		Control Inhibitor ^a	GS-7340
CYP1A2	Ethoxyresorufin O-deethylase	71.2 ± 1.9	-5.61 ± 9.16
		57.9 ± 3.1	
CYP2B6	Bupropion 4-hydroxylase	85.4 ± 0.8	-5.29 ± 3.52
CYP2C8	Paclitaxel 6 α -hydroxylase	60.3 ± 4.8	17.4 ± 14.2
CYP2C9	Diclofenac 4'-hydroxylase	79.6 ± 2.5	-7.36 ± 17.2
CYP2C19	S-Mephenytoin 4'-hydroxylase	62.3 ± 0.9	5.30 ± 4.10
CYP2D6	Dextromethorphan O-demethylase	80.1 ± 3.6	3.94 ± 16.1
CYP3A	Midazolam 1'-hydroxylase	60.1 ± 1.8	16.4 ± 5.87
		80.2 ± 1.2	
	Testosterone 6 β -hydroxylase	91.3 ± 0.5	10.3 ± 4.66
		70.7 ± 1.2	

a CYP1A2, furafylline and resveratrol; CYP2B6, ticlopidine; CYP2C8, gemfibrozil glucuronide; CYP2C9, tienilic acid; CYP2C19, ticlopidine; CYP2D6, paroxetine; CYP3A, mibefradil and mifepristone

Label recommendations

Section 7.2 of the E/C/F/TAF label describes the potential for E/C/F/TAF to affect other drugs. We agree with the decision to only describe the effects of COBI on enzymes and transporters in this section.

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4.2.3 Induction

4.2.3.1 AD-120-2005 - Induction of metabolizing enzymes by TAF in vitro

ADMINISTRATIVE	
Report date	3/4/2011
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2005

Methods

Two hepatoma-derived cell lines were used. DPX2 cells were stably transformed with human PXR and the enhancer regions of CYP3A4 linked to a reporter gene (luciferase). DRE12.6 cells were transformed with human AhR and a response element of human CYP1A2 linked to a luciferase reporter.

Cells were incubated with medium containing the test articles for 24 hours. Luciferase activity was measured by luminescence. Fold induction relative to DMSO negative control was calculated for each test article.

Results

TAF and positive control fold induction values are shown in Table 109 and Table 110.

Table 109. Human PXR Activation by TAF and Positive Control.

Concentration	Fold Induction Over 0.1% DMSO Control	
	GS-7340	Rifampicin
0.1 µM		1.56
0.15 µM	0.81	
0.5 µM	0.92	4.59
1.0 µM		6.36
1.5 µM	0.88	
5 µM	1.03	12.53
10 µM		13.43
15 µM	1.58	
20 µM		12.64
50 µM	3.89	

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Table 110. Human AhR Activation by TAF and Positive Control.

Concentration	Fold Induction Over 0.1% DMSO Control	
	GS-7340	β -Naphthoflavone
0.1 μ M		2.56
0.15 μ M	1.09	
0.5 μ M	1.04	6.37
1.0 μ M		11.07
1.5 μ M	0.97	
5 μ M	0.91	47.46
10 μ M		40.03
15 μ M	0.87	
20 μ M		27.66
50 μ M	0.90	

Discussion/Conclusion

The positive controls chosen were recommended for evaluating induction of CYP1A2 (β -naphthoflavone), along with CYP2C8, 2C9, 2C19, and 3A4 (rifampicin).¹¹

Label recommendations

Section 7.2 of the E/C/F/TAF label describes the potential for E/C/F/TAF to affect other drugs. We agree with the decision to only describe the effects of COBI on enzymes and transporters in this section.

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4.2.3.2 AD-120-2006 - In vitro assessment of human UGT1A1 inhibition potential of TAF

ADMINISTRATIVE	
Report date	3/4/2011
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2006

Methods

TAF or silybin (positive control) up to 50 μ M and estradiol 10 μ M (substrate) were incubated at 37°C for 30 minutes with insect cell microsomal fraction containing expressed human UGT1A1. Samples were analyzed for estradiol 3-glucuronide using LC/MS/MS.

Results

Silybin inhibited activity with a measured IC_{50} value of 1.69 μ M while TAF showed no detectable inhibition ($IC_{50} > 50 \mu$ M). TAF is thus unlikely to be a clinically relevant inhibitor of UGT1A1 in vivo.

Label recommendations

Section 7.2 of the E/C/F/TAF label describes the potential for E/C/F/TAF to affect other drugs. We agree with the decision to only describe the effects of COBI on enzymes and transporters in this section.

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4.2.3.3 AD-120-2032: Assessment of induction potential of TAF in human hepatocytes

ADMINISTRATIVE	
Report date	3/13/2014
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2032

Methods

TAF was incubated in three preparations of cryopreserved human hepatocyte cultures (n=3 separate donors) at concentrations of 1, 10, and 100 µM with vehicle control and positive controls (Table 111). Induction of CYP1A2, 2B6, and 3A4 was evaluated: after 3 days of exposure, induction was determined in situ by catalytic activity assays, and mRNA expression was determined using real-time PCR (RT-PCR) (Table 112). Additionally, the cytotoxic potential of TAF was assessed using the MTT assay. Metabolites were measured by LC/MS/MS.

Table 111. Incubation Conditions of TAF and Controls.

Incubation parameter	Test Article GS-7340	Positive Control Inducer Chemicals			
		BNF ¹	Omeprazole	Phenobarbital	Rifampicin
Enzymes assayed	CYPs 1A2, 2B6, & 3A4, P-gp, UGT1A1	UGT1A1	CYP1A2	CYP2B6, P-gp	CYP3A4
Concentration (µM) ² in the induction assay	1, 10 & 100	20	50	1000	10
Solvent	DMSO	DMSO	DMSO	10% DMSO in water	DMSO
Final solvent concentration (% v/v)	0.1	0.1	0.1	0.1	0.1
Exposure time (days)	3	3	3	3	3
Test compound renewal	Daily	Daily	Daily	Daily	Daily
Incubation temp (°C)	37	37	37	37	37
Atmosphere	5% CO ₂ in humidified air				
Termination	Medium removal				
Replicates	Triplicate	Triplicate	Triplicate	Triplicate	Triplicate

¹BNF: β-naphthoflavone

² Solvent only incubations were also included

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Table 112. Enzyme Methods for P450-Mediated Metabolite Formation.

Assay parameter	CYP1A2	CYP2B6	CYP3A4
Substrate	Phenacetin	Bupropion	Testosterone
Reaction catalyzed	O-Deethylation	Hydroxylation	6β-Hydroxylation
Substrate solvent	DMSO ¹	Methanol	DMSO
Substrate concentration (μM)	100	250	200
Final organic solvent concentration (%)	0.1	0.5	0.2
Incubation volume (mL)	0.2	0.2	0.2
Incubation time (min)	60	30	30
Incubation temp (°C)	37	37	37

¹DMSO: Dimethylsulfoxide

Induction was calculated using the following equations:

Equation 1:

$$\text{fold induction} = \frac{\text{activity (treated sample)}}{\text{mean activity (solvent vehicle control samples)}}$$

If applicable, the percent positive control inducer response exhibited by the test article was calculated using Equation 2.

Equation 2:

% of positive control response =

$$\frac{[(\text{activity of test article treated cells} - \text{mean activity of solvent vehicle control})]}{(\text{mean activity of positive control} - \text{mean activity of solvent vehicle control})} \times 100$$

Equation 3:

$$\% \text{ of positive control response} = \frac{[\text{fold induction of test article treated cells} - 1]}{\text{mean fold induction of positive control} - 1} \times 100$$

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Results

Demographics of hepatocyte donors are described in Table 113.

Table 113. Detail of Human Donors Used in the Study.

Lot#	Sex	Age	Race	Smoker	Cause of Death
228	F	43	Caucasian	Yes	Stroke
307	M	29	Caucasian	Yes	Head Trauma 2 nd to MVA
321	F	58	Caucasian	Yes	Anoxia 2 nd to Cardiovascular

Across three donors, TAF 1 μ M resulted in $\leq 3\%$ of positive control CYP1A2, 2B6, and 3A induction as assessed by mRNA expression and CYP1A2 activity. In addition, TAF 1 μ M resulted in $\leq 5\%$ of positive control UGT1A1 and Pgp induction as assessed by mRNA expression. Thus TAF is unlikely to be an in vivo inducer of CYP1A2, CYP2B6, CYP3A, UGT1A1, or Pgp.

Label recommendations

Section 7.2 of the E/C/F/TAF label describes the potential for E/C/F/TAF to affect other drugs. We agree with the decision to only describe the effects of COBI on enzymes and transporters in this section.

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4.3 Transporters

4.3.1 *Substrate*

4.3.1.1 AD-120-2018 – TAF as a substrate of Pgp and BCRP

ADMINISTRATIVE	
Report Date	1/30/14
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-bioma\5322-rep-hep-metab-interact-stud\ad-120-2018

Methods

STUDY DESIGN	
Study Rationale	Determine if TAF is a substrate of Pgp and BCRP
System	Wild type, Pgp transfected, and BCRP transfected MDCKII cells.
Substrate concentrations	TAF: One concentration of ~8-10 μ M tested
Inhibitor concentrations	Cyclosporin A (Pgp inhibitor): 10 μ M Ko134 (BCRP inhibitor): 10 μ M
Controls	Vinblastine (Pgp substrate) Prazosin (BCRP substrate)
Assessment of recovery, stability, and non-specific binding	The total amount of drug was quantified at the end of the experiment and compared to the material present in the original dosing solution.

Results

TAF percent recovery was generally high (>90%). Positive control substrates and markers of membrane integrity (TEER value and Lucifer yellow) met sponsor-established acceptance criteria.

The TAF efflux ratio increased from 4.8 in MDCK wild-type cells to 66.2 in Pgp-transfected MDCK cells, and decreased to 5.6 in the presence of cyclosporin A.

The TAF efflux ratio increased from 4.8 in MDCK wild-type cells to 6.2 in BCRP-transfected MDCK cells, and decreased to 1.4 in the presence of cyclosporin A.

Label recommendations

We propose the following to be added to the E/C/F/TAF label in section 7.3: “Tenofovir alafenamide, a component of [TRADENAME], is a substrate of P-gp, BCRP, OATP1B1 and OATP1B3. Drugs that inhibit P-gp and/or BCRP, such as cobicistat, may increase the absorption of tenofovir alafenamide (see Table)^{(b) (4)}”

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[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

4.3.1.2 AD-120-2022 - In vitro assessment of TAF as a substrate for human OATP1B1 and OATP1B3

ADMINISTRATIVE	
Report date	3/14/2013
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2022

Methods

Uptake of TAF and positive controls were evaluated in uptake assays (1 min incubation at 37°C) using wild type or human OATP1B1 and OATP1B3-transfected CHO cells. TAF and positive controls concentrations were assayed by LC/MS/MS.

The rate of uptake was calculated as follows:

Rate of uptake = $\frac{\text{concentration of compound in cell lysate} * \text{volume of sample}}$

$\text{Incubation time (minute) * millions of cells in sample}$

Results

Results are shown in Table 114.

Table 114. Uptake results.

Uptake Activities for GS-7340 and Control Compounds in CHO-WT and CHO-transfected Cells

Uptake Rate (pmole/minute/1.0x10 ⁶ cells)	GS-7340 10 μM	Atorvastatin 0.1 μM	Antipyrin 10μM
CHO-WT	9.0	0.38	23
CHO-OATP1B1	12.0	4.6	23
CHO-OATP1B3	24.1	5.5	24
OATP1B1 / WT Ratio	1.3	11.9	1.0
OATP1B3 / WT Ratio	2.7	14.5	1.0

Uptake Rates for GS-7340 and Control Compounds in CHO-WT and CHO-transfected Cells in the Presence of 40 μM Rifampicin

Uptake Rate (pmole/minute/1.0x10 ⁶ cells)	GS-7340 10 μM	Atorvastatin 0.1 μM	Antipyrin 10μM
CHO-WT	6.0	0.7	24
CHO-OATP1B1	6.2	0.9	23
CHO-OATP1B3	5.8	1.2	23

Uptake Ratios for GS-7340 and Control Compounds in CHO-WT and CHO-transfected Cells in the Presence of 40 μM Rifampicin

Uptake Ratio Cpd alone / cpd+rifampicin	GS-7340 10 μM	Atorvastatin 0.1 μM	Antipyrin 10μM
CHO-WT	1.5	0.5	1.0
CHO-OATP1B1	1.9	5.0	1.0
CHO-OATP1B3	4.2	4.8	1.0

Conclusions

These studies suggest that TAF is a substrate of OATP1B1 and OATP1B3. The rate of uptake of TAF in CHO-OATP1B1 and CHO-OATP1B3 cells increased by 30% and 168%, respectively, when compared to wild type cells. The uptake rate was decreased by 48% in CHO-OATP1B1 cells and 76% in CHO-OATP1B3 cells in the presence of rifampicin.

Label recommendations

We propose the following to be added to the E/C/F/TAF label in section 7.3: “Tenofovir alafenamide, a component of [TRADENAME], is a substrate of P-gp, BCRP, OATP1B1 and OATP1B3. Drugs that inhibit P-gp and/or BCRP, such as cobicistat, may increase the absorption of tenofovir alafenamide (see Table (b) (4))”

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

[REDACTED] (b) (4)

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4.3.2 Inhibition

4.3.2.1 AD-120-2019 - In vitro assessment of TAF inhibition of human OATP1B1, OATP1B3, P-gp, and BCRP

ADMINISTRATIVE	
Report date	11/7/2012
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2019

Methods

OATP influx assays were conducted using wild type or human OATP1B1 and OATP1B3-transfected chinese hamster ovary cells. The dose-dependent inhibition of OATP1B1 and OATP1B3-mediated transport of Fluo 3 by TAF was tested at seven concentrations ranging from 0.14 to 100 μ M.

MDCKII cells were used for Pgp and BCRP influx assays. The dose-dependent inhibition of Pgp mediated efflux of Calcein-AM and BCRP mediated efflux of pheophorbide A (PhA) by TAF was tested at six concentrations ranging from 0.41 to 100 μ M. Cells were analyzed for calcein or PhA fluorescence.

Percent inhibition was calculated as follows:

$$\text{Ratio (R)} = \text{TF}_{\text{Pgp}} / \text{TF}_{\text{WT}}$$

$$\text{Ratio (R)} = \text{TF}_{\text{BCRP}} / \text{TF}_{\text{WT}}$$

$$\% \text{ Inhibition} = ((R^{\text{I}} - R^{\text{NI}}) / (1 - R^{\text{NI}})) \times 100\%$$

Where,

TF is total fluorescence

R^{I} and R^{NI} represent the ratio observed in the presence and absence of test compound, respectively.

Results

TAF showed weak inhibition of OATP1B1 and OATP1B3 with respective 29.8% and 25.5% inhibition observed at the highest concentration tested (100 μ M). TAF showed no inhibition of Pgp and BCRP up to 100 μ M (Table 115).

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Table 115. Inhibition of OATP1B1/1B3-Mediated Transport of Fluo3, BCRP-Mediated Transport of Pheophorbide A, and Pgp-Mediated Transport of Calcein AM by TAF and Control Compounds.

Transporters	Uptake Transporters IC ₅₀ (μM)	
	OATP1B1	OATP1B3
GS-7340	>100	>100
Rifampicin	2.4 ± 1.1	1.7 ± 0.4
Transporters	Efflux Transporters IC ₅₀ (μM)	
	Pgp	BCRP
GS-7340	>100	>100
Verapamil	3.7 ± 3.1	N/A
Fumitremorgin C (FTC)	N/A	0.32± 0.03

Label recommendations

Section 7.2 of the E/C/F/TAF label describes the potential for E/C/F/TAF to affect other drugs. We agree with the decision to only describe the effects of COBI on enzymes and transporters in this section.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

4.3.2.2 AD-120-2036 - In vitro assessment of TAF as an inhibitor of OAT1, OAT3, OCT1, OCT2, MATE1, and BSEP or as a substrate for OCT1

ADMINISTRATIVE	
Report date	2/3/2014
Link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\ad-120-2036

Methods

Cells and experimental conditions for the transporter inhibition assays are summarized in Table 116.

Table 116. Transfected Cells, Membrane Vesicles, Substrates and Positive Control Inhibitors Used in the Transport Inhibition Assays.

Transporter	Transfected Cells	Model Substrate	Positive Control
OAT1	CHO	PAH	Benzbromarone
OCT1	CHO	TEA	Verapamil
MATE1	CHO	TEA	Quinidine
BSEP	Sf9 cell membrane vesicles	Taurocholate	Cyclosporin A
OAT3	Flp-In 293	Estrone 3-Sulfate	Probenecid
OCT2	CHO	TEA	Verapamil

(CHO) Chinese Hamster Ovary

(Sf9) Spodoptera frugiperda ovarian cells

(TEA) Tetraethylammonium

(PAH) Para-aminohippurate

(Flp-In 293) Parental Cells transfected with pFRT/lacZeo and selected for stable Zeocin™-resistant clones

Uptake transporter fractional activities (used for all transporters except BSEP) were calculated as follows:

$$\text{Activity \%} = (A-B/C-D) \times 100$$

Legend:

A: translocated amount of substrate in the presence of TA on transfected cells

B: translocated amount of substrate in the presence of TA on parental cells

C: translocated amount of substrate in the presence of solvent on transfected cells

D: translocated amount of substrate in the presence of solvent on parental cells

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

BSEP fractional transporter activity was calculated as follows:

$$\text{Activity \%} = (A-B/C-D) \times 100$$

Legend:

- A: translocated amount of substrate in the presence of TA and ATP
- B: translocated amount of substrate in the presence of TA
- C: translocated amount of substrate in the presence of solvent and ATP
- D: translocated amount of substrate in the presence of solvent

Where TA=TAF

The amount of substrate inside the cells was determined by liquid scintillation/fluorescence.

Results

Inhibition data is summarized in Table 117.

Table 117. Inhibition of Human BSEP, OCT1, OCT2, OAT1, OAT3 and MATE1 Transporters by TAF.

Vesicular Transport Inhibition		
Transporter	Maximum inhibition at 100 μ M (% of control)	IC ₅₀ (μ M)
BSEP	43	>100
Uptake Transporter Inhibition		
Transporter	Maximum inhibition at 100 μ M (% of control)	IC ₅₀ (μ M)
OCT1	26	>100
OCT2	NA	>100
OAT1	8	>100
OAT3	16	>100
MATE1	34	>100

Conclusions

Tenofovir alafenamide weakly inhibited BSEP, MATE1, OCT1, OAT3 and OAT1 activity by 43%, 34%, 26%, 16% and 8%, respectively, at the highest concentration tested (100 μ M). No transporter specific inhibition of OCT2 was observed for TAF when tested at up to 100 μ M. TAF was found not to be a substrate for OCT1 based on no transporter specific accumulation of TAF in the OCT1 transporter-expressing cells.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

Label recommendations

Section 7.2 of the E/C/F/TAF label describes the potential for E/C/F/TAF to affect other drugs. We agree with the decision to only describe the effects of COBI on enzymes and transporters in this section.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

4.4 Drug-drug interactions

4.4.1 *AD-120-2013 - Effect of GS-9350 on the Bidirectional Permeability of TAF Through Caco-2 Cells*

This study was not reviewed because the interaction between GS-9350 and TAF was evaluated in human study GS-US-311-0101.

CLINICAL PHARMACOLOGY REVIEW – INDIVIDUAL STUDY REVIEWS

5 Reference List

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CLINICAL PHARMACOLOGY REVIEW

5.2 Pharmacometrics Review

PHARMACOMETRICS REVIEW

NDA Number:	207561
Submission Type; Code:	NME
Applicant Name:	Gilead
Submission Dates:	11/5/2014
Brand Name:	Genvoya
Generic Name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Dosage Form:	Fixed dose combination tablet
Dosage Strengths:	150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide
Proposed Indication:	Treatment of HIV-1 in ages ≥ 12 years
OCP Division:	IV
Review Team:	Mario Sampson, PharmD, Islam Younis, PhD, Jeffrey Florian, PhD

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PHARMACOMETRICS REVIEW

2 ADMINISTRATIVE	
Title of report	Population Pharmacokinetic Analysis of Tenofovir Alafenamide and Tenofovir following Administration of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single Tablet Regimen
EDR study report link	\\CDSESUB1\evsprod\NDA207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-taf\report-body.pdf
EDR datasets link	\\CDSESUB1\evsprod\NDA207561\0000\m5\datasets\pop-pk-taf\analysis\legacy\programs
FDA Pharmacometrics link	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\TAF_NDA207561_S0000_MRS\PPK Analyses
Responses to Information Requests	\\CDSESUB1\evsprod\NDA207561\0021\m1\us\111-info-amendment

3 NOTES

Analyses and figures/tables shown in this review were prepared by the sponsor unless otherwise indicated.

4 METHODS

Nine studies were included in the analysis (Table 1). Subjects were included if dosing was verified and ≥ 1 plasma sample was collected. NONMEM 7.3 software was used to analyze the data. Due to very different time scales and long run times, the TAF and TFV models were developed separately and subsequently combined. Individual subject PK parameters were simulated to obtain concentration-time profiles; these profiles were then analyzed by noncompartmental analysis to calculate AUC and C_{max} measures for each subject. The following covariates were investigated: body size measures (body weight, body surface area, or body mass index), age, sex, race, creatinine clearance at baseline, and population (healthy subjects, treatment-naïve, treatment-experienced) (Table 2, Table 3).

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Table 1. Studies included in the TAF and TFV popPK analysis.

Study	Phase	Population	Intensive sampling	Sparse sampling
GS-US-292-0108	1	Healthy Japanese and Caucasians	All subjects	No
GS-US-292-0103	1	Healthy volunteers		
GS-US-292-0110	1	Healthy volunteers		
GS-US-292-0102	2	TN adults	Substudy	All subjects
GS-US-292-0106	3	HIV-infected adolescents		
GS-US-292-0112	3	HIV-infected adults with mild to moderate renal impairment		
GS-US-292-0104	3	TN adults		
GS-US-292-0111	3	TN adults		
GS-US-292-0109	3	Virologically-Suppressed, HIV-1 Positive Subjects	No	

Table prepared by reviewer.

Table 2. Summary of continuous covariates.

Covariate	Study									
	102	103	104	106	108	109	110	111	112	Total
N	111	17	426	23	20	327	42	415	241	1622
Age (years)	33 [18-71]	36 [18-44]	33 [18-74]	14 [12-17]	40.5 [23-51]	41 [22-71]	34 [21-45]	33 [18-66]	58 [24-82]	38 [12-82]
Weight (kg)	78 [56-133]	77 [58.9-92]	74.4 [43-141]	47.9 [35-80.3]	70.2 [48.1-106]	79.8 [45.5-219]	78.7 [57.7-99.3]	75.5 [40.5-176]	69.2 [37.8-118]	75.2 [35-219]
BMI (kg/m²)	25.6 [17.8-46]	25.6 [20.8-30.3]	24.4 [17-50.2]	19.2 [16.2-27.2]	23.5 [19.2-30.5]	25.9 [13.4-65.4]	25.5 [19.4-29.9]	24.4 [16.6-71]	24 [15.7-39.8]	24.7 [13.4-71]
BSA (m²)	1.95 [1.61-2.51]	1.93 [1.65-2.16]	1.9 [1.32-2.72]	1.5 [1.11-1.98]	1.84 [1.45-2.35]	1.97 [1.41-3.33]	1.93 [1.65-2.27]	1.92 [1.31-2.77]	1.81 [1.24-2.38]	1.91 [1.11-3.33]
CrCL (mL/min)	115 [72.6-239]	128 [95.8-209]	119 [63-287]	168 [111-234]	111 [79.3-217]	104 [53.1-344]	113 [80.6-167]	116 [33.7-286]	55.6 [26.2-89.7]	108 [26.2-344]

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Table 3. Summary of categorical covariates.

Covariate (Notation)	Level	Total	Study								
			102	103	104	106	108	109	110	111	112
Study ^a (STUD)		1622	111 (6.8%)	17 (1%)	426 (26.3%)	23 (1.4%)	20 (1.2%)	327 (20.2%)	42 (2.6%)	415 (25.6%)	241 (14.9%)
Sex (SEXF)	males	1357 (83.7%)	107 (96.4%)	12 (70.6%)	355 (83.3%)	12 (52.2%)	11 (55%)	284 (86.9%)	30 (71.4%)	355 (85.5%)	191 (79.3%)
	females	265 (16.3%)	4 (3.6%)	5 (29.4%)	71 (16.7%)	11 (47.8%)	9 (45%)	43 (13.1%)	12 (28.6%)	60 (14.5%)	50 (20.7%)
Race (RACE)	White	960 (59.2%)	73 (65.8%)	11 (64.7%)	246 (57.7%)	-	10 (50%)	221 (67.6%)	22 (52.4%)	226 (54.5%)	151 (62.7%)
	Black	400 (24.7%)	35 (31.5%)	6 (35.3%)	91 (21.4%)	19 (82.6%)	-	63 (19.3%)	18 (42.9%)	125 (30.1%)	43 (17.8%)
	Other	262 (16.2%)	3 (2.7%)	-	89 (20.9%)	4 (17.4%)	10 (50%)	43 (13.1%)	2 (4.8%)	64 (15.4%)	47 (19.5%)
Population (PAT)	Healthy	79 (4.9%)	-	17 (100%)	-	-	20 (100%)	-	42 (100%)	-	-
	Treatment Naive	975 (60.1%)	111 (100%)	-	426 (100%)	23 (100%)	-	-	-	415 (100%)	-
	Treatment experienced	568 (35%)	-	-	-	-	-	327 (100%)	-	-	241 (100%)
Sampling type (INTENS)	Sparse Sampling	1436 (88.5%)	92 (82.9%)	-	411 (96.5%)	-	-	327 (100%)	-	394 (94.9%)	212 (88%)
	Intensive sampling	186 (11.5%)	19 (17.1%)	17 (100%)	15 (3.5%)	23 (100%)	20 (100%)	-	42 (100%)	21 (5.1%)	29 (12%)

a. The number shows number of subjects in each study, and percent shows contribution of this study (number of subjects) to the whole analysis dataset.

5 STUDY RESULTS

5.1 Subjects and samples

1622 subjects contributed plasma PK samples. 111/3966 (2.8%) of TAF samples and 79/10187 (0.8%) of TFV samples were excluded because the dosing history was inconsistent with the PK profile (Table 4). Subjects from specific populations with regard to age, race, BMI, and renal impairment were included in the study population (Table 5).

Table 4. Summary of the number of PK samples included in the analysis.

Study	Number of subjects			Number of samples		Number of excluded samples	
	Total	With TAF	With TFV	TAF	TFV	TAF	TFV
102	111	65	111	269 ^a	1126	23 ^a	2
103	17	17	17	225	373	0	0
104	426	298	426	447	1646	19	1
106	23	23	23	133	383	0	0
108	20	20	20	318	688	0	0
109	327	272	262	431	981	8	2
110	42	42	42	976	1657	0	52
111	415	243 ^b	415	422 ^b	1469	21 ^b	0
112	241	213	241	745 ^c	1864 ^d	40 ^c	22 ^d
Total	1622	1193	1557	3966	10187	111	79

a. One additional TAF sample excluded from the covariate analysis and the final and joint models;

b. Three additional TAF samples excluded from the covariate analysis and the final and joint models, resulting in 419 TAF samples from 241 subjects in the analysis;

c. Two additional TAF samples excluded from the covariate analysis and the final and joint models;

d. One additional TFV sample excluded from the covariate analysis and the final and joint models.

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Table 5. Demographic and clinical characteristics.

Characteristic	N (% of total)
Age (years)	
<12	0 (0)
12 - <18	23 (1.4)
18 - <65	1522 (94)
≥65	71 (4.4)
Male	1357 (84)
Female	265 (16)
Race	
White	960 (59)
Black	400 (25)
Other	262 (16)
BMI (kg/m ²)	
<18.5 (underweight)	43 (3)
≥18.5-<25 (normal weight)	803 (50)
≥25.0-<30 (overweight)	547 (34)
≥30.0 (obese)	229 (14)
Population	
Healthy	79 (4.9)
Treatment naïve	975 (60)
Treatment experienced	568 (35)
Renal impairment based on baseline CrCL (mL/min)	
>90 (normal)	1169 (72)
60-89.9 (mild)	287 (18)
30-59.9 (moderate)	155 (9.6)
15-29.9 mL/min (severe)	6 (0.4)

Table prepared by reviewer.

5.2 TAF model

The base TAF model was a 2-compartment model with absorption lag time and sequential zero- and first-order absorption. PK parameter estimates had acceptable precision (Table 6). Four of nine interindividual variability parameters had shrinkage values >30% (calculated using the standard deviation-based equation in NONMEM 7.3). Minimum objection function value and PK parameters were nearly identical when the sponsor's model (without modifications) was run at FDA (Table 7). Goodness-of-fit and VPC plots reveal underprediction at high concentrations (Figure 1, Figure 2). Underprediction of TAF concentrations at 6-8 hours post-dose (Figure 2) is not a concern as few samples were above the limit of quantitation at the 6 and 8 hour timepoints (Figure 1, see CWRES versus time after dose plot). Bootstrap parameter estimates were in close agreement with final model parameter estimates (Table 8). No significant covariates for TAF were identified and thus the TAF base model was the same as the TAF final model.

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Table 6. Parameter estimates for the TAF final model (Model 412).

Parameter		Estimate	%RSE	95% CI	Variability	Shrinkage
CL (L/hr)	θ_1	56.3	3.31	52.7 - 60		
V _c (L)	θ_2	10.3	7.68	8.73 - 11.8		
Q (L/hr)	θ_3	7.44	5.09	6.69 - 8.18		
V _p (L)	θ_4	447	26	219 - 675		
k _a (1/hr)	θ_5	1.83	2.33	1.75 - 1.91		
DR (mg/hr)	θ_6	41.7	8.21	35 - 48.4		
ALAG1 (hr)	θ_7	0.134	4.3	0.122 - 0.145		
ω^2_{CL}	$\Omega(1,1)$	0.624	6.06	0.55 - 0.698	CV=70.0%	31.5%
ω^2_{VC}	$\Omega(2,2)$	1.74	13.6	1.27 - 2.2	CV=131.8%	52.6%
ω^2_{ALAG1}	$\Omega(3,3)$	0.155	18	0.1 - 0.209	CV=39.3%	62.5%
ω^2_{kaIOV}	$\Omega(4,4)$	0.0857	13.3	0.0634 - 0.108	CV=29.3%	62.6%
	$\Omega(5,5)$					28.0%
	$\Omega(6,6)$					12.7%
$\omega^2_{DR_IOV}$	$\Omega(7,7)$	2.75	10.5	2.19 - 3.31	CV=165.8%	45.9%
	$\Omega(8,8)$					14.0%
	$\Omega(9,9)$					10.6%
σ^2_{prop}	$\Sigma(1,1)$	0.286	2.84	0.27 - 0.302	CV=53.5%	15.4%
σ^2_{add} (ng/mL) ²	$\Sigma(2,2)$	1.39	7.13	1.2 - 1.59	SD=1.18	15.3%

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100•SE/PE.

95% CI: 95% confidence interval, 95% CI=PE +/- 1.96•SE.

SD: Standard Deviation; CV: coefficient of variation, CV = 100•SD %.

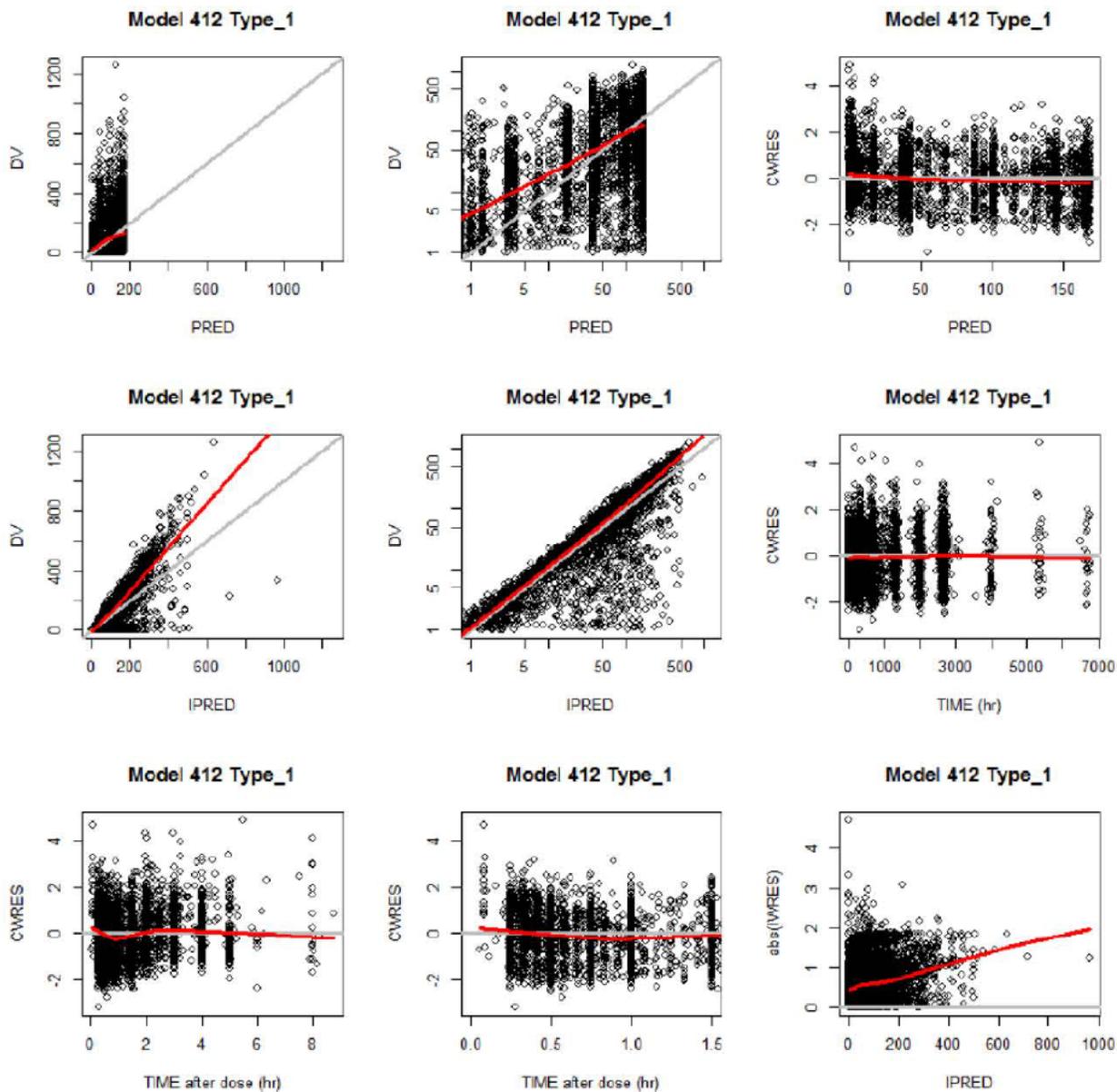
Table 7. Comparison of TAF fixed effect parameters between sponsor's model run and FDA model run.

Parameter	Sponsor value	FDA value
OFV	34867	34868
CL (L/h)	56.3	56.3
V _c (L)	10.3	10.3
Q (L/h)	7.44	7.42
V _p (L)	447	447
K _a (1/h)	1.83	1.83
DR (mg/h)	41.7	41.7
ALAG1 (h)	0.134	0.134

Table prepared by reviewer.

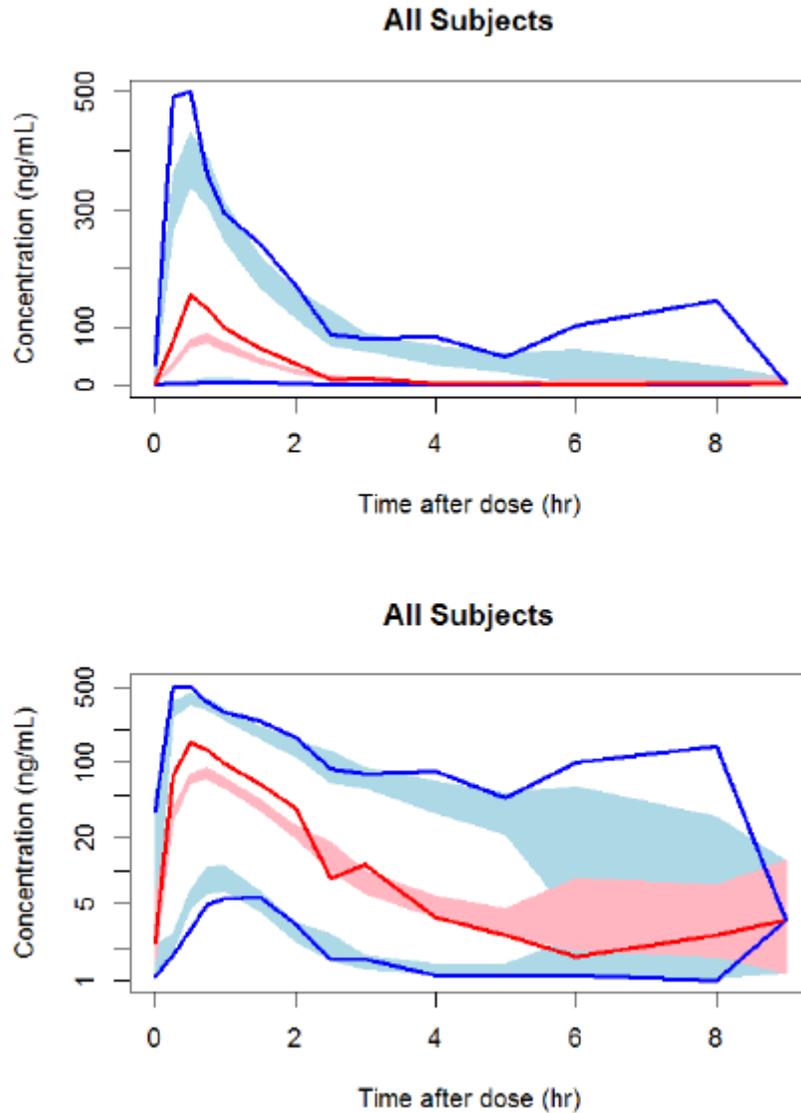
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Figure 1. Goodness-of-fit plots for the TAF final model (Model 412).



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Figure 2. TAF VPC (Model 412).



The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations. The shaded regions show the 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 100 simulations with dosing, sampling, and the covariate values of the analysis dataset.

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Table 8. Bootstrap parameter estimates for the TAF final model 412.

Parameter	Original Estimate	Bootstrap Median	Bootstrap 95% CI
CL (L/hr)	56.3	56.3	51.2 - 60.1
V _C (L)	10.3	10.3	9.22 - 12.2
Q (L/hr)	7.44	7.36	4.86 - 7.75
V _P (L)	447	447	162 - 505
k _a (1/hr)	1.83	1.83	1.73 - 1.99
DR (mg/hr)	41.7	41.7	39.3 - 57.4
ALAG1 (hr)	0.134	0.134	0.128 - 0.178
ω^2_{CL}	0.624	0.604	0.397 - 0.643
ω^2_{VC}	1.74	1.72	1.07 - 1.81
ω^2_{ALAG1}	0.155	0.154	0.0848 - 0.224
ω^2_{kaIOV}	0.0857	0.0856	0.0611 - 0.102
$\omega^2_{DR_{IOV}}$	2.75	2.75	2.48 - 3.61
σ^2_{prop}	0.286	0.286	0.259 - 0.316
$\sigma^2_{add} (\text{ng/mL})^2$	1.39	1.39	0.812 - 1.76
100* ω_{CL} (%)	79	77.7	63 - 80.2
100* ω_{VC} (%)	132	131	103 - 135
100* ω_{ALAG1} (%)	39.4	39.2	29.1 - 47.3
100* ω_{ka} (%)	29.3	29.3	24.7 - 31.9
100* ω_{Rate} (%)	166	166	157 - 190
100* σ_{prop} (%)	53.5	53.5	50.9 - 56.2
$\sigma_{add} (\text{ng/mL})$	1.18	1.18	0.901 - 1.33

5.3 TFV model

The final TFV model was a 2-compartment model with sequential zero- and first-order absorption. Based on statistical criteria, significant covariates were CrCL, HIV status (infected versus healthy), sex, and black race. Parameters were estimated with acceptable precision (Table 9). Four of nine interindividual variability parameters had shrinkage values >30%. Minimum objection function value and PK parameters were nearly identical when the sponsor's model (without modifications) was run at FDA (Table 10). Goodness-of-fit and VPC plots indicated good agreement between observed and predicted concentrations, and residual plots were without bias (Figure 3, Figure 4). Bootstrap parameter estimates were in close agreement with final model parameter estimates (Table 11).

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Table 9. Parameter estimates for the TFV final model (Model 540).

Parameter		Estimate	%RSE	95% CI	Variability	Shrinkage	
CL _M /F (L/hr)	θ ₁	30.2	0.789	29.7 - 30.7			
V _{CM} /F (L)	θ ₂	1600	3.97	1470 - 1720			
k _{aM} (1/hr)	θ ₃	2.33	10.4	1.85 - 2.8			
DR _M (mg/hr)	θ ₄	14.4	5.9	12.7 - 16			
Q _M /F (L/hr)	θ ₅	307	2.6	291 - 322			
V _{PM} /F (L)	θ ₆	1670	6.9	1440 - 1890			
CL _{M CRCL}	θ ₇	0.833	1.93	0.802 - 0.865			
V _{CM CRCL}	θ ₈	0.836	9.51	0.68 - 0.992			
V _{P CRCL}	θ ₉	1.52	7.95	1.28 - 1.76			
CL _{M female}	θ ₁₀	0.885	1.63	0.857 - 0.913			
CL _{M black}	θ ₁₁	1.12	1.43	1.09 - 1.15			
V _{CM healthy}	θ ₁₂	0.326	9.8	0.263 - 0.389			
V _{PM healthy}	θ ₁₃	0.639	8.23	0.536 - 0.742			
ω ² _{CLM}	Ω(1,1)	0.0473	2.72	0.0447 - 0.0498	CV=21.7%	9.20%	
R ω _{CLM} ω _{VCM}	Ω(2,1)	0.0433	15	0.0306 - 0.056	R=0.365		
ω ² _{VCM}	Ω(2,2)	0.297	8.87	0.245 - 0.349	CV=54.5%	41.60%	
R ω _{CL} ω _{VP}	Ω(3,1)	0.0459	15.1	0.0323 - 0.0596	R=0.659		
R ω _{VCM} ω _{VPM}	Ω(3,2)	0.092	22.2	0.0519 - 0.132	R=0.527		
ω ² _{VPM}	Ω(3,3)	0.103	22.6	0.0572 - 0.148	CV=32.1%	36.10%	
ω ² _{kaM}	Ω(4,4)	0.975	18.3	0.624 - 1.33	CV=98.7%	51.20%	
R ω _{kaM} ω _{DRM}	Ω(5,4)	0.501	14.7	0.357 - 0.646	R=0.612		
ω ² _{DRM}	Ω(5,5)	0.689	13.8	0.503 - 0.875	CV=83%	50.20%	
ω ² _{kaM}	Ω(6,6)	SAME					23.50%
R ω _{kaM} ω _{Rate}	Ω(7,6)						
ω ² _{DRM}	Ω(7,7)						18.40%
ω ² _{kaM}	Ω(8,8)	SAME					21.40%
R ω _{kaM} ω _{DRM}	Ω(9,8)						
ω ² _{DRM}	Ω(9,9)						17.70%
σ ² _{prop}	Σ(1,1)	0.0321	1.29	0.0313 - 0.0329	CV=17.9%	11.8%	
σ ² _{add (ng/mL)²}	Σ(2,2)	0.232	7.58	0.197 - 0.266	SD=0.481	11.8%	

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100•SE/PE.

95% CI: 95% confidence interval, 95% CI=PE +/- 1.96*SE.

SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

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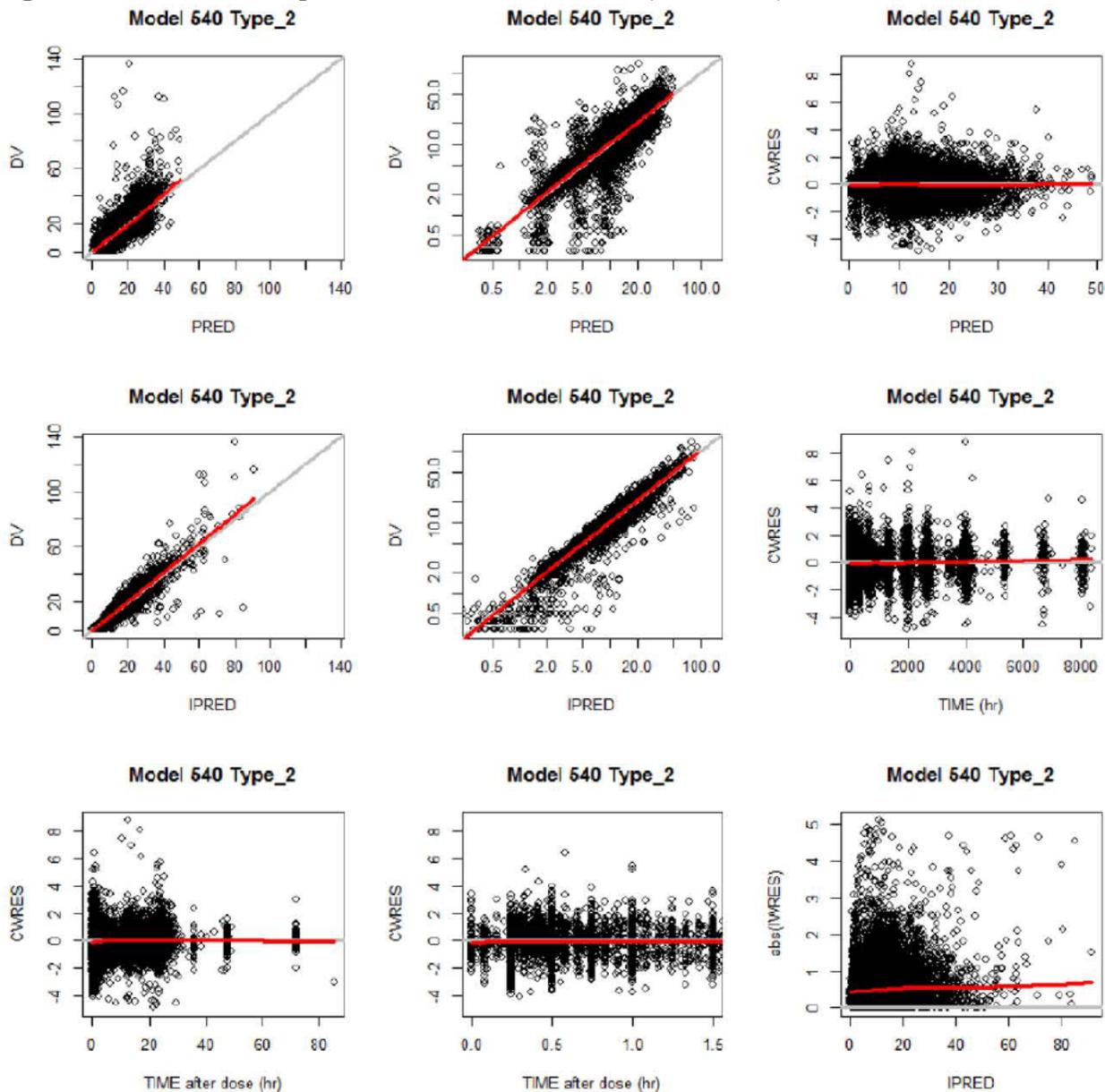
Table 10. Comparison of TFV fixed effect parameters between sponsor's model run and FDA model run.

Parameter	Sponsor's run	FDA run
CLM (L/h)	30.2	30.2
Vcm (L)	1600	1595
kaM (1/h)	2.33	2.33
DRm (mg/h)	14.4	14.3
Qm (L/h)	307	306
Vpm (L)	1670	1669
CLm CRCL	0.833	0.833
Vcm CRCL	0.836	0.832
Vp CRCL	1.52	1.52
CLm female	0.885	0.885
CLm black	1.12	1.12
Vcm healthy	0.326	0.327
Vpm healthy	0.639	0.638

Table prepared by reviewer.

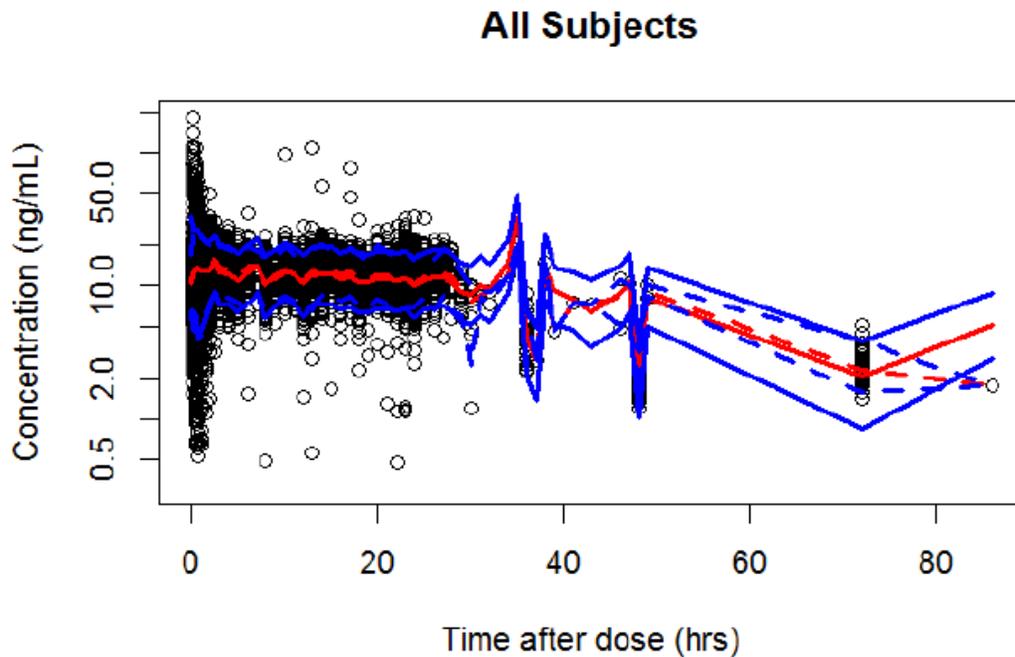
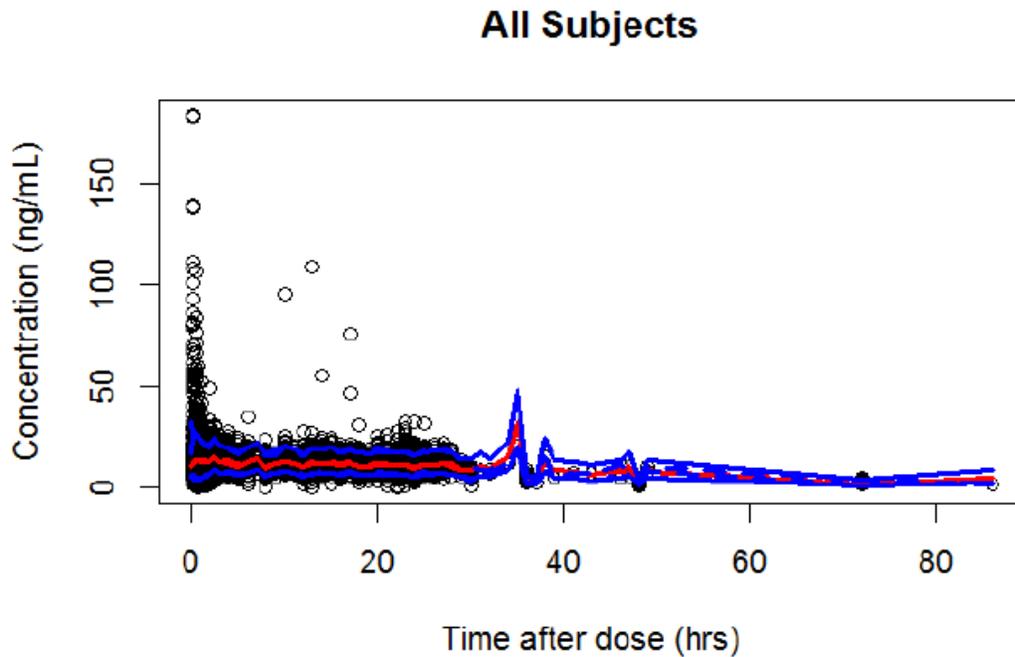
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Figure 3. Goodness-of-fit plots for the TFV final model (Model 540).



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Figure 4. TFV prediction-corrected VPC (Model 540).



The dashed lines show median (red), and the 5th and 95th percentiles (blue) of the observed prediction-corrected concentrations. The solid lines show the 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 100 simulations with dosing, sampling, and the covariate values of HIV patients in the analysis dataset.

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Table 11. Bootstrap parameter estimates for the TFV final model 540.

Parameter	Original Estimate	Bootstrap Median	Bootstrap 95% CI
CL _M /F (L/hr)	30.2	30.2	29.8 - 30.6
V _{CM} /F (L)	1620	1620	1460 - 1790
k _{aM} (1/hr)	2.34	2.37	2.1 - 2.67
DR _M (mg/hr)	14.7	14.3	12.8 - 15.9
Q _M /F (L/hr)	307	306	283 - 331
V _{PM} /F (L)	1670	1680	1370 - 2000
CL _{M CRCL}	0.832	0.834	0.795 - 0.87
V _{CM CRCL}	0.834	0.862	0.662 - 1.07
V _{P CRCL}	1.55	1.53	1.24 - 1.85
CL _{M female}	0.885	0.885	0.853 - 0.914
CL _{M black}	1.12	1.12	1.09 - 1.15
V _{CM healthy}	0.322	0.322	0.278 - 0.373
V _{PM healthy}	0.636	0.632	0.511 - 0.8
ω ² _{CLM}	0.0458	0.0467	0.0391 - 0.0554
R ω _{CLM} ω _{VCM}	0.0443	0.0421	0.0169 - 0.0609
ω ² _{VCM}	0.304	0.320	0.203 - 0.437
R ω _{CLM} ω _{VPM}	0.046	0.046	0.0261 - 0.0691
R ω _{VCM} ω _{VPM}	0.0972	0.0941	0.0357 - 0.154
ω ² _{VPM}	0.106	0.104	0.0595 - 0.179
ω ² _{kaM}	0.966	0.958	0.762 - 1.18
R ω _{kaM} ω _{DRM}	0.5	0.49	0.354 - 0.651
ω ² _{DRM}	0.698	0.678	0.543 - 0.872
σ ² _{prop}	0.0323	0.0318	0.029 - 0.0347
σ ² _{add} (ng/mL) ²	0.229	0.232	0.173 - 0.304
100*ω _{CLM} (%)	21.4	21.6	19.8 - 23.5
100*ω _{VCM} (%)	55.2	56.6	45.1 - 66.1
100*ω _{VPM} (%)	32.6	32.3	24.4 - 42.3
100*ω _{kaM} (%)	98.3	97.9	87.3 - 108
100*ω _{DRM} (%)	83.5	82.4	73.7 - 93.4
100*σ _{prop} (%)	18	17.8	17 - 18.6
σ _{add} (ng/mL)	0.479	0.482	0.417 - 0.552

Exposures for the typical subject and subjects enrolled in the pivotal studies were similar (Table 12, Table 13).

Table 12. Model-estimated steady-state TAF and TFV exposures for a typical subject.*

Parameter	TAF	TFV
AUC (ng*h/mL)	188.1	331.2
C _{max} (ng/mL)	165.6	16.9
C _{min} (ng/mL)	NA	12.1

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Table prepared by reviewer. *The typical subject is a non-black, HIV-infected male with CrCL of 100 mL/min.

Table 13. Model-estimated steady-state TAF and TFV exposures in the pivotal studies GS-US-292-0104 and GS-US-292-0111.

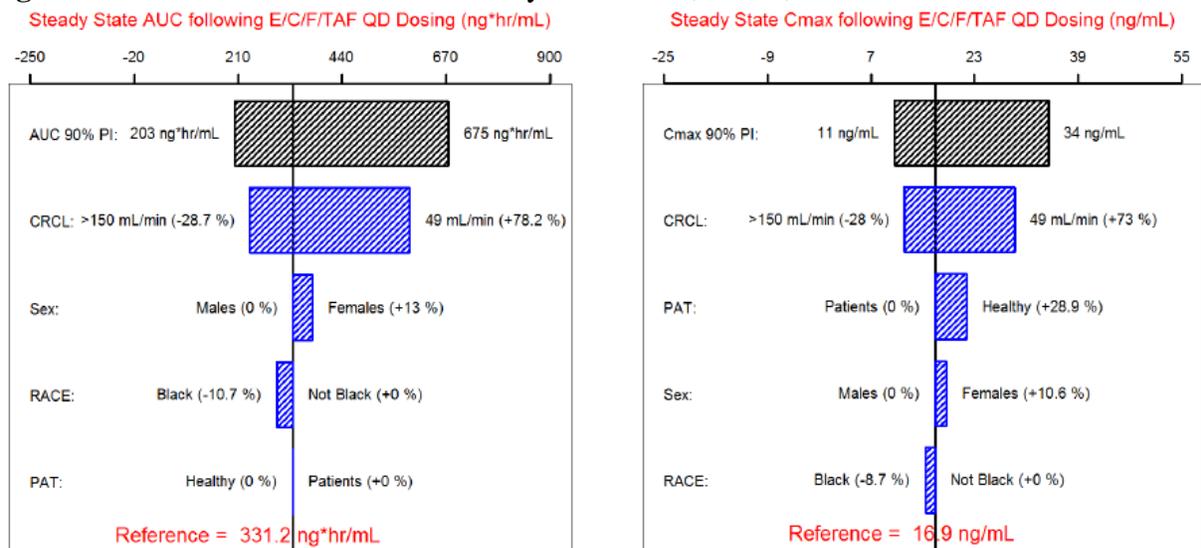
Parameter	TAF			TFV		
	Mean	95% CI	CV%	Mean	95% CI	CV%
AUC (ng*h/mL)	206.4	55.6-526.1	71.8	292.6	179.8-445.7	27.4
Cmax (ng/mL)	162.2	46.5-340	51.1	15.2	9.3-23.1	26.1
Cmin (ng/mL)	NA			10.6	6.4-16.6	28.5

Table prepared by reviewer.

As TFV exposure from E/C/F/TAF is 90% lower compared to E/C/F/TDF, the <2-fold differences in TFV exposure due to covariate effects are not clinically significant (Figure 5). Thus no dose adjustment is recommended for intrinsic factors, consistent with proposed E/C/F/TAF labeling.

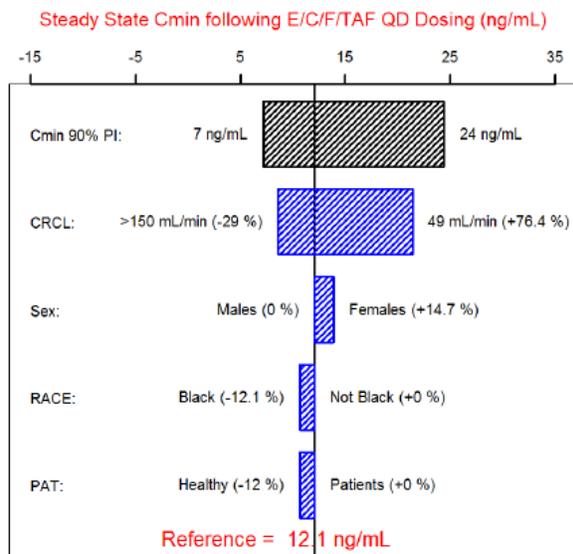
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Figure 5. Covariate Effects on TFV Steady-State AUC, Cmax, and Cmin.



Typical reference subject: not Black, male, patient, CRCL = 100 mL/min

Typical reference subject: not Black, male, patient, CRCL = 100 mL/min



Typical reference subject: not Black, male, patient, CRCL = 100 mL/min

5.4 Joint model

The joint model results from combination of the TAF and TFV models. The joint model assumes 100% of TAF is eliminated by conversion to TFV, which is supported by the tentative TAF metabolic scheme and the finding that <1.4% of the TAF dose is excreted unchanged. Parameter estimates for the joint TAF and TFV model were provided (Table 14); this model could not be run in a reasonable amount of time at FDA. In comparison to the separate TAF and TFV models, goodness-of-fit plots for the joint model were similar (Figure 1, Figure 3, Figure 6, Figure 7, Figure 8, Figure 9). Eight of twelve interindividual variability parameters had shrinkage values >30%.

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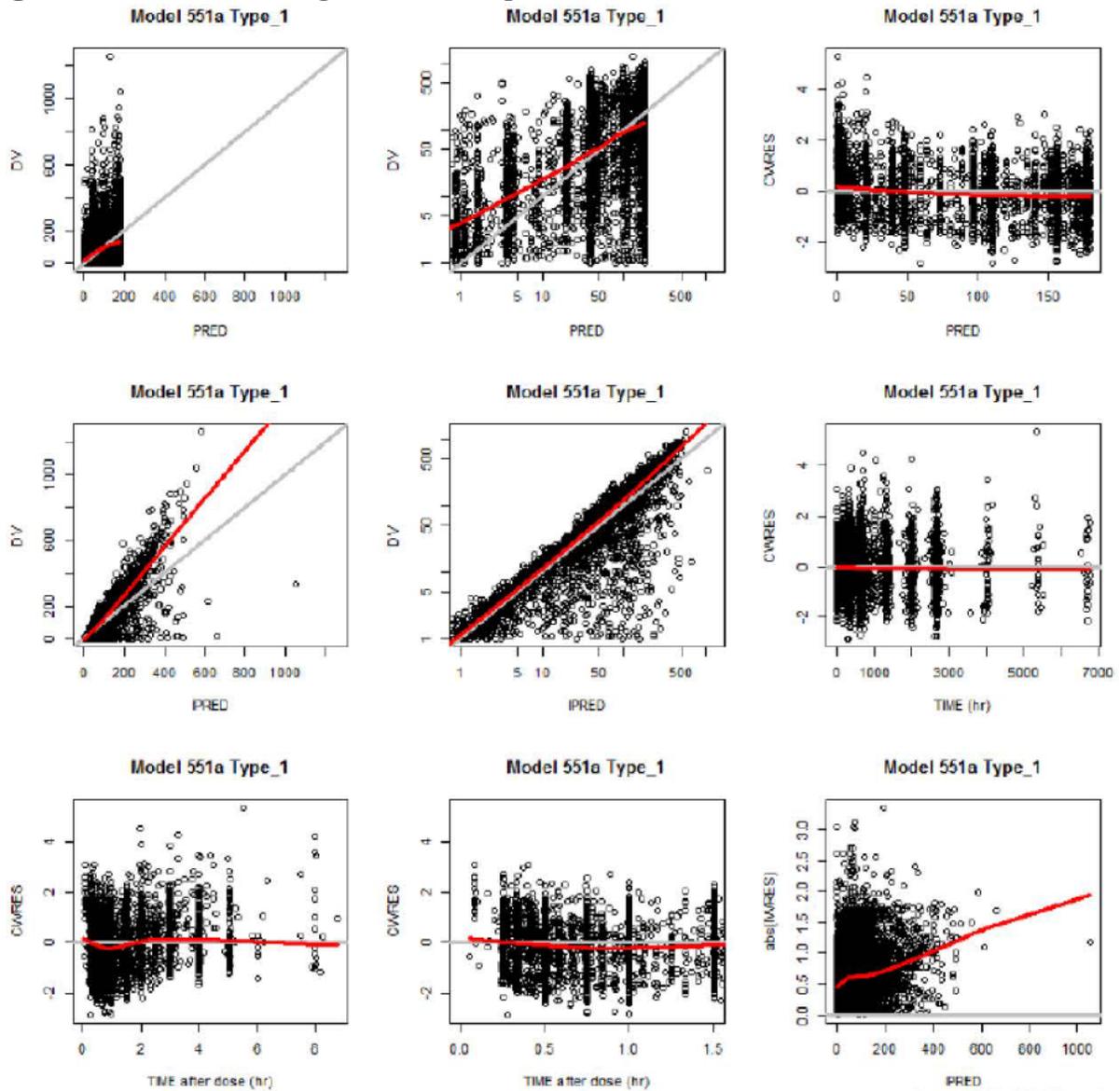
Due to the inability of NONMEM to calculate standard errors of the model parameters, the joint model was considered unstable. Comparing the separate and joint models, fixed effect parameters were similar with the exception of TFV central volume and intercompartmental clearance (Table 15, Table 16). Possible reasons for the inability to calculate standard errors in addition to a difference in TFV central volume and intercompartmental clearance are that fewer subjects were included in the joint model (only those with both TAF and TFV concentrations measured) and the assumption of complete conversion of TAF to TFV. Due to the PK parameters being similar between the separate and joint model, and instability of the final model, the separate models were considered to be the final model.

Table 14. Parameter estimates for joint TAF and TFV model (Model 551).

TAF Parameters					TFV Parameter				
Parameter		Estimate	Variability CV%	Shrinkage %	Parameter		Estimate	Variability CV%	Shrinkage %
CL (L/hr)	θ_1	51.8			CL _M /F (L/hr)	θ_{17}	30.0		
V _c (L)	θ_2	9.45			V _{CM} /F (L)	θ_{18}	892		
Q (L/hr)	θ_3	6.72			Q _M /F (L/hr)	θ_{19}	468		
V _p (L)	θ_4	459			V _{PM} /F (L)	θ_{20}	1740		
k _a (1/hr)	θ_5	1.76			CL _M CRCL	θ_{10}	0.859		
DR (mg/hr)	θ_6	45.8			V _{CM} CRCL	θ_{11}	0.815		
ALAG1 (hr)	θ_7	0.141			V _P CRCL	θ_{12}	1.43		
					CL _M female	θ_{13}	0.892		
			CL _M black	θ_{14}	1.12				
			V _{CM} healthy	θ_{15}	0.271				
			V _{PM} healthy	θ_{16}	0.627				
ω^2_{CL}	$\Omega(1,1)$	0.468	68.4	41.9	ω^2_{CLM}	$\Omega(10,10)$	0.0474	21.8	9.2
ω^2_{VC}	$\Omega(2,2)$	1.87	136.6	57.9	R ω^2_{CLM} ω^2_{VCM}	$\Omega(11,10)$	0.036	R=0.179	
ω^2_{ALAG1}	$\Omega(3,3)$	0.239	48.9	59.6	ω^2_{VCM}	$\Omega(11,11)$	0.851	92.2	37.8
ω^2_{kalOV}	$\Omega(4,4)$	0.131	36.2	59.2	R ω^2_{CL} ω^2_{VP}	$\Omega(12,10)$	0.0591	R=0.745	
	$\Omega(5,5)$			33.7	R ω^2_{VCM} ω^2_{VPM}	$\Omega(12,11)$	0.115	R=0.343	
	$\Omega(6,6)$			-20.8	ω^2_{VPM}	$\Omega(12,12)$	0.133	36.4	30.8
$\omega^2_{DR_JOV}$	$\Omega(7,7)$	3.42	185	50.5					
	$\Omega(8,8)$			10.6					
	$\Omega(9,9)$			3.7					
σ^2_{prop}	$\Sigma(1,1)$	0.333	57.7	16.3	σ^2_{prop}	$\Sigma(3,3)$	0.0328	18.1	11.5
$\sigma^2_{add} (ng/mL)^2$	$\Sigma(2,2)$	1.03	SD=1.02	16.1	$\sigma^2_{add} (ng/mL)^2$	$\Sigma(4,4)$	0.160	SD=0.40	11.5

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Figure 6. Joint model TAF goodness-of-fit plots.

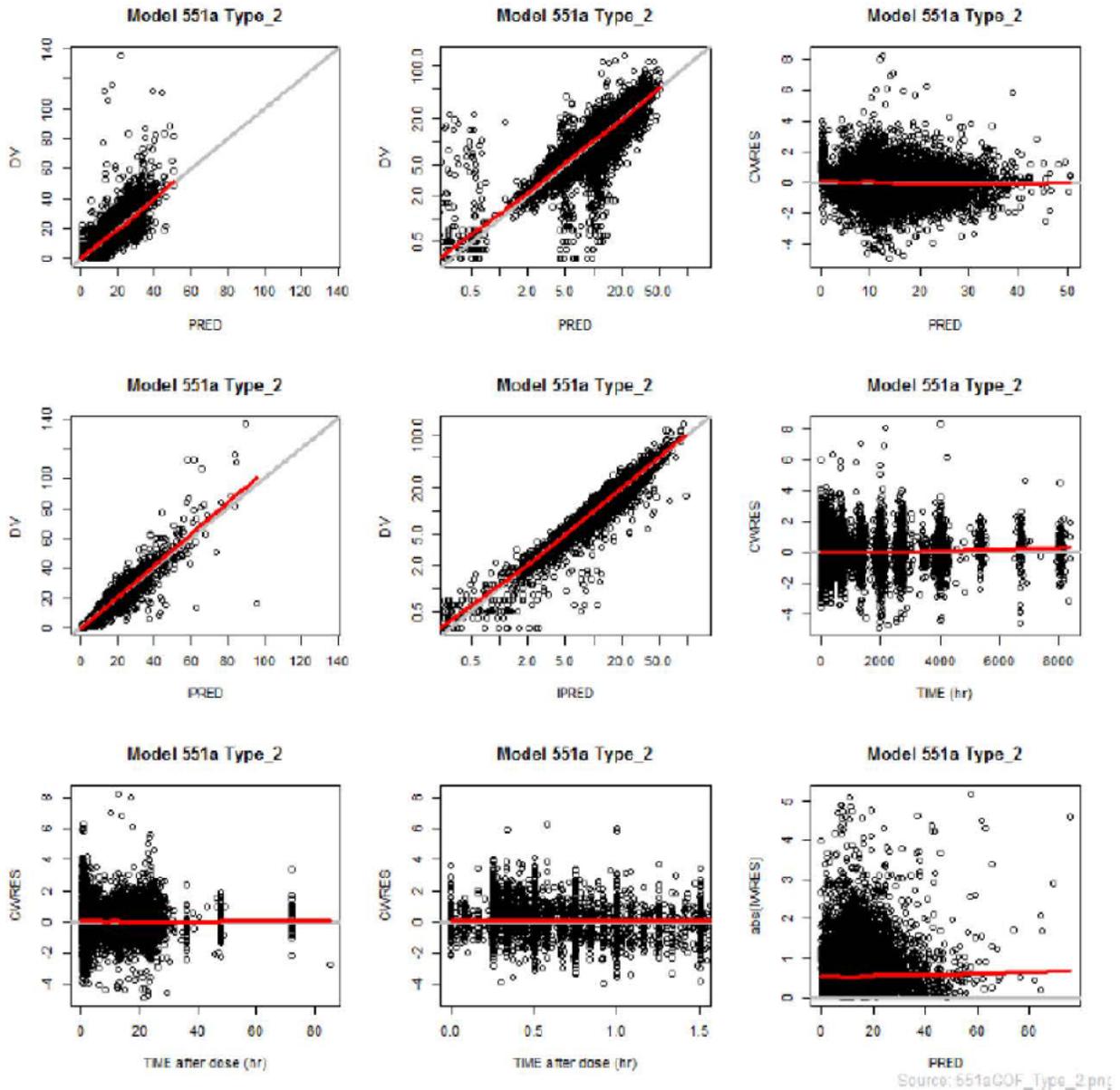


Source: 551aGOF_Type_1.png

DV: Observed TAF (Type 1) or TFV (Type 2) concentrations; **PRED:** population predictions of the model; **IPRED:** individual predictions of the model; **CWRES:** conditional weighted residuals; **IWRES:** individual weighted residuals; **TIME:** time after the first dose. The gray solid $y = x$ or $y = 0$ lines are included for reference. The bold red lines are the lowest (local regression smoother) trend lines.

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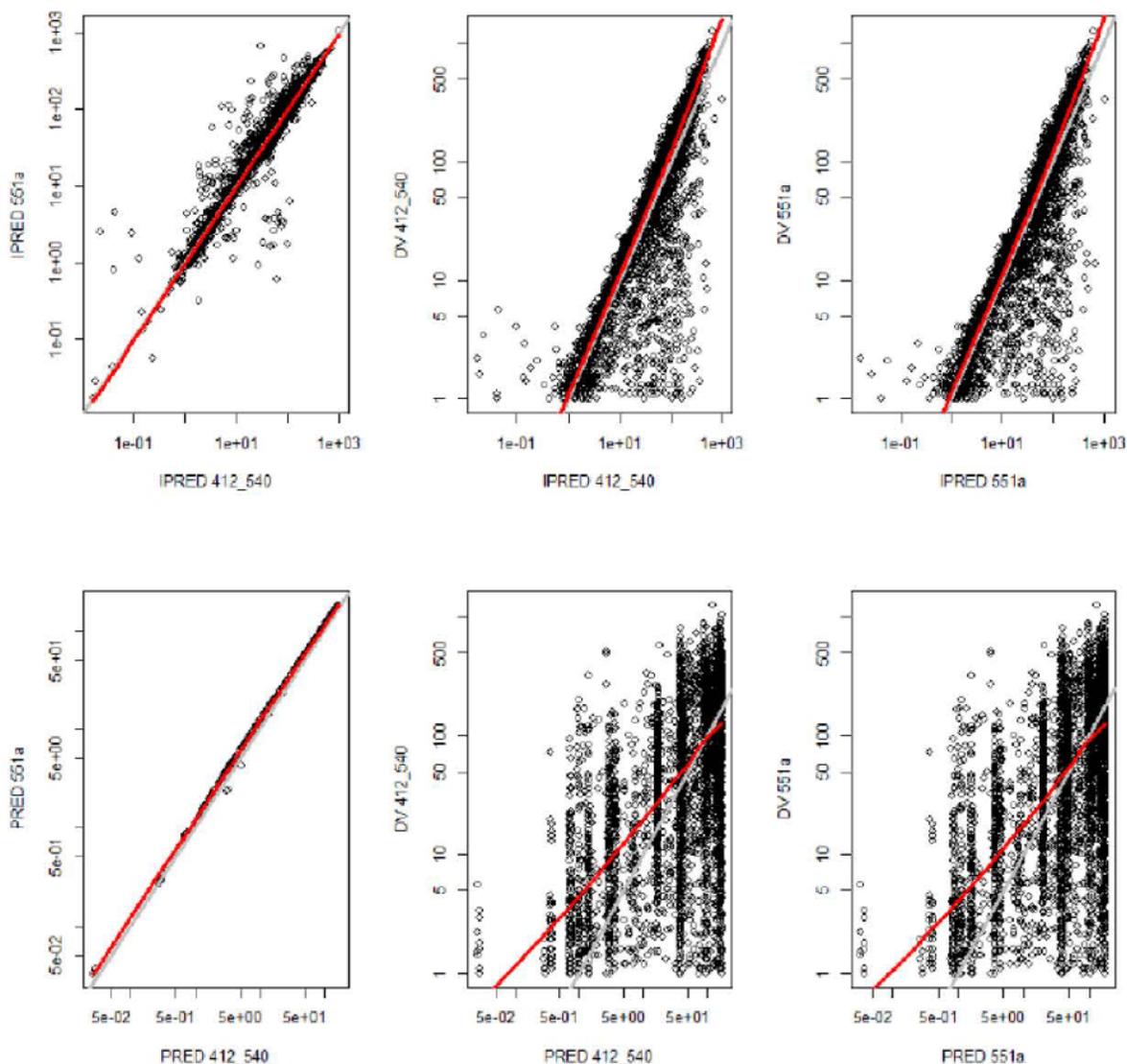
Figure 7. Joint model TFV goodness-of-fit plots.



DV: Observed TAF (Type 1) or TFV (Type 2) concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES: conditional weighted residuals; IWRES: individual weighted residuals; TIME: time after the first dose. The gray solid $y = x$ or $y = 0$ lines are included for reference. The bold red lines are the lowest (local regression smoother) trend lines.

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Figure 8. TAF goodness of fit comparison between individual models (TAF: 412 and TFV: 540) and joint model (551a).

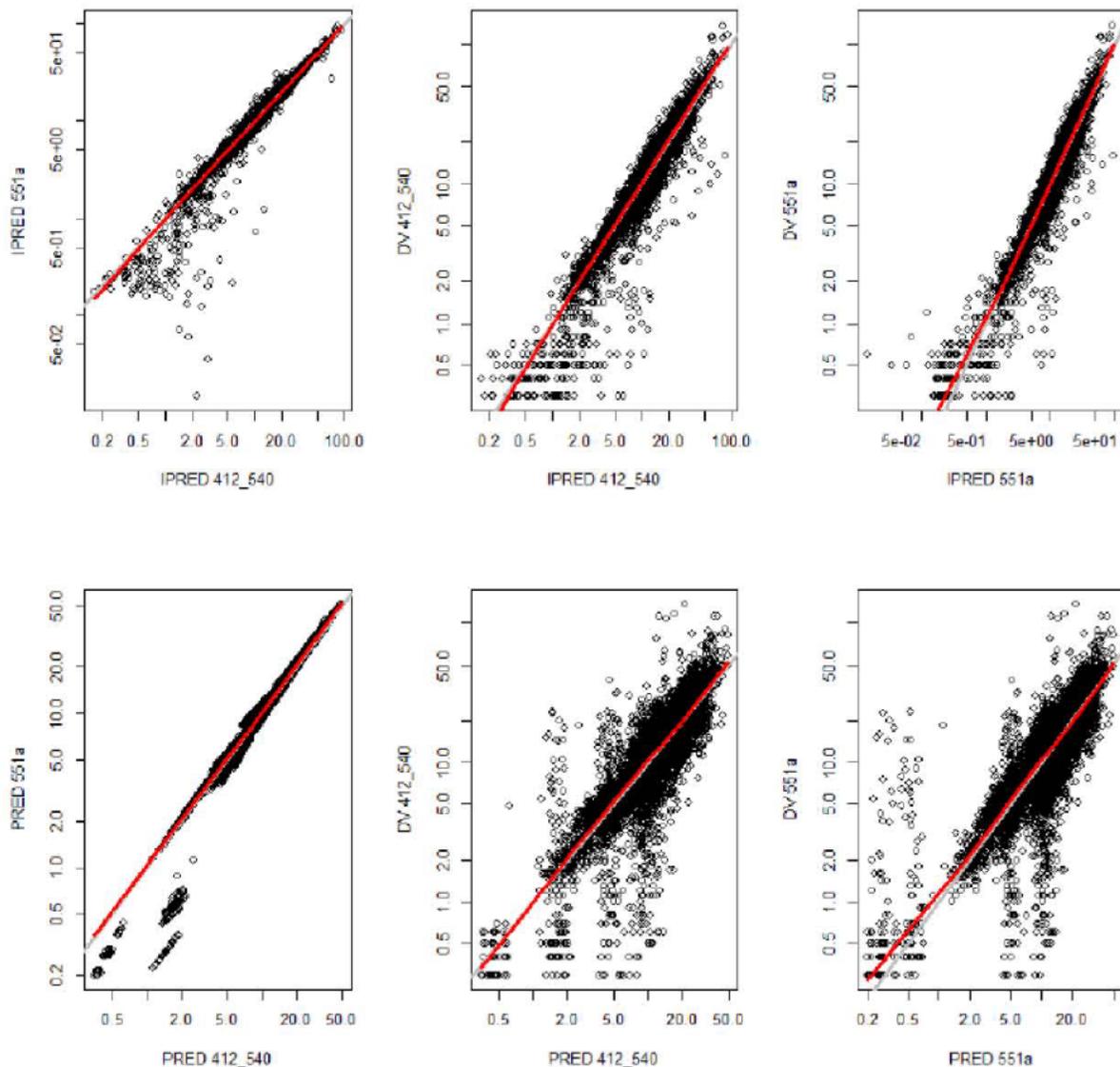


Source: 412_640vs551a.LogType_1.png

DV: Observed TAF (Type 1) or TFV (Type 2) concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES: conditional weighted residuals; IWRES: individual weighted residuals; TIME: time after the first dose. The gray solid $y = x$ or $y = 0$ lines are included for reference. The bold red lines are the lowest (local regression smoother) trend lines.

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Figure 9. TFV goodness of fit comparison between individual models (TAF: 412 and TFV: 540) and joint model (551a).



Source: 412_540vs551aLogType_2.png

DV: Observed TAF (Type 1) or TFV (Type 2) concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES: conditional weighted residuals; IWRES: individual weighted residuals; TIME: time after the first dose. The gray solid $y = x$ or $y = 0$ lines are included for reference. The bold red lines are the lowest (local regression smoother) trend lines.

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Table 15. Comparison of TAF PK parameters from the TAF and joint TAF/TFV models.

Parameter	TAF model (test)	Joint TAF/TFV model (reference)	% Difference
CL (L/h)	56.3	51.8	9%
Vc (L)	10.3	9.45	9%
Q (L/h)	7.44	6.72	11%
Vp (L)	447	459	-3%
Ka (1/h)	1.83	1.76	4%
DR (mg/h)	41.7	45.8	-9%
ALAG1 (h)	0.134	0.141	-5%
IIV CL	0.624	0.468	33%
IIV Vc	1.74	1.87	-7%
IIV ALAG1	0.155	0.239	-35%
IIV kaIOV	0.0857	0.131	-35%
IIV DR IOV	2.75	3.42	-20%
prop	0.286	0.333	-14%
add	1.39	1.03	35%

Table prepared by reviewer.

PHARMACOMETRICS REVIEW

Table 16. Comparison of TFV PK parameters from the TFV and joint TAF/TFV models.

Parameter	TFV model (test)	Joint TAF/TFV model (reference)	% Difference
CLM (L/h)	30.2	30	1%
Vcm (L)	1600	892	79%
kaM (1/h)	2.33	NA	NA
DRm (mg/h)	14.4	NA	NA
Qm (L/h)	307	468	-34%
Vpm (L)	1670	1740	-4%
CLm CRCL	0.833	0.859	-3%
Vcm CRCL	0.836	0.815	3%
Vp CRCL	1.52	1.43	6%
CLm female	0.885	0.892	-1%
CLm black	1.12	1.12	0%
Vcm healthy	0.326	0.271	20%
Vpm healthy	0.639	0.627	2%
IIV CLm	0.0473	0.0474	0%
R CLm Vcm	0.0433	0.036	20%
IIV Vcm	0.297	0.851	-65%
R CL Vp	0.0459	0.0591	-22%
R Vcm Vpm	0.092	0.115	-20%
IIV Vpm	0.103	0.133	-23%
IIV kaM	0.975	NA	NA
R kaM DRm	0.501	NA	NA
IIV DRm	0.689	NA	NA
prop	0.0321	0.0328	-2%
add	0.232	0.16	45%

Table prepared by reviewer.

6 DISCUSSION

Separate TAF and TFV models, as well as a joint TAF/TFV model, were developed with adequate model performance. One limitation was that several parameters in the TAF and TFV model had high shrinkage, resulting in less confidence in individual predicted concentrations and empirical bayes estimates.^{1,2} The separate and joint models were comparable and due to greater stability the separate models were considered the final model. The final separate models were run at FDA and resulted in very similar output; the joint model could not be run at FDA in a reasonable amount of time. Inability to run the joint model has no impact as the separate models are the final models.

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Significant covariates were only identified for TFV. All covariate effects resulted in a <2-fold TFV exposure change. As TFV concentrations resulting from E/C/F/TAF are 90% lower compared to administration of E/C/F/TDF, and flat exposure-response relationships were identified for TFV after administration of E/C/F/TAF, a 2-fold TFV exposure increase is not considered to be clinically relevant. Thus no dose adjustments are required based on the intrinsic factors evaluated in this TAF and TFV population PK analysis.

7 LABEL RECOMMENDATIONS

The following statements in section 12.3 of the label cite or are addressed by the popPK analysis:

- 1) No dosage adjustment is recommended based on race.
- 2) No dose adjustment is recommended based on gender.
- 3) “Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of [TRADENAME] showed that (b) (4) age did not have a clinically relevant effect on exposures of tenofovir alafenamide.”

We propose changing #3 to the following (b) (4)
“Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of [TRADENAME] showed that age did not have a clinically relevant effect on exposures of tenofovir alafenamide up to 75 years of age.”

8 REFERENCES

- 1.Savic,R.M. & Karlsson,M.O. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. *AAPS J* **11**, 558-569 (2009).
- 2.Xu,X.S. *et al.* Shrinkage in nonlinear mixed-effects population models: quantification, influencing factors, and impact. *AAPS J* **14**, 927-936 (2012).

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/s/

MARIO SAMPSON
07/10/2015

JEFFRY FLORIAN
07/10/2015

ISLAM R YOUNIS
07/10/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	207561	SDN	1
Applicant	Gilead	Submission Date	11/5/2014
Generic Name	Elvitegravir (EVG), Cobicistat (COBI), Emtricitabine (FTC), and Tenofovir alafenamide (TAF) fixed dose combination (E/C/F/TAF FDC)	Brand Name	Genvoya (proposed)
Drug Class	Antiretroviral		
Indication	Treatment of HIV-1 in patients ≥ 12 years of age		
Dosage Regimen	150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF		
Dosage Form	Tablet	Route of Administration	Oral
OCP Division	IV	OND Division	DAVP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Mario Sampson, PharmD	Islam Younis, PhD	
Pharmacometrics		Jeffrey Florian, PhD	
Genomics	NA		
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	1/4/2015	74-Day Letter Date	1/18/2015
Review Due Date	7/11/2015	PDUFA Goal Date	11/5/2015
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
<input checked="" type="checkbox"/> Yes			
<input type="checkbox"/> No			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
<input type="checkbox"/> Yes			
<input checked="" type="checkbox"/> No			
Is there a need for OSI inspection?			
<input type="checkbox"/> Yes			
<input checked="" type="checkbox"/> No			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary
Bioanalytical and Analytical Methods		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Labeling
			<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
			<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	
In Vitro Studies			
<input checked="" type="checkbox"/> Metabolism Characterization	7		
<input checked="" type="checkbox"/> Transporter Characterization	7	Will not review two of them.	
<input checked="" type="checkbox"/> Distribution	1		
<input type="checkbox"/> Drug-Drug Interaction			
In Vivo Studies			

Biopharmaceutics					
<input type="checkbox"/> Absolute Bioavailability					
<input checked="" type="checkbox"/> Relative Bioavailability	1	Will not review	(b) (4)		
<input checked="" type="checkbox"/> Bioequivalence	1				
<input checked="" type="checkbox"/> Food Effect	1				
<input type="checkbox"/> Other					
Human Pharmacokinetics					
Healthy Subjects	<input checked="" type="checkbox"/> Single Dose	0	Obtained from BE study		
	<input checked="" type="checkbox"/> Multiple Dose	0	Obtained from BE study		
Patients	<input checked="" type="checkbox"/> Single Dose	1			
	<input checked="" type="checkbox"/> Multiple Dose	1			
<input checked="" type="checkbox"/> Mass Balance Study		1			
<input checked="" type="checkbox"/> Other (e.g. dose proportionality)		1	Dose proportionality from TAF monotherapy study		
Intrinsic Factors					
<input checked="" type="checkbox"/> Race		1	PK study comparing Caucasians and Asians		
<input type="checkbox"/> Sex					
<input type="checkbox"/> Geriatrics					
<input type="checkbox"/> Pediatrics					
<input checked="" type="checkbox"/> Hepatic Impairment		1			
<input checked="" type="checkbox"/> Renal Impairment		1			
<input type="checkbox"/> Genetics					
Extrinsic Factors					
<input checked="" type="checkbox"/> Effects on Primary Drug		0	Will obtain data on effect of COBI on TAF from BE study		
<input checked="" type="checkbox"/> Effects of Primary Drug		3	Will not review studies with RPV and EFV as no additional ARVs can be used with this FDC		
Pharmacodynamics					
<input type="checkbox"/> Healthy Subjects					
<input type="checkbox"/> Patients					
Pharmacokinetics/Pharmacodynamics					
<input type="checkbox"/> Healthy Subjects					
<input type="checkbox"/> Patients					
<input checked="" type="checkbox"/> QT		1	Will not review as was already reviewed by IRT		
Pharmacometrics					
<input checked="" type="checkbox"/> Population Pharmacokinetics		1			
<input checked="" type="checkbox"/> Exposure-Efficacy		1			
<input checked="" type="checkbox"/> Exposure-Safety		1			
Total Number of Studies		In Vitro	15	In Vivo	17
Total Number of Studies to be Reviewed			13		13

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Final formulation selected in Phase 2
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist

Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Modeling of exposure-response data was not conducted. Analyses consisted of plotting exposures by quartile vs the outcomes of interest.
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

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/s/

MARIO SAMPSON
01/20/2015

ISLAM R YOUNIS
01/20/2015