CLINICAL PHARMACOLOGY REVIEW

NDA	208215
Submission Type	505(b)(1) Non-NME NDA
Applicant Name	Gilead
Submission Dates	4/7/2015
Generic Name	Emtricitabine/tenofovir alafenamide (F/TAF or FTC/TAF)
Dosage Form (Strength)	Tablet (b) (4) 200/25 mg)
Indication	Treatment of HIV-1 in patients aged ≥12 years who lack resistance mutations to the components of F/TAF
Review Team	Mario Sampson, PharmD, Islam Younis, PhD

1 Contents

2 Executive summary

Emtricitabine (FTC) is a nucleotide reverse-transcriptase inhibitor that was approved in 2003 for the treatment of HIV. Tenofovir alafenamide (TAF) is a prodrug of the nucleotide reverse-transcriptase inhibitor tenofovir (TFV), and was approved in 2015 as a component of Elvitegravir/Cobicistat/FTC/TAF (E/C/F/TAF), a complete regimen for the treatment of HIV. F/TAF is intended to be combined with other antiretrovirals (ARV) for the treatment of HIV.

Two pivotal relative bioavailability (BA) studies comparing the exposures of FTC and TAF between the fixed dose combination F/TAF and E/C/F/TAF form the basis of F/TAF approval. Both studies were conducted in the fed state. (b) (4) utilized F/TAF 200/25 mg. Similar exposures of FTC and TAF between F/TAF and E/C/F/TAF were demonstrated (NDA 208215 Biopharmaceutics review). The data was accepted without an

on-site inspection (NDA 208215, Office of Study Integrity and Surveillance review dated 6/12/2015).

Unlike E/C/F/TAF, F/TAF is not a complete HIV-1 regimen. To form a complete regimen, F/TAF should be combined with a member of one of the following drug classes: 1) integrase inhibitor; 2) protease inhibitor coadministered + CYP3A inhibitor (RTV or COBI); or 3) non-nucleotide reverse transcriptase inhibitor. Of the above drug classes, there are drug interactions only with protease inhibitors + CYP3A inhibitor

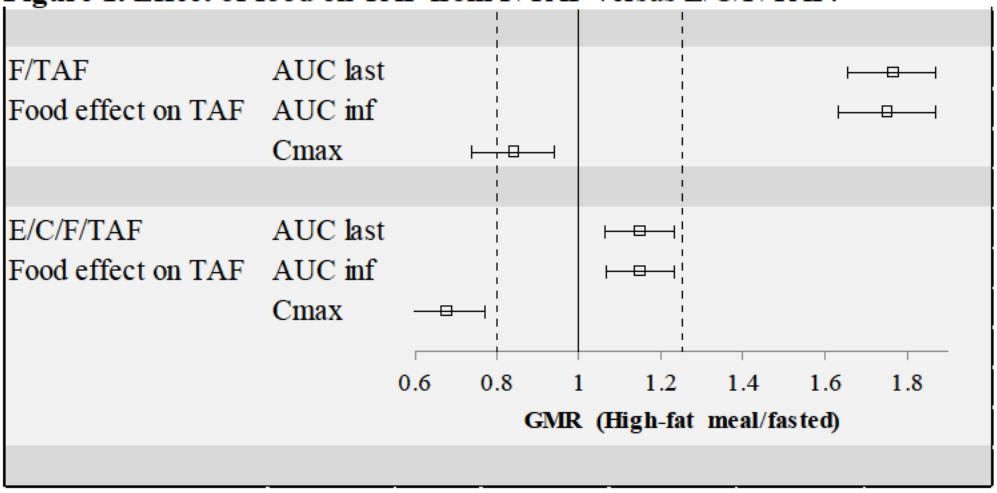
The current application includes one phase 3 switch study, one phase 2 study, one food effect study, and four drug-drug interaction studies. The focus of this review is on labeling recommendations regarding: 1) food effect; and 2) the appropriate dose of TAF when coadministered with protease inhibitors.

2.1 Summary of clinical pharmacology findings

2.1.1 Food effect

The effect of food on TAF exposure is larger for F/TAF (77% ↑ in AUC) versus E/C/F/TAF (17% ↑ in AUC) (Figure 1). This differential food effect on TAF exposure observed between the two formulations is not likely due to formulation because both products are immediate release formulations with rapid dissolution and manufactured using standard excipients. The sponsor hypothesized that this differential food effect can be attributed to the significant increase in TAF bioavailability (estimated to be ~40% in humans) in the presence of a Pgp inhibitor such as COBI in E/C/F/TAF, thus the presence of food does not lead to a further substantial increase in TAF bioavailability (NDA 208215, SN 0012) and the relative changes in TAF exposure is low. On the other hand, in the case of F/TAF alone, where no Pgp inhibitor is present, the coadministration with food leads to a substantial increase in TAF bioavailability. We agree with the sponsor's hypothesis.

Figure 1. Effect of food on TAF from F/TAF versus E/C/F/TAF.



Source: prepared by reviewer. GMR = geometric mean ratio. Bars are 90% CIs. The high-fat meal was an 800 calorie meal containing ~50% fat in both studies. Data comes from F/TAF study 311-1386 (NDA 208215) and E/C/F/TAF study 292-0110 (NDA 207561).

The sponsor's proposed labeling states that F/TAF should be administered with or without food. The initial concern with this proposal was the impact of a 44% reduction in TAF exposure when given under fasted conditions on the efficacy of the various TAF-containing HIV regimens given the unknown TAF exposure-efficacy relationships for these regimens. We concluded based on the totality of evidence that reduced TAF exposures from F/TAF in the fasted state are not expected to have a significant impact on the efficacy of the various TAF-containing HIV regimens based on the following:

1. The reduction in TAF exposure in the fasted state relative to the fed state is expected to be ~15% when F/TAF is combined with a regimen containing a CYP3A4 inhibitor such as ritonavir or cobicistat because of increased bioavailability due to Pgp inhibition.
2. The lower TAF exposures from F/TAF in the fasted state are predicted to maintain antiviral activity based on a TAF monotherapy antiviral activity study (Figure 3). In this study (Study 120-0104, NDA 207561), TAF and TDF were administered under fasted conditions and TAF exposures from F/TAF were associated with maximal antiviral activity (Figure 3).
3. Durability of response is expected to be maintained at lower TAF exposures based on the following observations from study 311-1089:
    a. Week 48 virologic success was 93-97% across TAF AUC quartiles (Table 1). The first quartile exposure range is below the expected exposure of TAF from F/TAF 25 mg under fasted conditions.
    b. Regardless of 3rd agent, TFV-DP concentrations in PBMC (site of action) were higher in the TAF-containing arm relative to the TDF-containing arm (Figure 4).

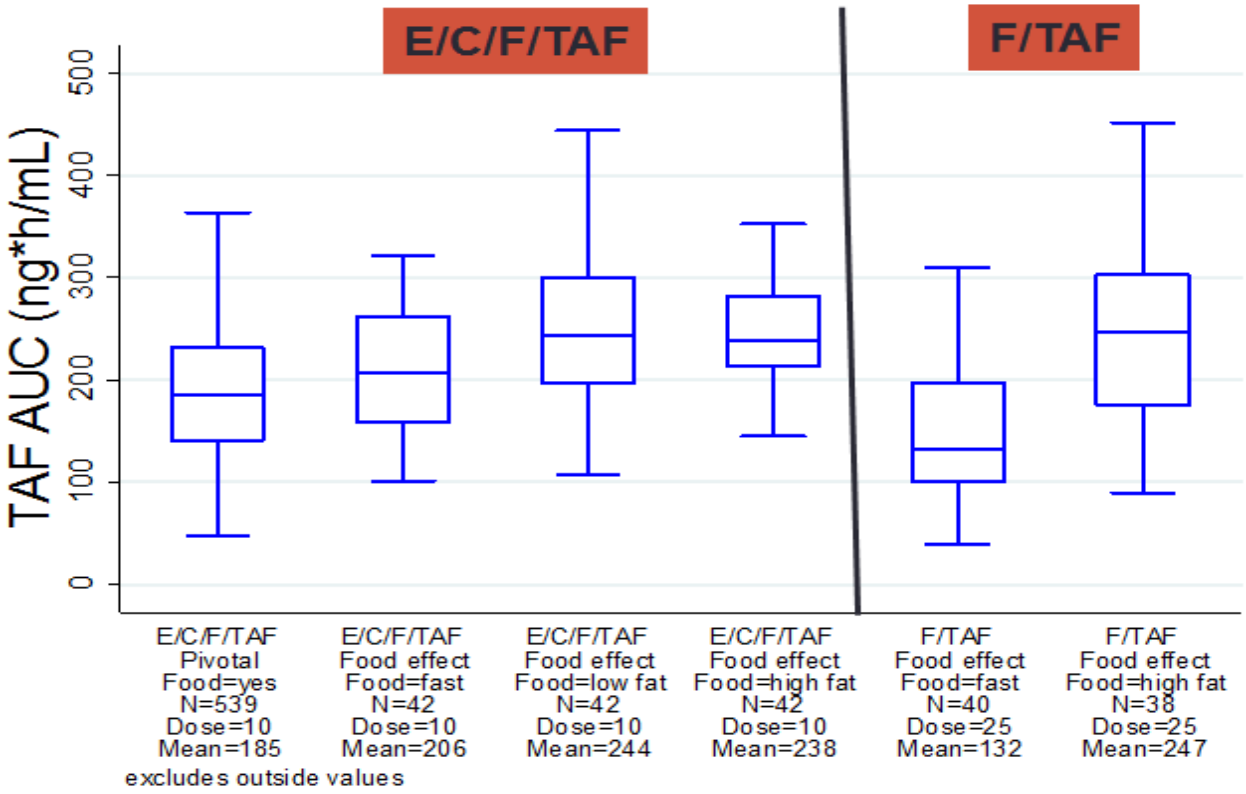
    Note that study 311-1089 is a switch study where 292 HIV-1 patients were randomized to continue an FTC/TDF-containing regimen or switch to F/TAF-containing regimen and regimens were administered without regard to food.

Table 1. Week 48 virologic outcome by TAF AUC quartile in study 311-1089.

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

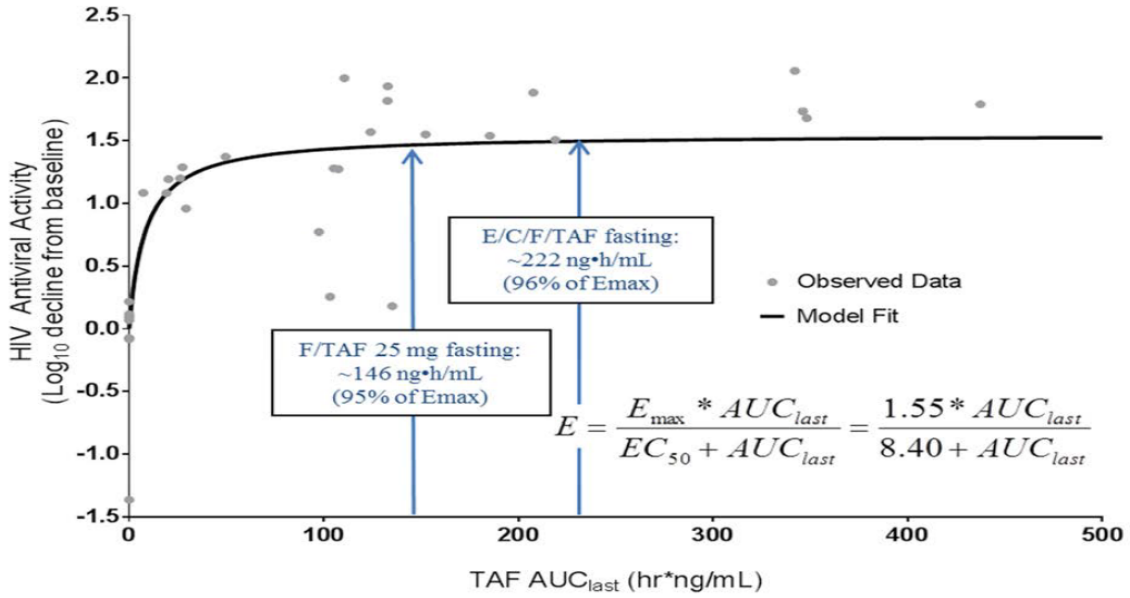
Ad hoc PKPD TFL Table 3.1.1, Ad hoc efficacy TFL Table 1.1 (GS-US-311-1089)
* N = 1 virologic failure at week 48

Figure 2. TAF AUCs across F/TAF (food effect) and E/C/F/TAF (pivotal and food effect) studies.



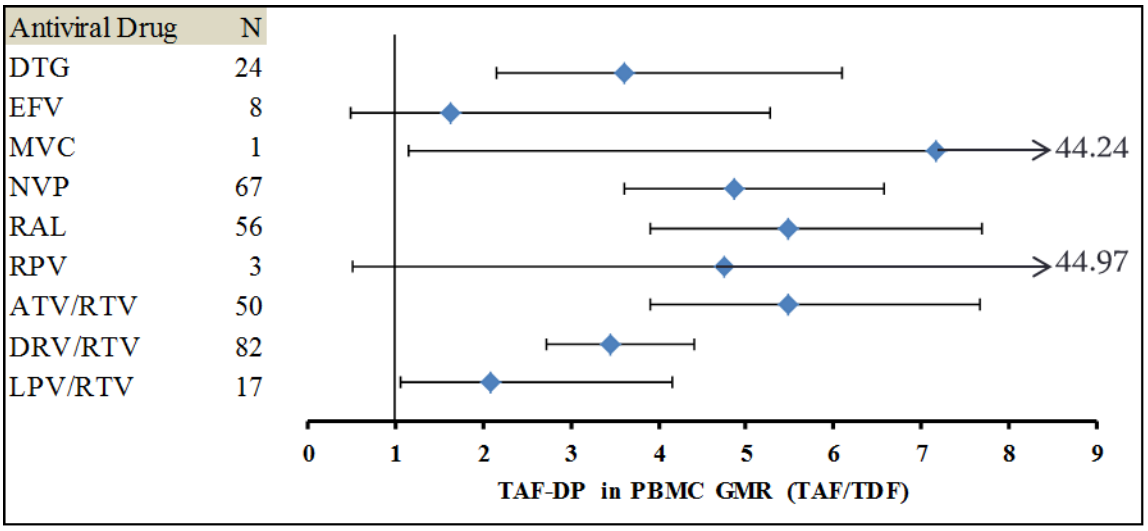
Source: prepared by reviewer. Mean = arithmetic mean.

Figure 3. Emax model of antiviral activity versus TAF AUC based on TAF monotherapy study 120-0104.



Source: NDA 208215, SDN 11.

Figure 4. PBMC TFV-DP concentrations from the TAF-containing versus TDF-containing arm in study 311-1089.



Source: prepared by reviewer. Error bars are 90% CIs. The upper 90% CI for MVC is 3840 and for RPV is 4531.

2.1.2 Drug interactions between F/TAF and other ARVs

FTC is not known to be a perpetrator or victim of enzyme or transporter-mediated drug interactions. However, as FTC and TFV are mainly excreted by a combination of glomerular filtration and active tubular secretion, coadministration of medications that reduce renal function or compete for active tubular secretion may increase the concentrations of FTC, TFV, and other coadministered drugs and may increase the risk of adverse reactions.

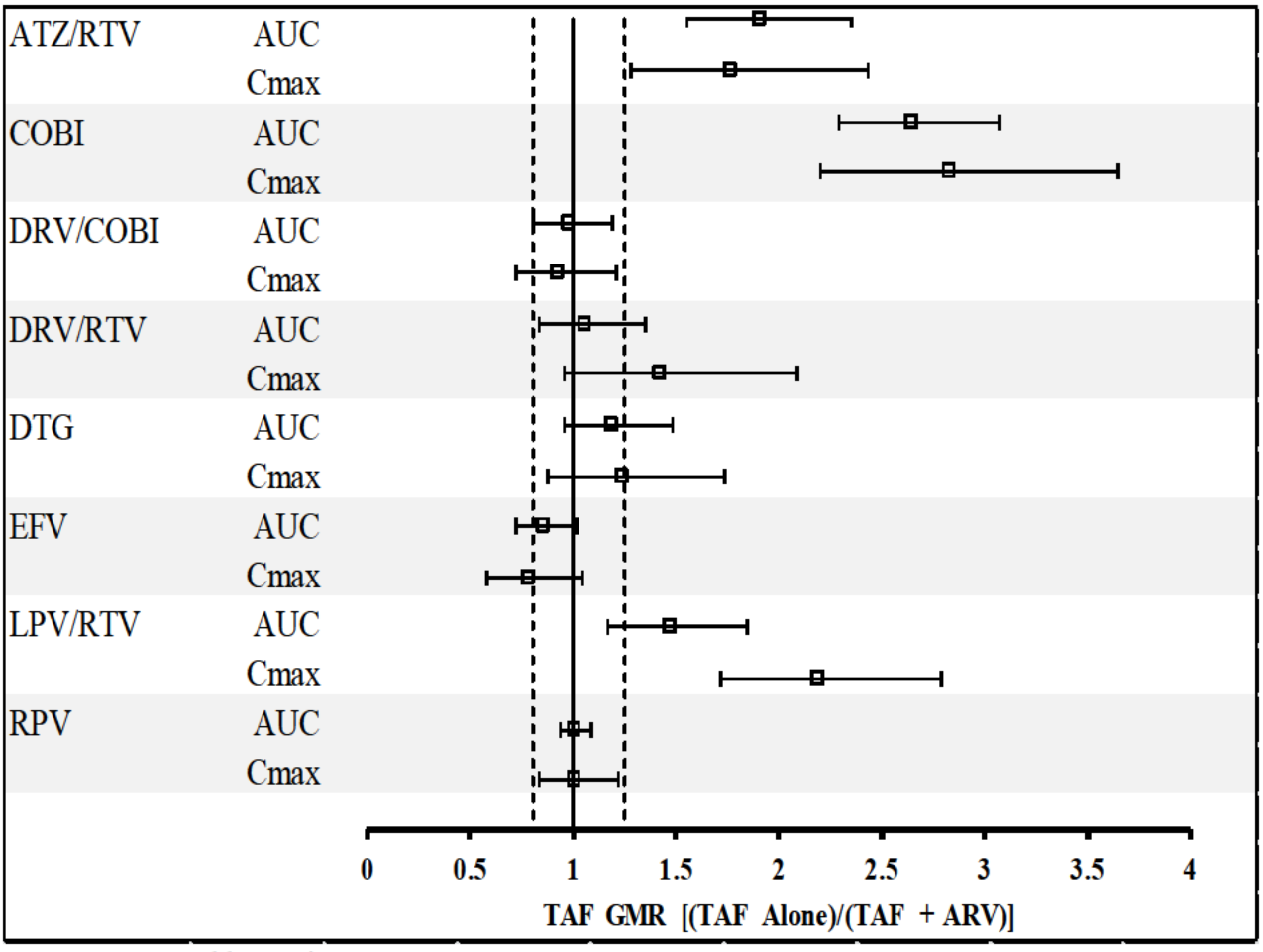
TAF is not a significant enzyme or transporter inhibitor or inducer. In drug interaction studies, TAF had no significant effect on the PK of ARVs. TAF is primarily metabolized by enzymes cathepsin A and carboxylesterase 1, and is a substrate of transporters Pgp, BCRP, and OATP. Inducers of transporters such as rifabutin, rifampin, rifapentine, and St. John's wort are not recommended to be coadministered with TAF. Also, alternative anticonvulsants to carbamazepine, oxcarbazepine, phenobarbital, and phenytoin (all transporter inducers) should be considered for coadministration with TAF.

Tipranivir/r (known Pgp inducer) is not recommended for coadministration with TAF. The effect of protease inhibitors other than LPV, ATV, and DRV on the exposure of TAF is not known (no in vivo DDI studies were conducted) and therefore dosing recommendations for coadministration with TAF cannot be made.

In drug interaction studies with other ARVs, dolutegravir (DTG), efavirenz (EFV), and rilpivirine (RPV) had no clinically significant effect on the PK of TAF; darunavir/ ritonavir (DRV/r), lopinavir/r (LPV/r), atazanavir/r (ATV/r), and COBI had variable but significant effects on the PK of TAF (Figure 5, Figure 6).

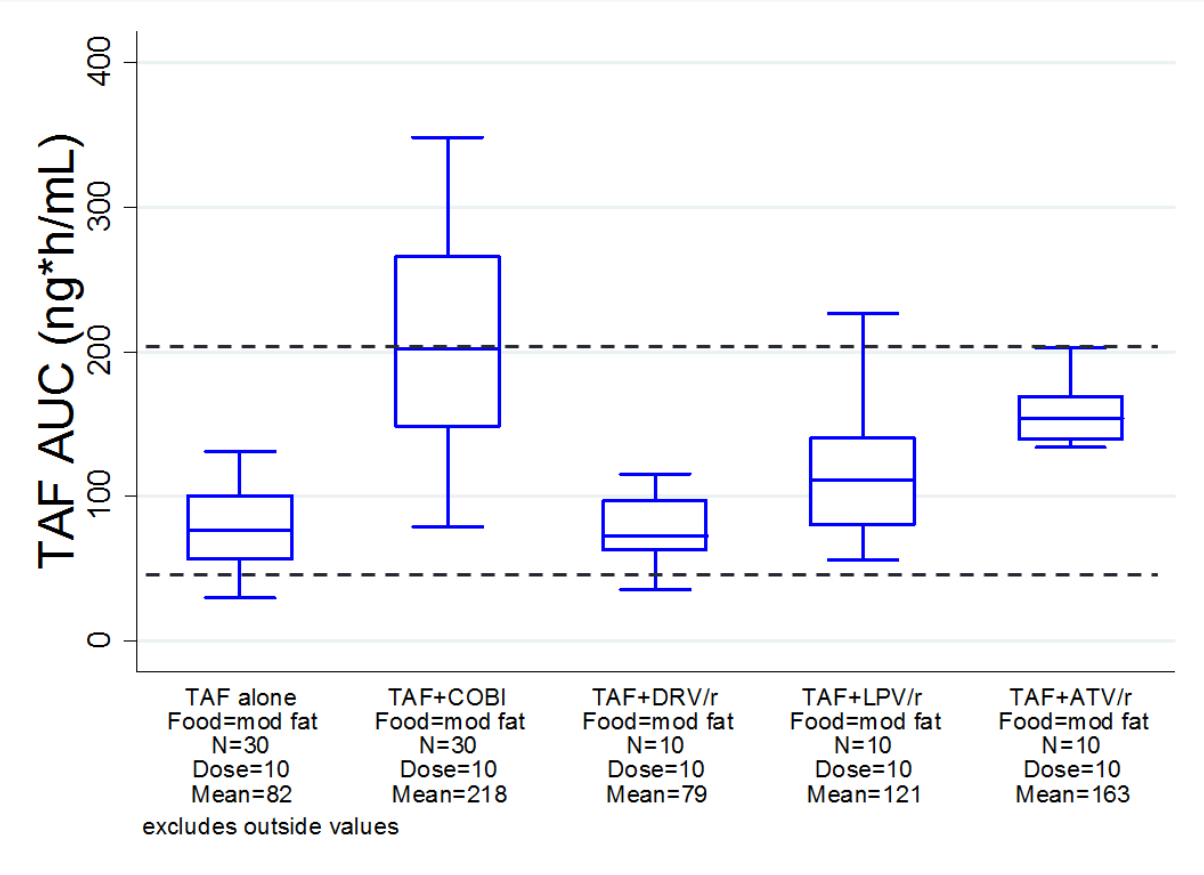
As TAF AUC is increased 2.65-fold when coadministered with COBI (Figure 5, Table 29), an (b) (4) a 200/25 mg formulation was developed for use with ARVs in regimens that do not contain a CYP3A4 inhibitor. The mechanism of this drug-drug interaction is thought to be due to inhibition of Pgp and/or BCRP and OATP by COBI and RTV because TAF is minimally metabolized by CYP3A4 and TAF is a substrate of those transporters. The effect of RTV and COBI on TAF exposure was shown to be similar. However, the degree of TAF exposure increase differed according to coadministered protease inhibitor/CYP3A inhibitor, with no TAF exposure increase occurring when coadministered with DRV/r (Figure 5, Figure 6). Despite the variability in the effect of protease inhibitors/CYP3A inhibitor on TAF exposure, (b) (4) to administer F/TAF 200/25 mg with COBI- or RTV-containing regimens.

Figure 5. Effect of coadministered ARVs on the PK of TAF.



Source: prepared by reviewer.

Figure 6. TAF exposure increases when coadministered with various protease inhibitors.



Source: prepared by reviewer. The TAF+COBI cohort is from study 311-0101 where an 8 mg dose of TAF was used and where TAF AUC was increased 2.65-fold when coadministered with COBI; the TAF+COBI box was obtained by multiplying each of the values in the "TAF alone" box by 2.65. All other data are from study 120-0118. A mean TAF AUC of ~200 ng*h/mL was observed in the E/C/F/TAF pivotal trials. A minimum TAF AUC of ~55 ng*h/mL was found to have antiviral activity similar to TDF 300 mg in TAF monotherapy trial 120-0104 (NDA 207561).

Several lines of evidence support the sponsor's proposal and suggest that the lower TAF exposures observed when coadministered with DRV/r are nonetheless sufficient:

1. Near-maximal TAF antiviral activity was observed in a monotherapy study at a TAF AUC of ~≥55 ng*h/mL (Figure 3), which is lower than the median AUC observed when F/TAF is coadministered with DRV/r.
2. In study 311-1089 where subjects received F/TAF- or FTC/TDF-containing regimens, virologic success of >90% was reported in both treatment arms and TFV-DP concentrations were higher in the F/TAF arm regardless of third agent, including protease inhibitors (Figure 4).). In this study 82 patients were on a DRV/r containing regimen.
3. In phase 2 study 299-0102 where subjects received either D/C/F/TAF (TAF 10 mg) or DRV+COBI+FTC+TDF, TAF AUCs were lower compared to historical data (mean TAF AUC_{last} of 131 ng*h/mL in this study versus 227 ng*h/mL for E/C/F/TAF in a phase 2 trial) (NDA 207561 Clinical Pharmacology review dated 7/10/2015). In this study, week 48 virologic outcomes were not statistically different between the treatment arms, and there was no relationship between TAF exposure and virologic outcome. It should be

noted that although the results of these study are deemed inconclusive (see NDA 208215 Biometrics review), they provide additional evidence that F/TAF when combined with DRV/r is expected to produce virologic success rates not worse than those observed in other studies in treatment-naïve adults using DRV-based regimens. The median (range) efficacy rate for previous studies using DRV-based regimens is 84% (78-87, n=7 NDA 208215, SDN 11).

It should be noted that the administration of F/TAF (TAF 25 mg) with DRV/r would be expected to produce TAF exposures similar to those observed in the pivotal E/C/F/TAF trials but would also increase systemic TFV exposure. However, as stated above, TAF exposures from F/TAF (b) (4) are sufficient, and a dose modification for DRV/r alone would complicate the dosing instructions in product label. Finally, because the exposure reduction of TAF is greatest with DRV/r, compared to ATV/r and LPV/r, and we concluded that F/TAF (b) (4) can be administered with DRV/r, this recommendation applies to these HIV protease inhibitors.

2.2 Recommendations

The Office of Clinical Pharmacology review team finds this application acceptable and recommends approval. No PMRs/PMCs are warranted at this time.

2.3 Labeling recommendations

We do not anticipate significant labeling modifications to the clinical pharmacology labeling. As stated above, we agree with the sponsor's labeling recommendations regarding coadministration with regard to food intake and with regard to dosing recommendations for coadministration with other antiretrovirals. Internal discussion is ongoing regarding how to label combination products and to what extent labeling from other approved products should be duplicated versus referred to in the combination label. Labeling negotiations have yet to begin.

3 Individual study reviews

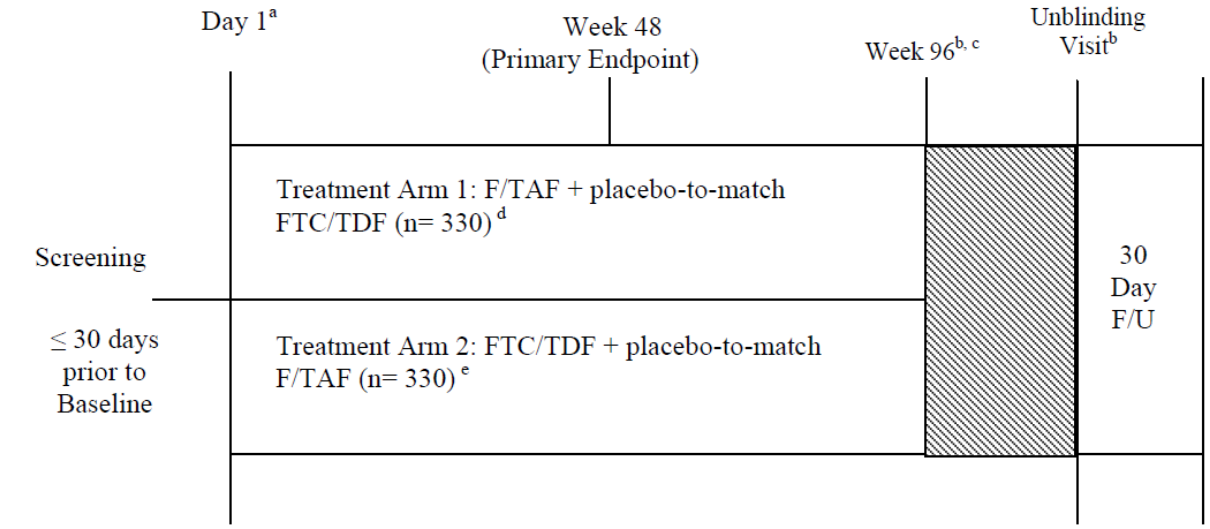
Figures and tables shown in the individual study reviews were obtained from the sponsor's respective study reports unless otherwise noted. The "Discussion/Reviewer's Comments" section of the individual study reviews contains our interpretation of the data; other sections contain summaries of the data as reported by the sponsor.

APPEARS THIS WAY ON ORIGINAL

3.1 GS-US-311-1089 – Phase 3 study evaluating switching from an FTC/TDF-containing regimen to an F/TAF-containing regimen

A Phase 3, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed on Regimens Containing FTC/TDF	
Study Period	5/6/2014-8/21/2015
Link	Interim 48 week CSR: (b) (4) [redacted] PBMC PK report: (b) (4) [redacted]

STUDY DESIGN



F/U = follow-up

a Following the Day 1 visit, subjects were scheduled to return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 96.

b After Week 96, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded, at which point all subjects will return for an Unblinding Visit and will be given the option to receive F/TAF until F/TAF becomes commercially available or until Gilead Sciences terminates the F/TAF clinical development. Subjects who do not wish to receive open-label F/TAF will be required to return to the clinic for an Unblinding Visit and a 30-Day follow-up visit.

c Subjects who have discontinued study drug before the Unblinding Visit will not be eligible to receive open-label F/TAF; these subjects will be asked to continue attending the scheduled study visits through the Unblinding Visit.

d F/TAF + placebo-to-match FTC/TDF was administered orally in combination with the third ARV agent, once daily in the morning at approximately the same time each day.

e FTC/TDF + placebo-to-match F/TAF was administered in combination with the third ARV agent, once daily in the morning at approximately the same time each day.

- **Treatment Group 1 (referred to herein as F/TAF+3rd Agent):**
  F/TAF + Placebo-to-match FTC/TDF; third agent remains the same (planned N = 330); a TAF dose of 10 or 25 mg was administered based on the general recommendation that F/TAF 200/25 mg should be used with unboosted third agents and F/TAF 200/10 mg should be used with boosted third agents (Table 7-2)

- **Treatment Group 2 (referred to herein as FTC/TDF+3rd Agent):**
  FTC/TDF + Placebo-to-match F/TAF; third agent remains the same (planned N = 330)

Study drugs were administered without regard to food. Allowable third agents included ATV/r, LPV/r, DRV/r, EFV, RPV, NVP, RAL, DTG, and MVC.

Population	Virologically suppressed, HIV-infected subjects
Objectives	Primary: Efficacy and safety Secondary: PK of TAF and TFV in plasma, and PK of TFV-DP in PBMCs

<table>
<tr><td>Formulation</td><td>
<table>
<tr><th>Product</th><th>Strength</th><th>Lot Number</th></tr>
<tr><td>F/TAF</td><td>FTC 200 mg/ TAF 10 mg</td><td>CR1308B1
CR1407B1
CR1411B1</td></tr>
<tr><td>F/TAF Placebo-to-Match (FTC 200 mg/ TAF 10 mg)</td><td>0 mg</td><td>CR1312B1</td></tr>
<tr><td>F/TAF</td><td>FTC 200 mg/ TAF 25 mg</td><td>CR1305B1
CR1408B1
CR1412B1</td></tr>
<tr><td>F/TAF Placebo-to-Match (FTC 200 mg/ TAF 25 mg)</td><td>0 mg</td><td>CR1312B1</td></tr>
<tr><td>FTC/TDF</td><td>FTC 200 mg/ TDF 300 mg</td><td>V1206B1
V1207B1</td></tr>
<tr><td>FTC/TDF Placebo-to-Match (FTC 200 mg/ TDF 300 mg)</td><td>0 mg</td><td>V1107B1</td></tr>
</table>
</td></tr>
<tr><td>Dose Selection Rationale</td><td>FTC/TDF doses are approved.
The F/TAF doses were studied in the pivotal relative BA trials.</td></tr>
<tr><td>Interfering Substances Excluded</td><td>
<table>
<tr><th>Medication Class</th><th>Prohibited Medications[a]</th></tr>
<tr><td>Anticonvulsants</td><td>carbamazepine, oxcarbazepine, phenobarbital, phenytoin</td></tr>
<tr><td>Antimycobacterials</td><td>rifapentine, rifabutin, rifampin</td></tr>
<tr><td>Bisphosphonate</td><td>Any agent in this class (for example: alendronate, ibandronate, risedronate, zoledronate, pamidronate, teriparatide)</td></tr>
<tr><td>Herbal/Natural Supplements</td><td>St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)</td></tr>
<tr><td>Other</td><td>probenecid</td></tr>
</table>
a Administration of any of the above prohibited medications was required to be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.
</td></tr>
<tr><td>Sampling Times</td><td>All subjects had a single PK blood sample collected at Weeks 4, 8, 12, 24, 36, and 48. At the Week 8, 24, and 48 visits, the single PK blood sample was collected between 15 minutes and 4 hours postdose.

All subjects had a single blood sample collected at Week 4 for analysis of intracellular PBMC TFV-DP concentrations.</td></tr>
<tr><td>Bioanalytical methods</td><td>Concentrations of TAF, TFV, and TFV-DP were determined using LC/MS/MS</td></tr>
</table>

RESULTS

Protocol deviations

Reported protocol deviations are shown below (Table 2).

Table 2. Protocol deviations.

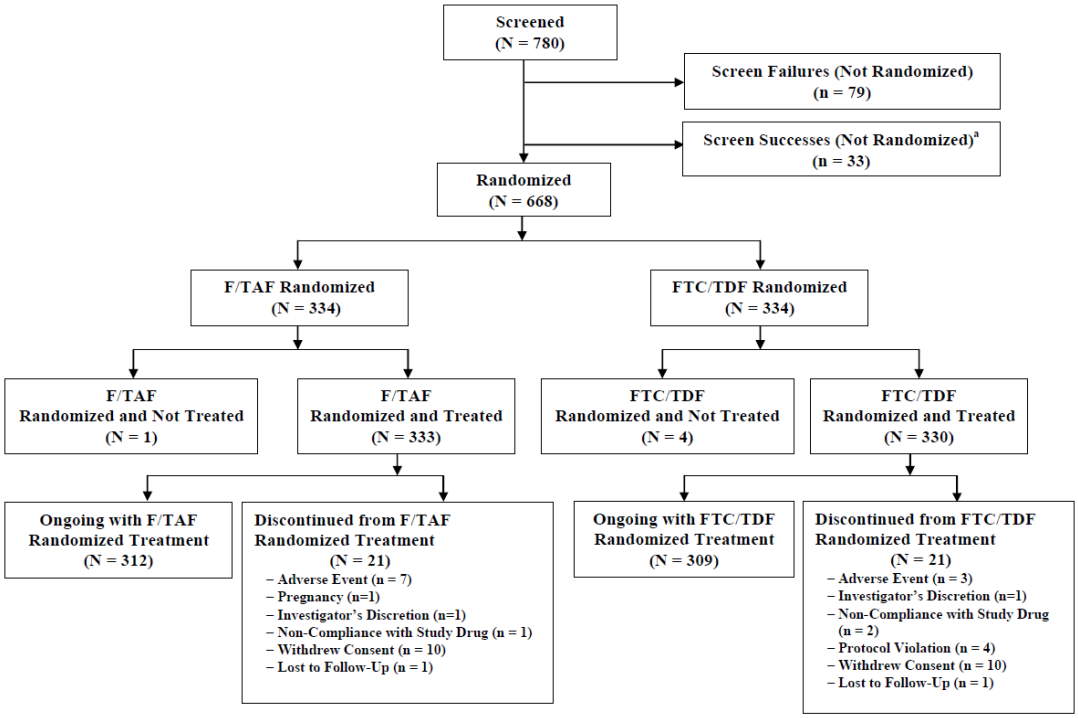
Protocol Deviation[a], n (%)	**F/TAF + 3rd Agent (N = 333)**	**FTC/TDF + 3rd Agent (N = 330)**
Number of Subjects with at Least 1 Important Protocol Deviation	44 (13.2%)	41 (12.4%)
Procedural Deviation	20 (6.0%)	17 (5.2%)
Non-Adherence of Study Drug	10 (3.0%)	11 (3.3%)
Deviation of Inclusion/Exclusion Criteria	6 (1.8%)	12 (3.6%)
Received Prohibited Concomitant Medications	10 (3.0%)	5 (1.5%)
Overdose	2 (0.6%)	4 (1.2%)
Incorrect Dispensing or Dosing of Study Drug	1 (0.3%)	1 (0.3%)

a Protocol deviations are not mutually exclusive. Thus, subjects may be counted multiple times across categories.

Study population

Subject disposition and demographics are summarized below (Figure 7, Table 3). Adherence of >90% at week 48 was reported in >90% of subjects in both arms.

Figure 7. Subject disposition.



a Of the 33 subjects who were successfully screened, but not randomized, 18 withdrew consent, 5 had a visit outside the visit window, 6 were lost to follow-up, and 4 were due to other reasons.

Table 3. Subject demographics.

	F/TAF+ 3rd Agent (N = 333)	FTC/TDF+ 3rd Agent (N = 330)	Total (N = 663)
Age (Years)			
N	333	330	663
Mean (SD)	47 (9.9)	48 (9.7)	48 (9.8)
Median	48	49	49
Q1, Q3	42, 54	42, 54	42, 54
Min, Max	22, 78	22, 79	22, 79
Sex			
Male	285 (85.6%)	276 (83.6%)	561 (84.6%)
Female	48 (14.4%)	54 (16.4%)	102 (15.4%)
Race[a]			
American Indian or Alaska Native	2 (0.6%)	1 (0.3%)	3 (0.5%)
Asian	6 (1.8%)	0	6 (0.9%)
Black	69 (20.7%)	67 (20.3%)	136 (20.5%)
Native Hawaiian or Pacific Islander	2 (0.6%)	1 (0.3%)	3 (0.5%)
White	244 (73.3%)	253 (76.7%)	497 (75.0%)
Not Permitted	1 (0.3%)	1 (0.3%)	2 (0.3%)
Other	9 (2.7%)	7 (2.1%)	16 (2.4%)
Ethnicity			
Hispanic or Latino	48 (14.4%)	78 (23.6%)	126 (19.0%)
Not Hispanic or Latino	285 (85.6%)	252 (76.4%)	537 (81.0%)
Baseline Weight (kg)			
N	333	330	663
Mean (SD)	83.3 (17.06)	83.7 (17.29)	83.5 (17.16)
Median	80.4	81.6	80.7
Q1, Q3	72.4, 91.2	72.1, 93.9	72.3, 92.5
Min, Max	42.0, 167.8	46.3, 147.8	42.0, 167.8
Baseline Height (cm)			
N	333	330	663
Mean (SD)	174.9 (8.72)	174.2 (9.69)	174.6 (9.21)
Median	175.3	175.2	175.3
Q1, Q3	170.2, 180.3	168.0, 180.3	170.0, 180.3
Min, Max	142.2, 200.7	134.6, 203.2	134.6, 203.2

	F/TAF+ 3rd Agent (N = 333)	FTC/TDF+ 3rd Agent (N = 330)	Total (N = 663)
Baseline Body Mass Index (kg/m^2)			
N	333	330	663
Mean (SD)	27.3 (5.54)	27.6 (5.76)	27.4 (5.65)
Median	26.1	26.4	26.3
Q1, Q3	23.6, 29.3	23.8, 30.1	23.7, 29.7
Min, Max	17.3, 58.5	17.9, 63.6	17.3, 63.6

a For Subjects 1236-1116 and 0947-1226, collection of race information was not permitted.

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.

	F/TAF+ 3rd Agent (N = 333)	FTC/TDF+ 3rd Agent (N = 330)	Total (N = 663)
Baseline Third Agent (N)			
ATV/r	53 (15.9%)	50 (15.2%)	103 (15.5%)
DRV/r	84 (25.2%)	82 (24.8%)	166 (25.0%)
LPV/r	18 (5.4%)	18 (5.5%)	36 (5.4%)
DTG	26 (7.8%)	23 (7.0%)	49 (7.4%)
EFV	8 (2.4%)	6 (1.8%)	14 (2.1%)
MVC	1 (0.3%)	6 (1.8%)	7 (1.1%)
NVP	74 (22.2%)	66 (20.0%)	140 (21.1%)
RAL	66 (19.8%)	73 (22.1%)	139 (21.0%)
RPV	3 (0.9%)	6 (1.8%)	9 (1.4%)
Estimated Glomerular Filtration Rate by Cockcroft-Gault (mL/min)[b]			
N	333	329[b]	662
Mean (SD)	104.7 (31.07)	105.3 (30.22)	105.0 (30.63)
Median	99.4	100.2	99.8
Q1, Q3	83.8, 120.3	83.8, 121.2	83.8, 120.6
Min, Max	24.8, 275.4	53.8, 237.5	24.8, 275.4

a A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
b For Subject 3614-1170, predose serum creatinine was not assessed and therefore eGFR could not be assessed.

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.

Efficacy

An efficacy rate of >90% was reported in both arms of the study (Table 4).

Table 4. Virologic outcome at week 48.

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

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

Concomitant medications

At least one non-ARV concomitant medication was used by >95% of subjects in each arm. Commonly used medications in the F/TAF arm included analgesics (43%), antibiotics (43%), antiinflammatory agents (34%), and lipid lowering agents (29%).

Pharmacokinetics

TFV-DP

Plasma PK data of TAF and TFV was not included in this interim report. Overall TFV-DP concentrations in PBMCs were ~4-fold higher in the F/TAF arm relative to the FTC/TDF arm, and were higher in the F/TAF arm for all third agents (Table 5, Figure 8). The distribution of TFV-DP concentrations by third agent is shown in Figure 9.

Table 5. TFV-DP concentrations in PBMCs.

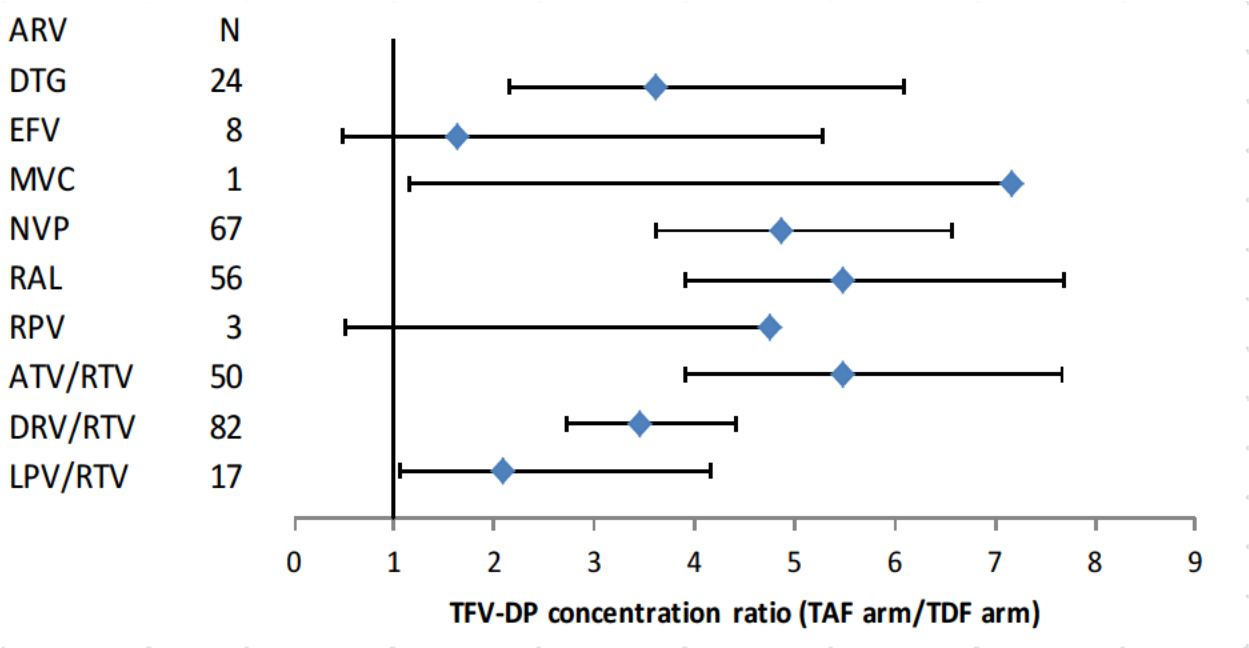
PBMC TFV-DP Concentration[a, b]	F/TAF+3rd Agent (Test)		FTC/TDF+3rd Agent (Reference)		GLSM Ratio (%)	90% CI (%)
	n	GLSM	n	GLSM		
pg/million						
Overall	304	113.541	265	27.287	416.100	(362.390, 477.771)
ATV/r	50	126.292	34	23.208	544.164	(389.197, 760.833)
DRV/r	82	78.879	69	23.317	338.294	(264.774, 432.228)
LPV/r	16	96.052	14	31.070	309.144	(146.581, 651.992)
DTG	24	106.571	19	32.724	325.664	(198.902, 533.213)
EFV	8	54.224	6	32.002	169.441	(64.761, 443.327)
MVC	1	268.000	5	28.276	947.810	(233.900, 3840.727)
NVP	65	137.937	56	31.464	438.402	(323.162, 594.737)
RAL	55	167.293	57	29.920	559.127	(396.255, 788.945)
RPV	3	161.478	5	36.695	440.057	(42.736, 4531.321)
nM						
Overall	304	1270.032	265	305.223	416.100	(362.390, 477.771)
ATV/r	50	1412.664	34	259.603	544.164	(389.197, 760.833)
DRV/r	82	882.316	69	260.814	338.294	(264.774, 432.228)
LPV/r	16	1074.405	14	347.542	309.144	(146.581, 651.992)
DTG	24	1192.072	19	366.044	325.664	(198.902, 533.213)
EFV	8	606.537	6	357.963	169.441	(64.761, 443.327)
MVC	1	2997.763	5	316.283	947.810	(233.900, 3840.727)
NVP	65	1542.923	56	351.942	438.402	(323.162, 594.737)
RAL	55	1871.286	57	334.680	559.127	(396.255, 788.945)
RPV	3	1806.244	5	410.457	440.057	(42.736, 4531.321)

GLSM = geometric least-squares mean

a For each subject, a trough blood sample was collected at Week 4, Week 8, or Week 12.

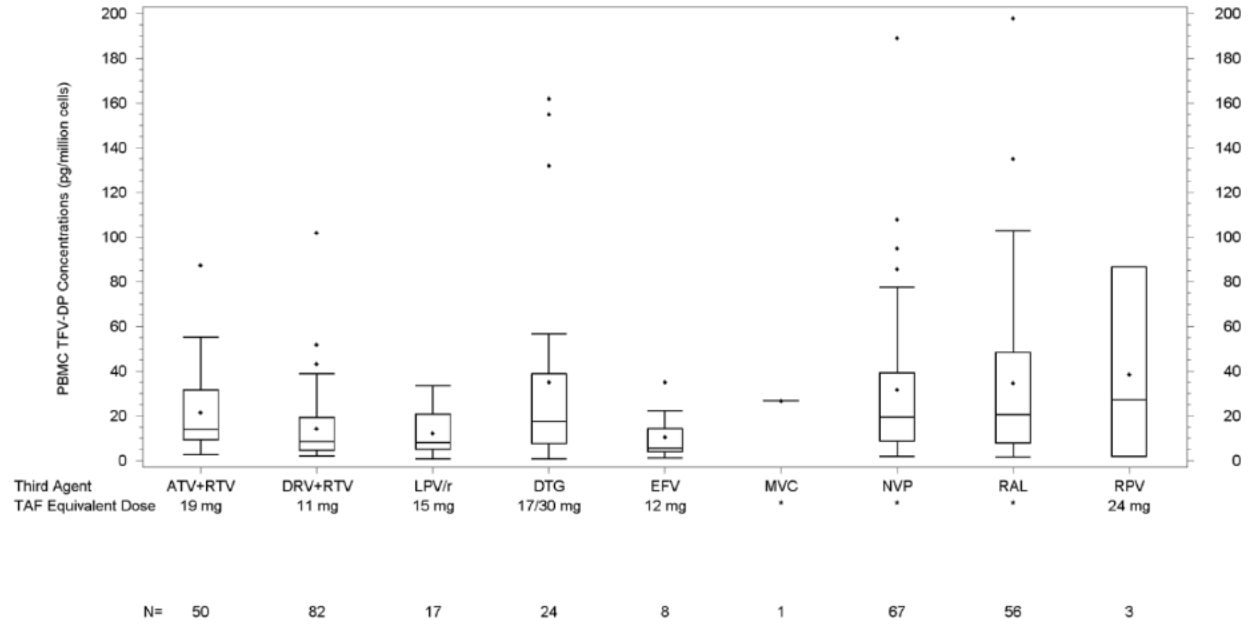
b Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie, sample age ≥ 61 days)

Figure 8. TFV-DP concentrations in PBMCs.



Source: prepared by reviewer.

Figure 9. TFV-DP concentrations by third agent.



Safety

The most common AEs in the F/TAF arm were upper respiratory infection (9%), headache (8%), and nasopharyngitis (8%), and in the FTC/TDF arm were upper respiratory infection (14%), diarrhea (10%), and sinusitis (7%). Increases in hip and spine bone mineral density were reported in the F/TAF arm along with minimal changes in the FTC/TDF arm. Mean $eGFR_{CG}$ increased from baseline to week 48 by 8.4 mL/min in the F/TAF arm and 2.8 mL/min in the FTC/TDF arm. No clinically relevant changes from baseline in laboratory abnormalities were reported within or between groups. Lipid-related AEs and laboratory abnormalities were more common in the F/TAF arm; none led to discontinuation of study drugs.

DISCUSSION/REVIEWER'S COMMENTS

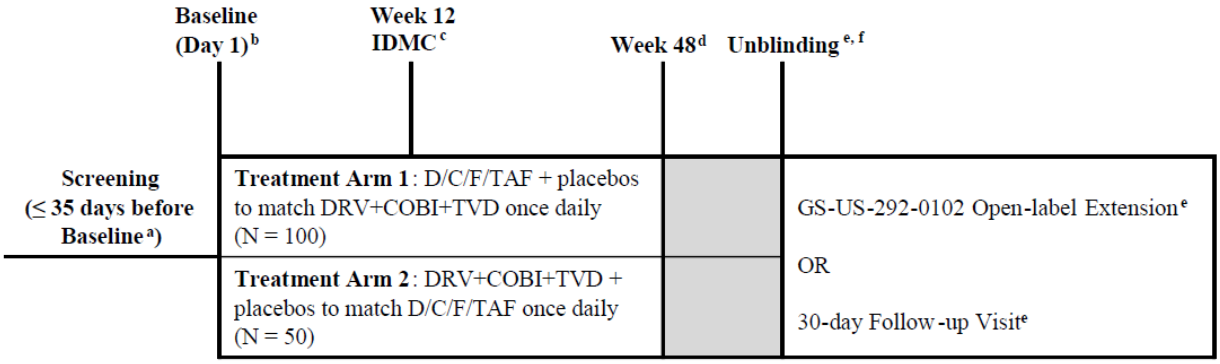
Each of the categories of protocol deviations were similar between treatment groups and were thus unlikely to affect the interpretation of the TFV-DP data. With the exception of one subject in the TAF arm who used rifabutin, concomitant medications that may reduce TAF exposure (such as inducers) were not used in the study. The TFV-DP bioanalysis was overall acceptable; however, 12% of samples were measured outside the duration of stability.

TFV-DP is the active moiety resulting from administration of TAF and TDF, and higher TFV-DP concentrations in the TAF versus TDF arms regardless of third agent in this study. This suggests that therapeutic TAF concentrations are achieved when F/TAF 200/10 mg is coadministered with COBI- or RTV-containing regimens and when F/TAF 200/25 is not coadministered with COBI- or RTV-containing regimens.

3.2 GS-US-299-0102 – Phase 2 study comparing D/C/F/TAF to DRV+COBI+FTC/TDF

A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-boosted Darunavir plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	
Study Period	4/16/2012-2/19/2014
Link	\\cdsesub1\evsprod\nda208215\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5351-stud-rep-contr\gs-us-299-0102\report-body.pdf

STUDY DESIGN



a Screening window was extended to 42 days for subjects who required repeat testing of HIV-1 genotype.
b Following the Baseline visit, subjects returned for study visits at Weeks 2, 4, 8, 12, 16, and then every 8 weeks through Week 48.
c An external Independent Data Monitoring Committee (IDMC) reviewed the progress, efficacy, and safety profile of the study regimens while the study was ongoing. The committee convened after the last subjects enrolled completed Week 12 of the study (Section 8.7 of the protocol, Appendix 16.1.1).
d Subjects continued to attend visits every 12 weeks following Week 48 until treatment assignment was unblinded.
e Once Gilead Sciences provided unblinded treatment assignments to the Investigators, all subjects returned to the clinic within 30 days (+6 days) for an Unblinding Visit. At the Unblinding Visit all subjects discontinued blinded study drugs and were given an option to participate in the Study GS-US-292-0102 open-label rollover extension. Subjects who did not wish to participate in the open-label rollover extension discontinued blinded study drugs and returned for a 30-day Follow-up visit following the Unblinding Visit.
f Subjects who discontinued study drug prior to the Unblinding Visit were not eligible for the open label rollover extension; these subjects discontinued the study after the Unblinding Visit.

- **Treatment Arm 1**: FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg + placebos to match DRV 800 mg (400mg tablet x 2) and COBI 150 mg tablet and FDC tablet FTC 200 mg/TDF 300 mg once daily (5 tablets in total)

- **Treatment Arm 2**: DRV 800 mg (400 mg tablet x 2) + COBI 150 mg tablet + FDC tablet FTC 200 mg/TDF 300 mg + placebos to match an FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg once daily (5 tablets in total)

Both treatments were to be taken orally once daily with food.

Population	Treatment naïve, HIV-infected adults
Study Rationale	Safety and efficacy

<table>
<tr><td>Dose Selection Rationale</td><td>DRV, COBI, FTC, TDF, and TAF doses are approved</td></tr>
<tr><td>Formulation</td><td>
<table>
<tr><th>Product</th><th>Strength</th><th>Lot Number</th></tr>
<tr><td>D/C/F/TAF</td><td>DRV 800 mg,
COBI 150 mg,
FTC 200 mg,
TAF 10 mg</td><td>DB1103B1
DB1103B2
DB1201B1
DB1204B1</td></tr>
<tr><td>D/C/F/TAF placebo</td><td>Not applicable</td><td>DB1104B1
DB1302B1</td></tr>
<tr><td>DRV</td><td>400 mg</td><td>DF1202A1</td></tr>
<tr><td>DRV placebo</td><td>Not applicable</td><td>DF1201B1</td></tr>
<tr><td>COBI</td><td>150 mg</td><td>BB1004B2
BB1201B1
BB1205B1</td></tr>
<tr><td>COBI placebo</td><td>Not applicable</td><td>BB1005B1
BB1202B1</td></tr>
<tr><td>TVD</td><td>FTC 200 mg
TDF 300 mg</td><td>V1201B1
V1105B1</td></tr>
<tr><td>TVD placebo</td><td>Not applicable</td><td>V1022B1
V1023B1
V1018B1
V1019B1
V1104B1</td></tr>
</table>
</td></tr>
<tr><td>Interfering Substances Excluded</td><td>Excluded medications included alfuzosin, modafinil, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, astemizole, terfenadine, rifampin, rifapentine, rifabutin, non-study drug ARVs, bepridil, ergot derivatives, cisapride, St. John’s Wort, Echinaccea, simvastatin, lovastatin, cerivastatin, pimozide, midazolam and triazolam excepting one-time procedures, and systemic corticosteroids. In addition, various agents were to be discouraged or used with caution.</td></tr>
<tr><td>Sampling Times</td><td>• Single sample from all subjects at any time pre- or post-dose on weeks 2, 4, 12, 16, 32, and 40.
• Single trough sample from all subjects on weeks 8, 24, and 48
• PK substudy (n=36) between weeks 4-8: samples collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose.</td></tr>
</table>

RESULTS

Bioanalytical methods

The sponsor reports that concentrations of TAF, TFV, COBI, DRV, and FTC plasma samples were determined using fully validated LC/MS/MS and that samples were analyzed within the duration of stability (Table 6). The sponsor reports that TFV-DP concentrations were not determined using a validated method.

Table 6. Summary of bioanalytical methods.

	TAF[a]	TFV		COBI[a]	DRV	FTC
Linear Range (ng/mL)	1 to 1000	0.3 to 300	5 to 3000	5 to 2500	20 to 10,000	5 to 3000
Lower limit of quantitation (ng/mL)	1	0.3	5	5	20	5
Interassay Precision Range (%CV)	1.8 to 7.3	2.7 to 8.4	2.4 to 6.5	3.9 to 8.3	2.8 to 10.6	1.4 to 5.7
Interassay Accuracy Range (%RE)	–3.7 to 6.5	0.0 to 3.0	–4.7 to 2.0	-0.3 to 9.7	–3.9 to –1.0	–7.8 to 2.4
Stability in frozen matrix (days)	161 at –70°C	366 at –20°C 369 at –70°C	190 at –20°C 340 at –70°C	121 at –10 °C to –30 °C 365 at –60 °C to –80 °C	301 at –20°C and –70°C	190 at -20°C 340 at -70°

a TAF is refererred to as GS-7340 and COBI is referred to as GS-9350 in the bioanalytical and validation reports.
Source: Appendix 16.1.10, QPS 60-1115 Amendment 2, QPS 60-1116 Amendment 2, QPS validation report 60-0949 Amendment 5, QPS 42-0902 Amendment 1, QPS 42-0831 Amendment 4

Protocol deviations

Numerous important protocol deviations occurred, with the most frequent being associated with dispensing or dosing of study drug (Table 7). The most common dispensing/dosing-related deviations were reported for subjects with compliance <70% and for dispensing of the incorrect study medication bottles (in some cases the subject still received the correct medication for their treatment arm).

Table 7. Protocol deviations.

Protocol Deviation	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)
Number of Subjects with at Least 1 Important Protocol Deviation	21 (20.4%)	14 (28.0%)
Deviation of Inclusion/Exclusion Criteria	0 (0.0%)	1 (2.0%)
Incorrect Dispensing or Dosing of IMP	27 (26.2%)	13 (26.0%)
Procedural Deviation	1 (1.0%)	1 (2.0%)
Regulatory Deviation	6 (5.8%)	0 (0.0%)
Received Prohibited Concomitant Medication	1 (1.0%)	2 (4.0%)

Study population

Subject disposition and demographics are shown below (Table 8, Table 9). The reported adherence rate was ≥90% for 86% of subjects in the D/C/F/TAF arm and 80% of subjects in the control arm.

Table 8. Subject disposition.

Subject Disposition	D/C/F/TAF n (%)	DRV+COBI+TVD n (%)	Total n (%)
Screened			232
Screen Failures Not Randomized			79
Randomized	103	50	153
Treated	103	50	153
Completed Study Treatment	84 (81.6%)	42 (84.0%)	126 (82.4%)
Rolled Over to Study GS-US-292-0102	70 (68.0%)	38 (76.0%)	108 (70.6%)
Prematurely Discontinued Study Treatment	19 (18.4%)	8 (16.0%)	27 (17.6%)
Adverse Event	1 (1.0%)	2 (4.0%)	3 (2.0%)
Death	0	0	0
Lost to Follow-up	10 (9.7%)	4 (8.0%)	14 (9.2%)
Investigator's Discretion	2 (1.9%)	0	2 (1.3%)
Lack of Efficacy	0	0	0
Subject Non-compliance	2 (1.9%)	0	2 (1.3%)
Pregnancy	0	0	0
Protocol Violation	0	0	0
Study Discontinued by Sponsor	0	0	0
Withdrew Consent	4 (3.9%)	2 (4.0%)	6 (3.9%)
Completed Study	83 (80.6%)	42 (84.0%)	125 (81.7%)
Rolled Over to Study GS-US-292-0102	70 (68.0%)	38 (76.0%)	108 (70.6%)
Prematurely Discontinued Study[a]	20 (19.4%)	8 (16.0%)	28 (18.3%)
Adverse Event	0	1 (2.0%)	1 (0.7%)
Death	0	0	0
Lost to Follow-up	12 (11.7%)	4 (8.0%)	16 (10.5%)
Investigator's Discretion	2 (1.9%)	1 (2.0%)	3 (2.0%)
Lack of Efficacy	0	0	0
Subject Non-compliance	2 (1.9%)	0	2 (1.3%)
Pregnancy	0	0	0
Protocol Violation	0	0	0
Study Discontinued by Sponsor	0	0	0
Withdrew Consent	4 (3.9%)	2 (4.0%)	6 (3.9%)

The denominator for percentages is based on the number of subjects in the safety analysis set.
The number of screen failures is counted by unique subject based on the date of birth, race, ethnicity, country, and initials.
a Subjects prematurely discontinuing study drug could still be in the study (ie, not prematurely discontinued from the study).

Table 9. Subject demographics.

Characteristic	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)	D/C/F/TAF vs DRV+COBI+TVD (p-value)
Age (years)				
N	103	50	153	0.23
Mean (SD)	35 (11.3)	37 (10.9)	35 (11.2)	
Median	31	36	33	
Q1, Q3	25, 42	28, 44	26, 43	
Min, Max	20, 68	18, 57	18, 68	
Sex (n, %)				
Male	95 (92.2%)	47 (94.0%)	142 (92.8%)	0.69
Female	8 (7.8%)	3 (6.0%)	11 (7.2%)	
Race (n, %)				
White	62 (60.2%)	30 (60.0%)	92 (60.1%)	0.99
Black or African American	36 (35.0%)	17 (34.0%)	53 (34.6%)	
Asian	2 (1.9%)	1 (2.0%)	3 (2.0%)	
Native Hawaiian or Other Pacific Islander	1 (1.0%)	1 (2.0%)	2 (1.3%)	
Other	2 (1.9%)	1 (2.0%)	3 (2.0%)	
Ethnicity (n, %)				
Hispanic or Latino	23 (22.3%)	9 (18.0%)	32 (20.9%)	0.54
Not Hispanic or Latino	80 (77.7%)	41 (82.0%)	121 (79.1%)	
Baseline Body Mass index (kg/m^2)				
N	103	50	153	0.94
Mean (SD)	26.3 (4.97)	26.1 (4.53)	26.2 (4.81)	
Median	25.1	24.7	24.9	
Q1, Q3	22.4, 29.6	22.7, 29.0	22.7, 29.2	
Min, Max	18.2, 42.7	17.6, 37.9	17.6, 42.7	

The denominator for percentages is based on the number of subjects in the safety analysis set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.

Concomitant medications

Use of excluded drugs included modafinil (prior to the baseline visit in n=1 subject), Echinacea (one-time use in one subject, use over several weeks in a second subject), dexamethasone (one administration, n=1). The most commonly used concomitant medications were antibacterials, vitamins, vaccines, and analgesics.

Efficacy

Virologic success was reported to be similar at 48 weeks (Table 10).

Table 10. Week 48 virologic outcomes.

	D/C/F/TAF (N=103)	DRV+COBI +TVD (N=50)	D/C/F/TAF vs. DRV+COBI+TVD	
			p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 48[c]				
HIV-1 RNA < 50 copies/mL	79 (76.7%)	42 (84.0%)	0.35	-6.2% (-19.9% to 7.4%)
Virologic Failure at Week 48[c]	16 (15.5%)	6 (12.0%)		
HIV-1 RNA ≥ 50 copies/mL	7 (6.8%)	4 (8.0%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[d]	9 (8.7%)	2 (4.0%)		
Added New ARV	0	0		
No Virologic Data in Week 48 Window[c]	8 (7.8%)	2 (4.0%)		
Discontinued Study Drug Due to AE/Death	1 (1.0%)	1 (2.0%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	7 (6.8%)	1 (2.0%)		

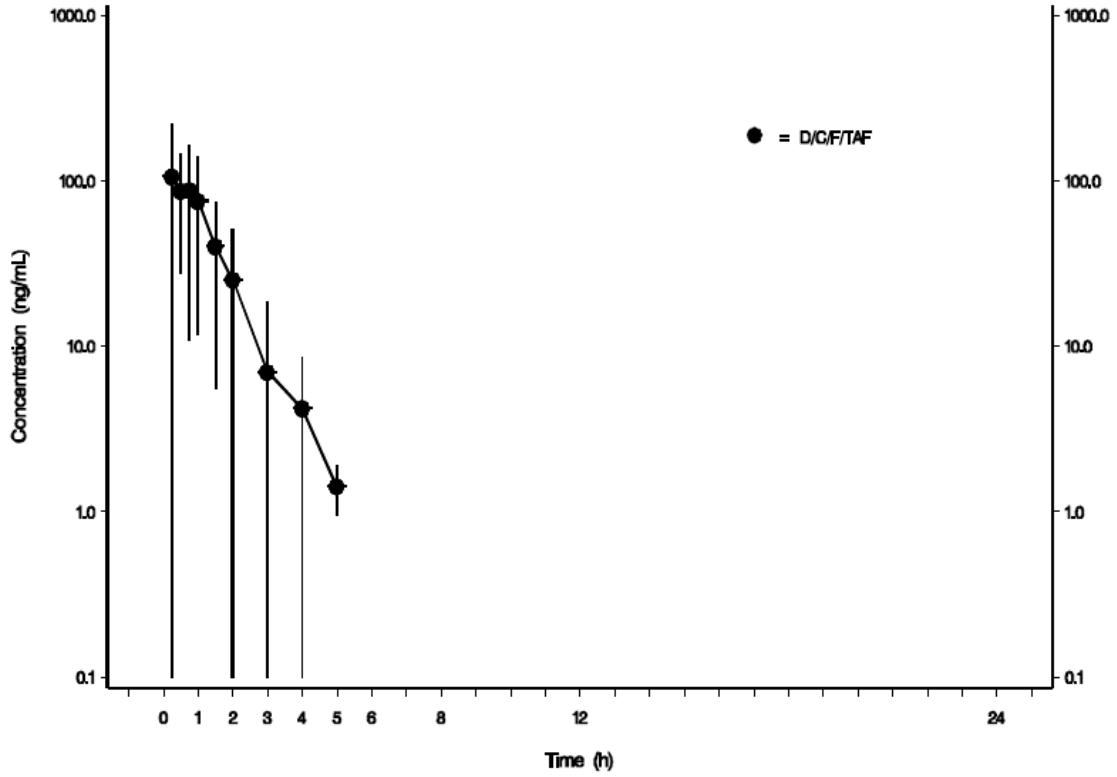
a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and race strata.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 48 window was between Day 308 and 337 (inclusive).
d 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.

Pharmacokinetics

TAF, TFV, and TFV-DP PK data for both treatment arms are shown below. DRV, COBI, and FTC PK data are shown below for PK substudy subjects in the D/C/F/TAF arm.

TAF

Figure 10. Mean (SD) TAF plasma concentration-time profiles.



Plasma concentrations below the limit of quantitation (BLQ) were treated as 0 for summary purposes and were excluded from log-normalized data.
For each subject in the PK substudy, intensive PK was done at one time at Weeks 4 or 8.

Table 11. TAF PK parameters.

	AUC_{last} (ng·h/mL) Mean (%CV) (N = 21)	C_{max} (ng/mL) Mean (%CV) (N = 21)	T_{max} (h) Median (Q1, Q3) (N = 21)	$t_{1/2}$ (h) Median (Q1, Q3) (N = 21)
TAF	130.5 (34.1)	163.0 (51.9)	0.53 (0.50, 1.00)	0.45 (0.38, 0.66)

TFV

Figure 11. Mean (SD) TFV plasma concentration-time profiles.

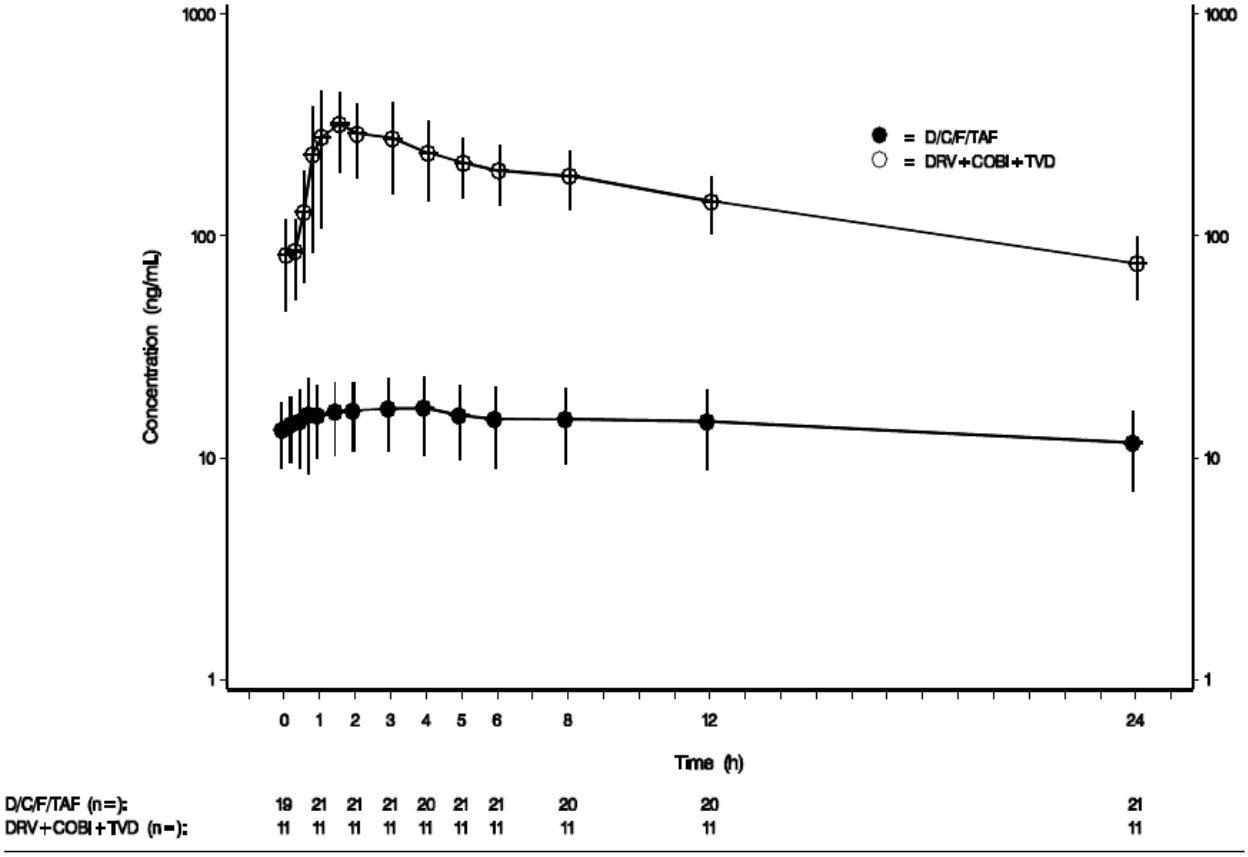


Table 12. TFV PK parameters.

Parameter	Units	D/C/F/TAF (N = 21)	DRV+COBI+TVD (N = 11)
AUC_{tau}	ng·h/mL	339.0 (37.1)	3737.0 (26.8)
C_{max}	ng/mL	18.8 (37.6)	413.2 (28.3)
T_{max} [a]	h	2.00 (1.50, 3.13)	1.00 (1.00, 3.00)
C_{tau}	ng/mL	11.7 (39.3)	75.4 (30.9)
$t_{½}$ [a]	h	43.82 (32.03, 59.23)	11.85 (11.35, 16.15)

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

Table 13. Statistical comparison of TFV PK parameters.

TFV PK Parameter	GLSM by Treatment		GLSM Ratio (%)	90% CI (%)
	D/C/F/TAF (N = 21)	DRV+COBI+TVD (N = 11)		
AUC_{tau} (ng·h/mL)	312.95	3620.60	8.64	(6.99, 10.68)
C_{tau} (ng/mL)	10.68	72.20	14.79	(11.67, 18.75)
C_{max} (ng/mL)	17.44	397.70	4.39	(3.53, 5.45)

GLSM = geometric least square means

TFV-DP

Table 14. Median (Q1, Q3) PBMC TFV-DP concentration-time profiles.

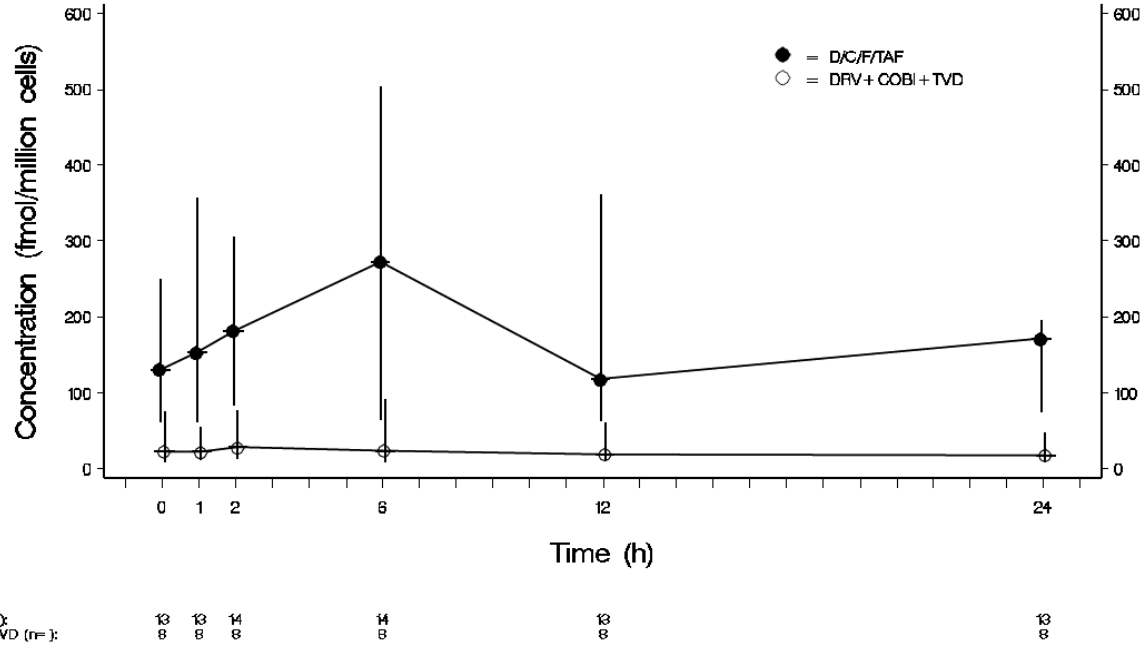


Table 15. Statistical comparison of TFV-DP PK parameters.

TFV-DP PK Parameter	GLSM by Treatment		GLSM Ratio (%)	90% CI (%)
	D/C/F/TAF (N = 14)	DRV+COBI+TVD (N = 8)		
AUC_{tau} (µM·h)	17.12	2.62	652.09	(268.28, 1585.00)

GLSM = geometric least square means

DRV, COBI, and FTC

Figure 12. Mean (SD) DRV plasma concentration-time profiles.

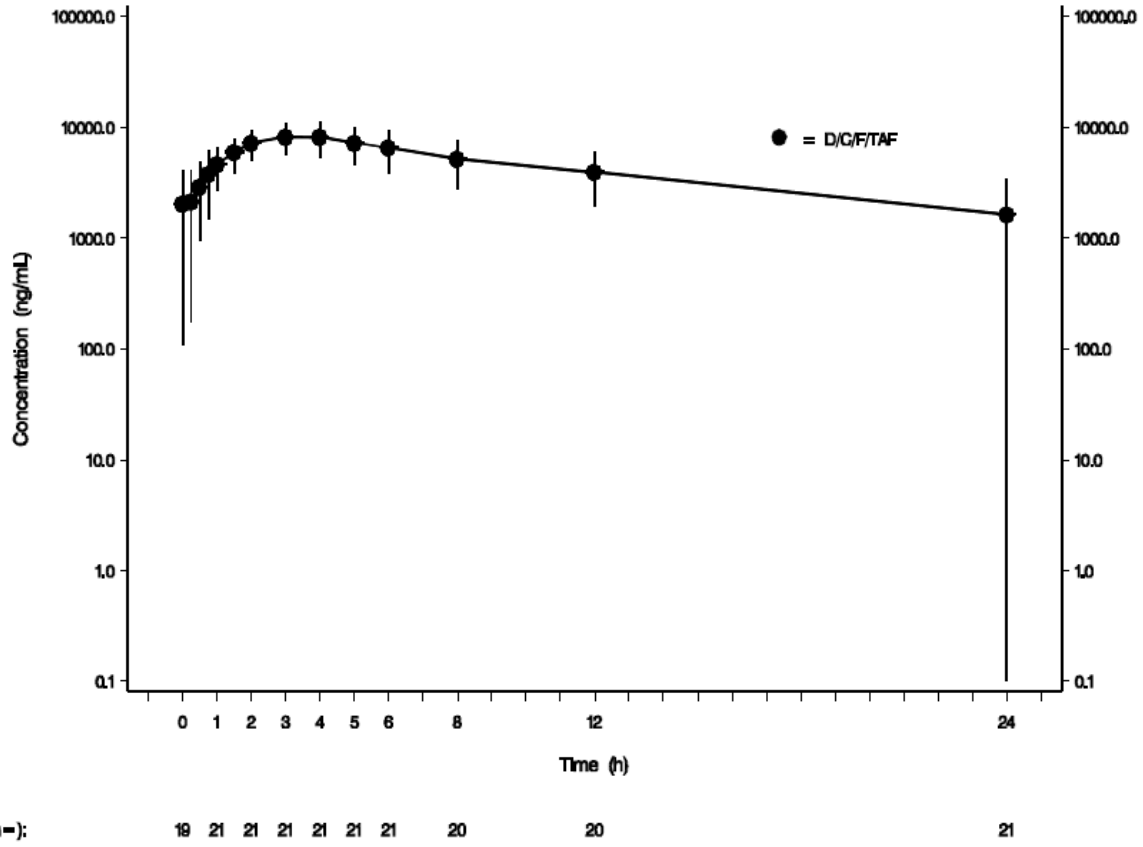


Figure 13. Mean (SD) COBI plasma concentration-time profiles.

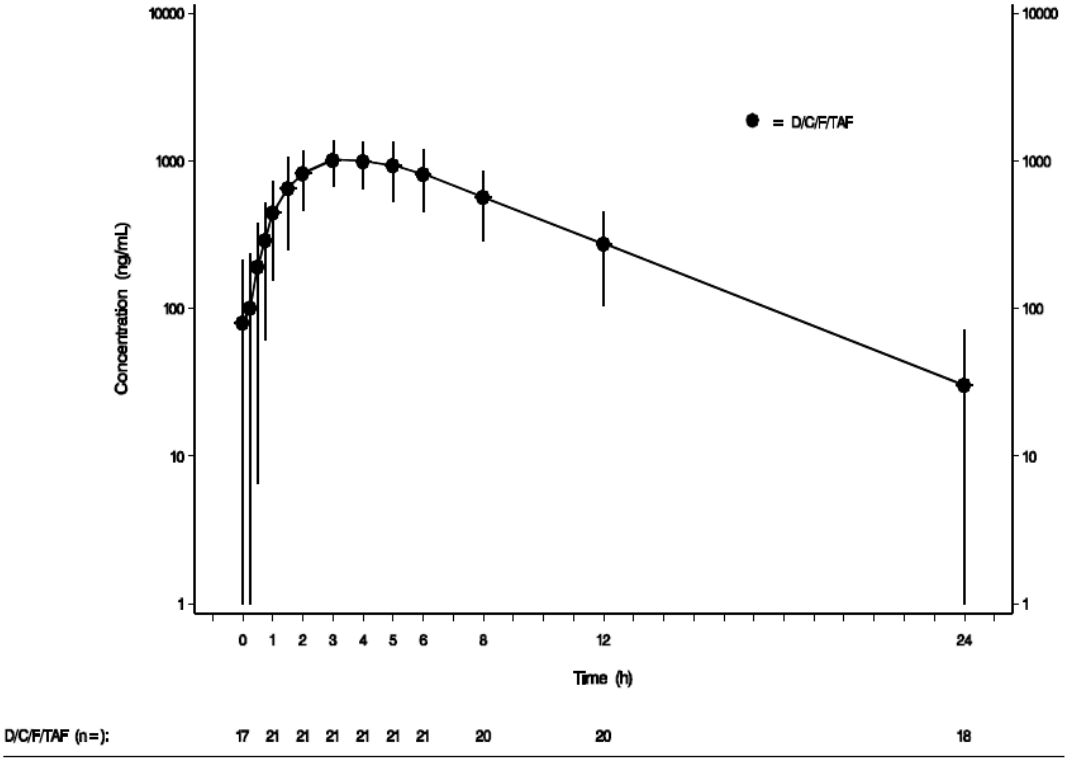


Figure 14. Mean (SD) FTC plasma concentration-time profiles.

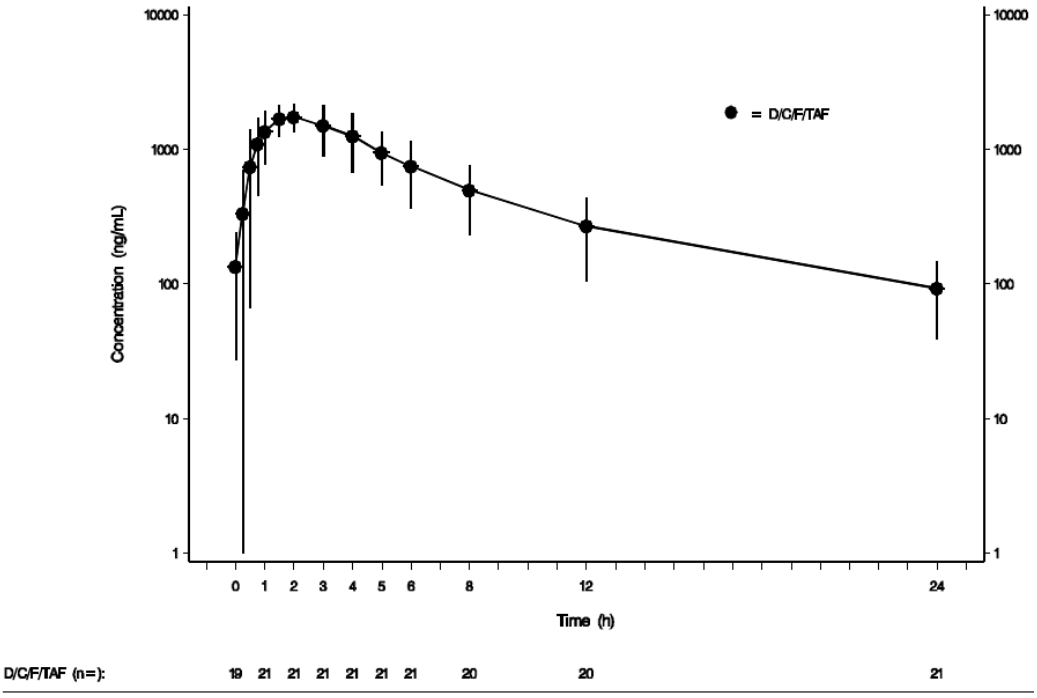


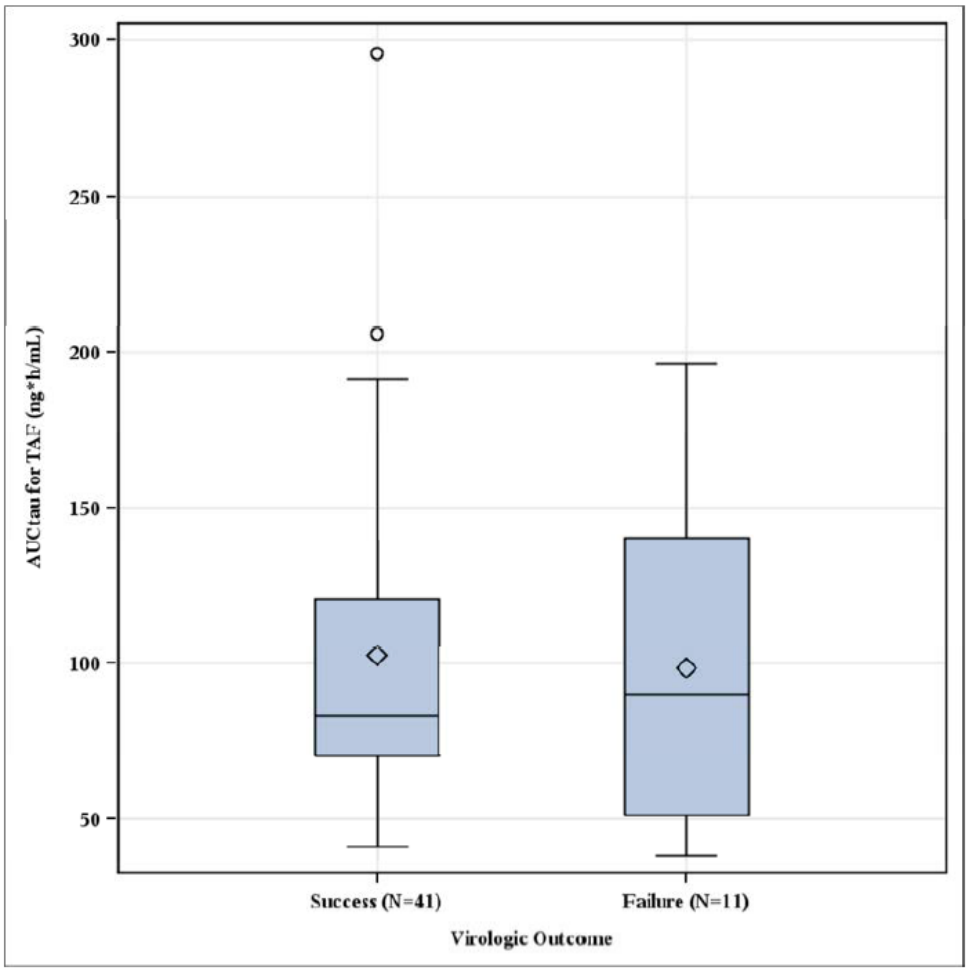
Table 16. DRV, COBI, and FTC PK parameters.

	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)	$T_{½}$ (h) Median (Q1, Q3)
DRV	99301.8 (45.3)	8826.2 (33.3)	1651.0 (108.0)	3.00 (2.00, 4.00)	9.42 (6.31, 13.87)
COBI	8744.5 (43.9)	1128.7 (35.3)	30.5 (135.1).	3.03 (3.00, 4.00)	3.16 (2.77, 3.70)
FTC	11918.0 (35.9)	2056.4 (25.3)	93.1 (58.3)	1.52 (1.50, 2.00)	7.51 (6.40, 8.79)

Exposure-response

In the D/C/F/TAF arm, Cmax (not shown) and AUC of TAF, DRV, FTC, and COBI did not appear to differ between those who experienced virologic success and virologic failure (Figure 15, Figure 16, Figure 17, Figure 18).

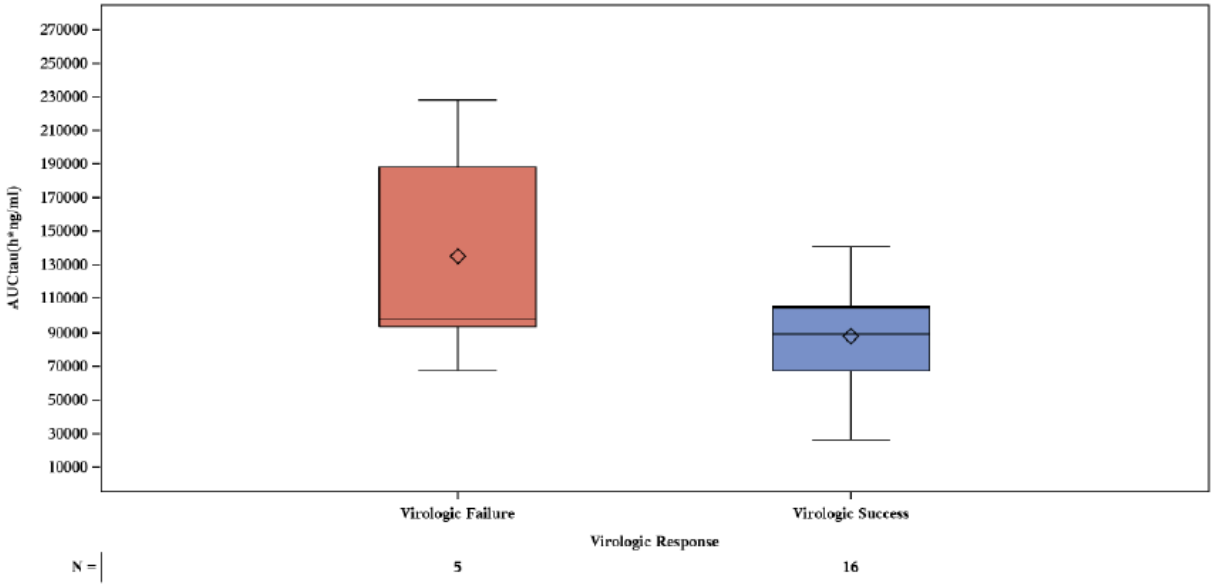
Figure 15. TAF AUC in the D/C/F/TAF arm by virologic outcome.



The TAF PK/PD analysis set includes all subjects who were randomized and had at least one dose of D/C/F/TAF and who had at least one nonmissing TAF PK parameter (ie AUC_{tau} or C_{max}) estimated from the population PK analysis

Source: NDA 208215, SDN 11.

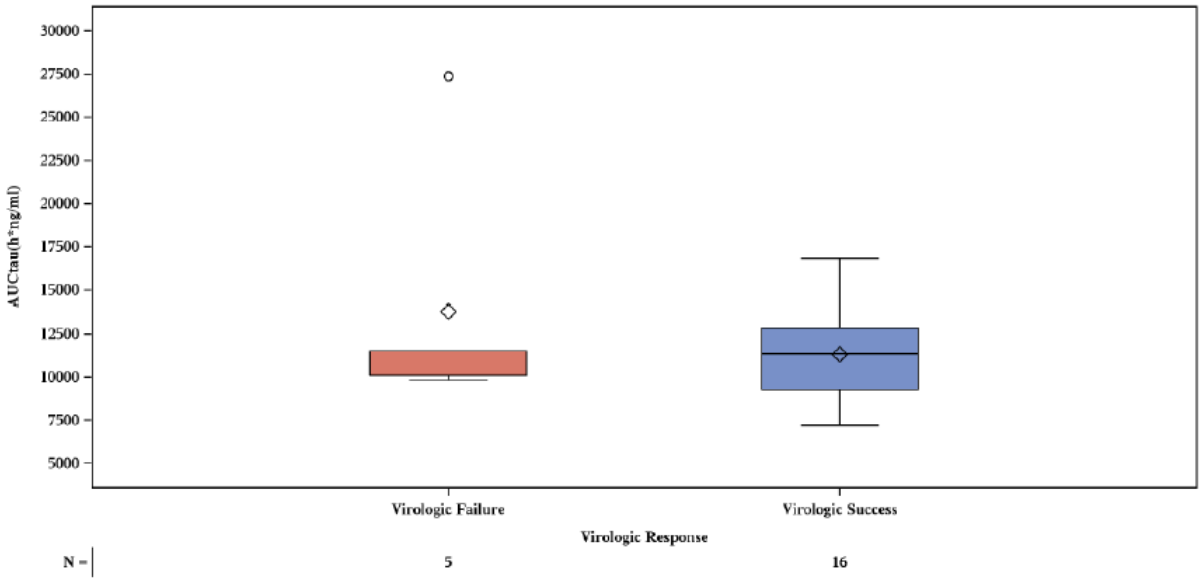
Figure 16. DRV AUC in the D/C/F/TAF arm by virologic outcome.



Intensive PK data is presented for subjects who were treated with D/C/F/TAF treatment GS-US-299-0102.
Boxplot whiskers include data within 1.5 times the interquartile range above and below the box. Circle = outlier; line inside box = median

Source: NDA 208215, SDN 11.

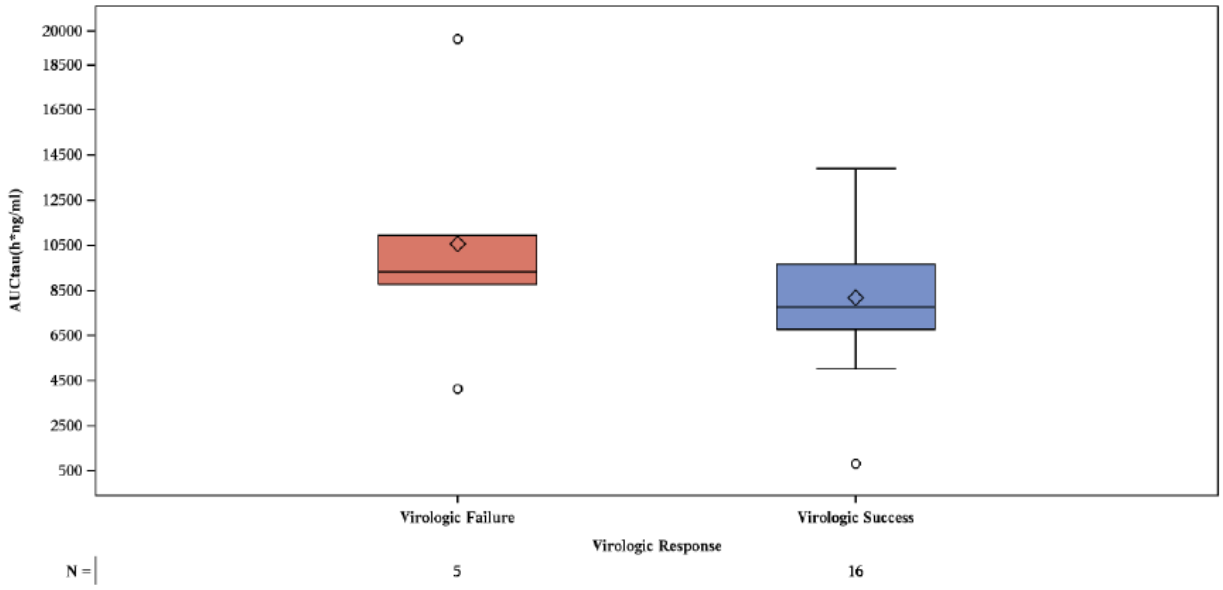
Figure 17. FTC AUC in the D/C/F/TAF arm by virologic outcome.



Intensive PK data is presented for subjects who were treated with D/C/F/TAF treatment GS-US-299-0102
Boxplot whiskers include data within 1.5 times the interquartile range above and below the box. Circle = outlier; line inside box = median

Source: NDA 208215, SDN 11.

Figure 18. COBI AUC in the D/C/F/TAF arm by virologic outcome.



Intensive PK data is presented for subjects who were treated with D/C/F/TAF treatment GS-US-299-0102
Boxplot whiskers include data within 1.5 times the interquartile range above and below the box. Circle = outlier; line inside box = median
Source: NDA 208215, SDN 11.

Safety

AEs are summarized below (Table 17). The most common AEs in the D/C/F/TAF group were diarrhea (21%), upper respiratory tract infection (16%), and fatigue (14%). The most common AEs in the DRV + COBI + TVD group were diarrhea (26%), fatigue (18%), and upper respiratory tract infection (14%). Decreases in hip or spine bone mineral density and $eGFR_{CG}$ were reported to be smaller in the D/C/F/TAF group relative to control. Increases from baseline in lipid parameters were greater in the D/C/F/TAF arm relative to control.

Table 17. Summary of AEs.

Subjects Experiencing Any	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)
Treatment-Emergent AE	95 (92.2%)	47 (94.0%)
Any Grade 2, 3, or 4 Treatment-Emergent AE	57 (55.3%)	24 (48.0%)
Any Grade 3 or 4 Treatment-Emergent AE	7 (6.8%)	4 (8.0%)
Any Treatment-Emergent Study Drug–Related AE	43 (41.7%)	19 (38.0%)
Any Grade 2, 3, or 4 Treatment-Emergent Study Drug–Related AE	10 (9.7%)	3 (6.0%)
Any Grade 3 or 4 Treatment-Emergent Study Drug–Related AE	1 (1.0%)	1 (2.0%)
Any Treatment-Emergent SAE	5 (4.9%)	2 (4.0%)
Any Treatment-Emergent Study Drug–Related SAE	1 (1.0%)	0
Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	2 (1.9%)	2 (4.0%)
Treatment-Emergent Death	0	0

DISCUSSION/REVIEWER'S COMMENTS

Concentration determination for all analytes except TFV-DP utilized validated LC/MS/MS methods. Samples for all analytes except TFV-DP were determined within the duration of stability. TFV-DP PK data from this data is not acceptable. Few subjects took interacting concomitant medications and thus drug interactions are unlikely to have affected the results of this study. We did not critically review the adherence data that was reported by the sponsor. DRV, COBI, and FTC PK parameters were similar to historical data (mean DRV AUCtau of ~99000 ng*h/mL in this study versus ~93000 h*ng/mL in the DRV label; mean COBI AUCtau of ~8700 ng*h/mL in this study versus ~8500 ng*h/mL in the GENVOYA label; mean FTC AUCtau of ~11900 ng*h/mL in this study versus ~11700 ng*h/mL in the GENVOYA label).

TAF AUCs were lower in this study compared to historical data (mean TAF AUClast of 131 ng*h/mL in this study versus 227 ng*h/mL for GENVOYA in a phase 2 trial) (NDA 207561 Clinical Pharmacology review dated 7/10/2015). However, several lines of pharmacologic evidence suggest TAF exposures were adequate: 1) A TAF AUC of 130 ng*h/mL is predicted to be efficacious based on a TAF monotherapy study (Figure 3); 2) there was no relationship between TAF exposure and virologic outcome in this study; and 3) in study 311-1089, TFV-DP concentrations were higher in subjects administered DRV/r + F/TAF (10 mg TAF) versus DRV/r + FTC/TDF (Table 5). In addition, the efficacy rate in this study was not statistically different from the guideline-recommended DRV + COBI + TVD active control arm in this study, where the only difference between the treatment arms was TAF versus TDF (https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Recommendations.pdf). Also, the median (range) efficacy rate for other studies in treatment-naïve adults using DRV-based regimens is 84% (78-87, n=7), which is nearly within the range of both treatment arms in this small study (NDA 208215, SDN 11).

LABEL RECOMMENDATIONS

(b) (4)

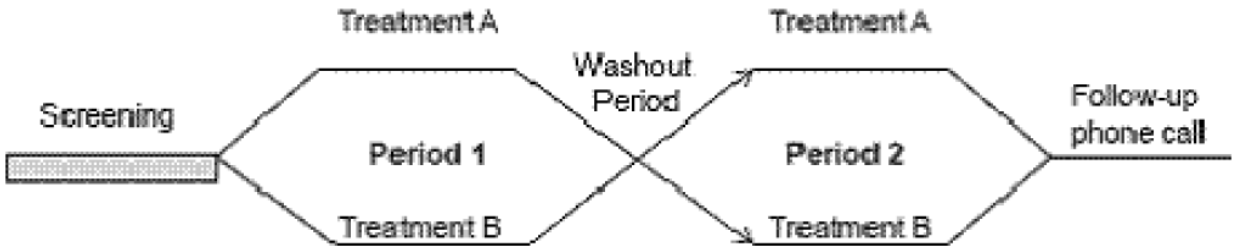
3.3 GS-US-311-1386 – Effect of food on F/TAF

A Phase 1, Randomized, Open-Label Study to Determine the Effect of Food on the Pharmacokinetics of Tenofovir Alafenamide When Administered as Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Tablet in Healthy Volunteers	
Study Period	6/2/2014 – 7/30/2014
Link	\\cdsesub1\evsprod\nda208215\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-1386\report-body.pdf

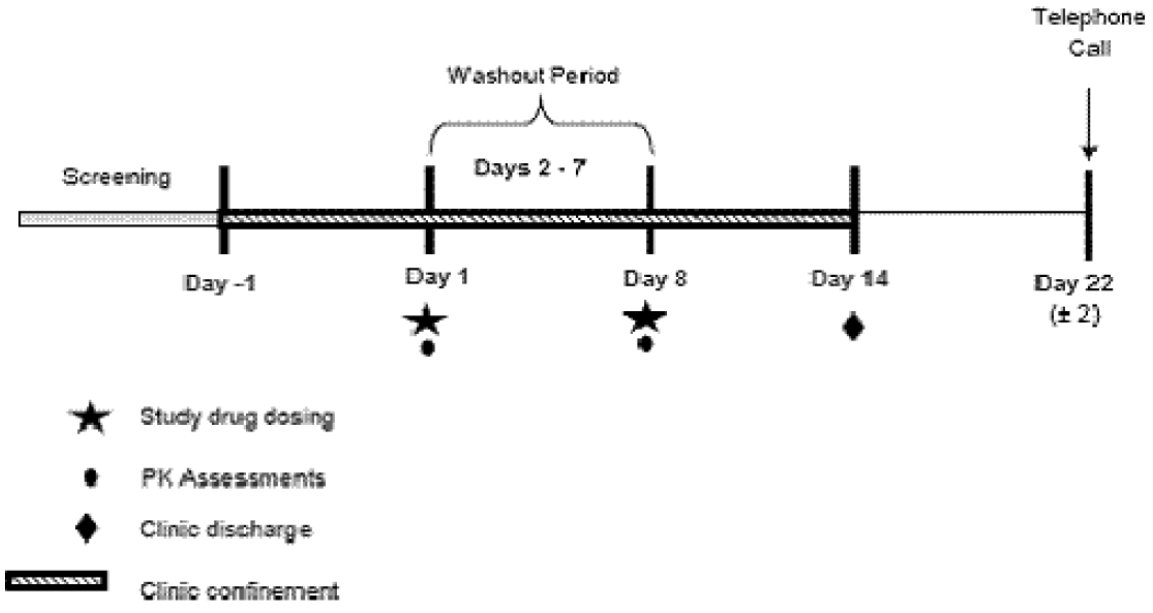
STUDY DESIGN

Randomized, open-label, single-dose, 2-treatment, 2-period, crossover study.

Study schematic



Study design



Treatments

Treatment A: Single dose F/TAF orally under fasted conditions in the morning.

Treatment B: Single dose F/TAF orally under fed conditions in the morning. The meal was a standard high-fat breakfast (800 kcal with 50% of calories from fat).	
Population	Healthy volunteers
Study Rationale	Determine the effect of food on the PK of TAF and FTC
Dose Selection Rationale	Same dose as proposed for commercialization
Formulation	200/25 mg tablet (lot # CR1305B2)
Interfering Substances Excluded	Any prescription and over-the-counter medications except acetaminophen, ibuprofen, hormonal contraceptives, and topical hydrocortisone. Subject to sponsor approval, other medications can be used to treat a short term minor illness.
Sampling Times	Day 1 and 8: 0 (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours postdose.
Bioanalytical methods	• FTC and TAF were measured using LC/MS/MS • Full method validation assessments were conducted for each analyte • FTC and TAF were reported to have been measured within their respective durations of stability

RESULTS

Protocol deviations

No "important" protocol deviations were reported.

Study population

40 subjects were enrolled (Table 18); two subjects discontinued study drug and one subject withdrew consent after completing study drug but before completing the study. 37 subjects completed the study.

Table 18. Study demographics.

Characteristic	Overall (N = 40)
Age at Day -1 (years)	
N	40
Mean (SD)	29 (6.2)
Median	28
Q1, Q3	24, 33
Min, Max	20, 45
Sex (n, %)	
Male	24 (60.0%)
Female	16 (40.0%)
Race (n, %)	
Asian	3 (7.5%)
Black	8 (20.0%)
White	29 (72.5%)
Ethnicity (n, %)	
Hispanic or Latino	1 (2.5%)
Not Hispanic or Latino	39 (97.5%)
Body Mass Index (kg/m^2)	
N	40
Mean (SD)	25.9 (2.77)
Median	26.5
Q1, Q3	24.1, 27.8
Min, Max	19.7, 31.9
Estimated Glomerular Filtration Rate by Cockcroft-Gault Formula (mL/min)	
N	40
Mean (SD)	122.1 (21.46)
Median	121.8
Q1, Q3	108.5, 132.5
Min, Max	85.4, 169.1

Concomitant medications

Several subjects used allowed medications including over-the-counter painkillers and hormonal contraceptives. Two subjects used concomitant medications that required approval by the sponsor as they were not among those listed as allowed. One subject used calamine lotion for one day (day -24 relative to start of study drug) and one subject ended Adderall XR on day -36.

Pharmacokinetics

TAF

Relative to the fasted state, in the fed state mean TAF AUC was increased 75% (range: +19%, +160%) and mean Cmax was decreased 15% (range: -25%, -5%) (Figure 19, Table 19, Table 20).

Figure 19. TAF plasma concentration-time profiles.

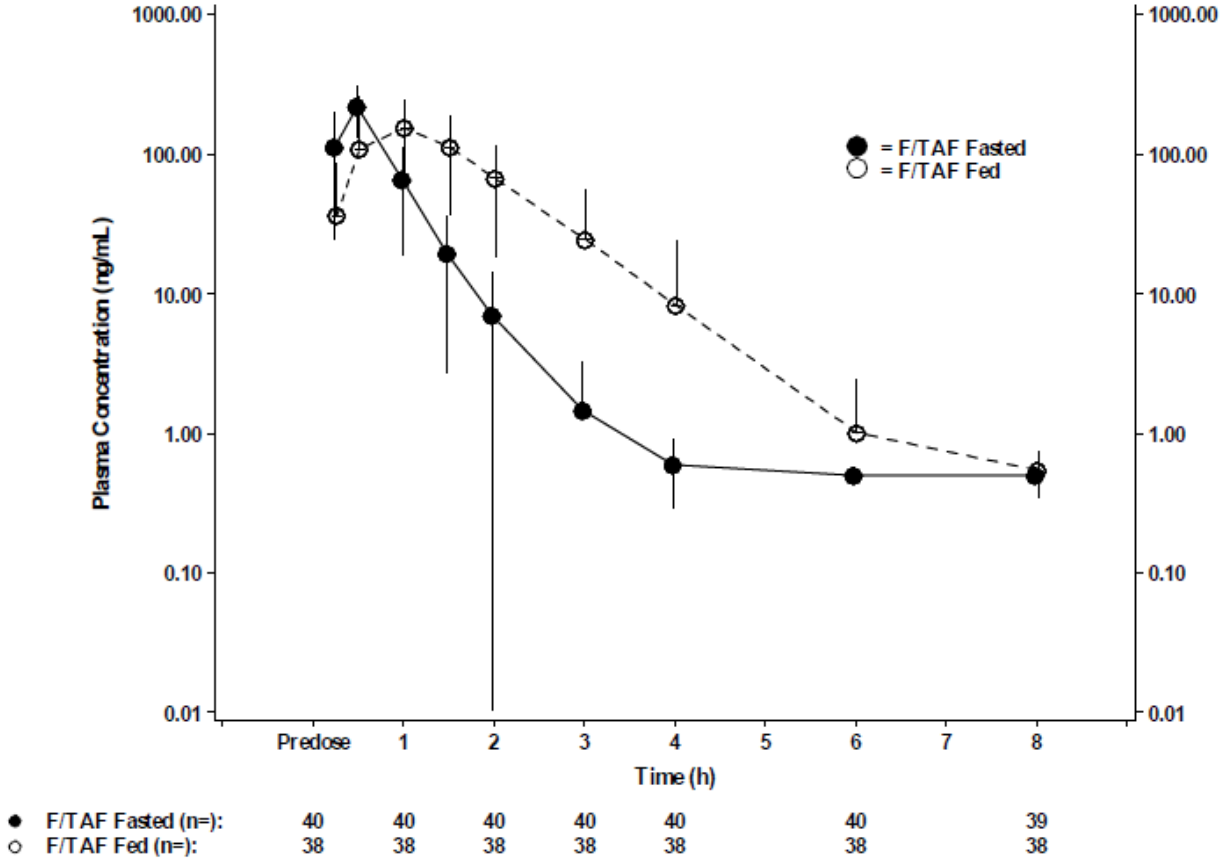


Table 19. TAF PK parameters.

TAF PK Parameter[a]	Treatment A: F/TAF (Fasted) (N = 40)	Treatment B: F/TAF (Fed) (N = 38)[b]
AUC_{last} (h•ng/mL)	145.8 (42.9)	254.5 (42.6)
AUC_{inf} (h•ng/mL)	147.0 (42.5)	266.8 (42.0)[c]
AUC_{exp} (%)	1.03 (76.9)	1.30 (141.6)[c]
C_{max} (ng/mL)	230.1 (36.2)	207.2 (63.2)
C_{last} (ng/mL)	2.65 (47.7)	3.69 (77.1)
$t_{½}$ (h)	0.30 (0.26, 0.41)	0.46 (0.39, 0.56)[c]
T_{last} (h)	2.00 (2.00, 3.00)	4.00 (4.00, 4.00)
T_{max} (h)	0.50 (0.50, 0.50)	1.00 (0.52, 1.50)

a Data are mean (%CV), except $t_{½}$, T_{last}, and T_{max} that are reported as median (Q1, Q3).
b Subjects 1020 and 1037 did not have TAF PK concentrations with Treatment B.
c N = 33; PK parameters AUC_{inf}, λ_z, $t_{½}$, AUC_{exp}, V_z/F, and CL/F could not be calculated in 5 subjects for analyte TAF with Treatment B.

Table 20. Statistical comparison of TAF PK parameters between study treatments.

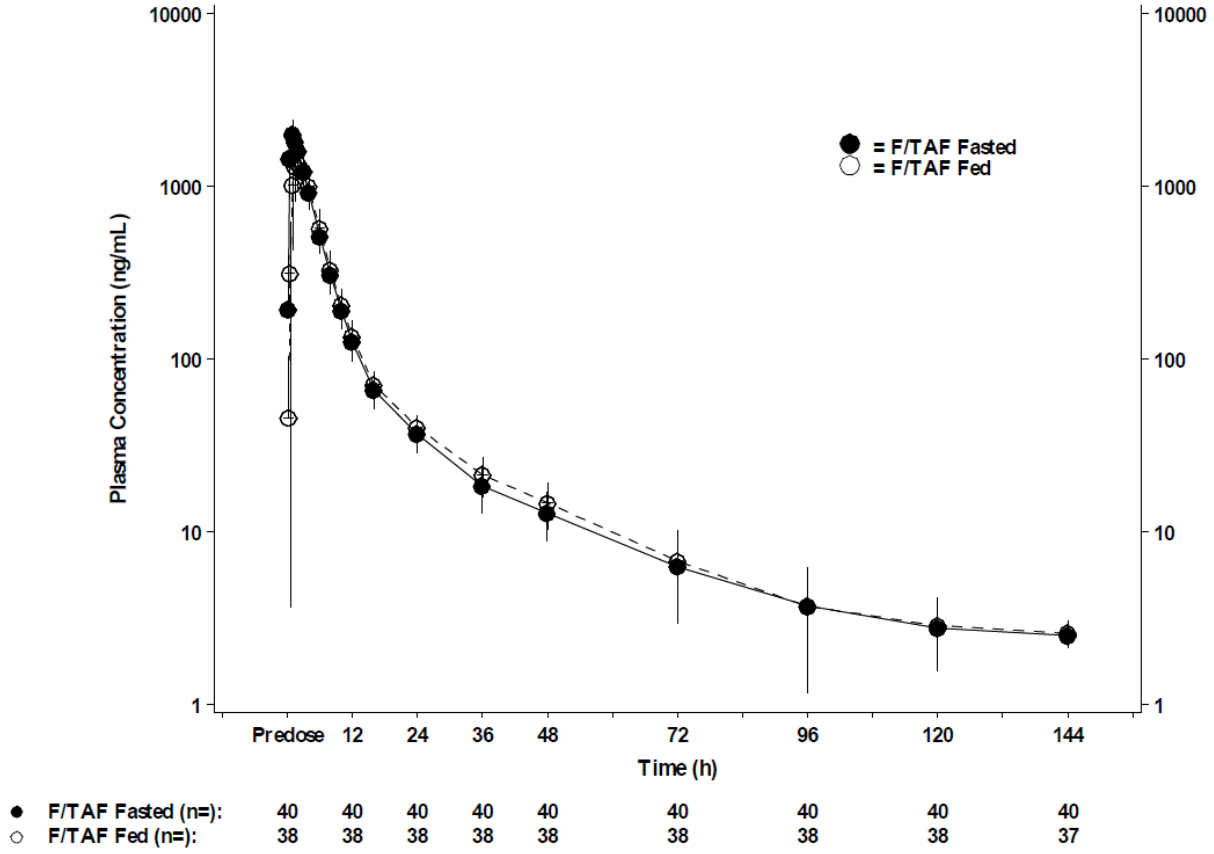
TAF PK Parameter (Test/Reference)	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	Test Treatment B: (F/TAF Fed) (N = 38)	Reference Treatment A: (F/TAF Fasted) (N = 40)		
AUC_{inf} (h•ng/mL)	234.86[a]	133.91	175.38	(163.93, 187.63)
AUC_{last} (h•ng/mL)	234.02	132.53	176.57	(166.19, 187.60)
C_{max} (ng/mL)	180.00	212.94	84.53	(74.92, 95.37)

a N = 33; AUC_{inf} could not be calculated in 5 subjects for analyte TAF with Treatment B.

FTC

Relative to the fasted state, in the fed state mean FTC AUC was decreased 9% (range: -11%, -7%) and mean Cmax decreased 27% (range: -50%, +19%) (Figure 20, Table 21, Table 22).

Figure 20. FTC plasma concentration-time profiles.



BLQ plasma concentrations were treated as 0 at predose and half the LLQ for postdose time points.
LLQ for FTC is 5 ng/mL.
FTC plasma concentrations were analyzed at time points from 0 (predose) to 144 hours postdose.

Table 21. FTC PK parameters.

FTC PK Parameter[a]	Treatment A: F/TAF (Fasted) (N = 40)	Treatment B: F/TAF (Fed) (N = 38)[b]
AUC_{last} (h•ng/mL)	9876.4 (15.6)	8964.4 (15.6)
AUC_{inf} (h•ng/mL)	10,122.6 (15.5)	9181.9 (15.6)
AUC_{exp} (%)	2.43 (54.8)	2.38 (38.1)
C_{max} (ng/mL)	2097.8 (19.1)	1551.2 (22.6)
C_{last} (ng/mL)	7.17 (26.2)	7.01 (27.1)
$t_{½}$ (h)	23.83 (14.42, 30.97)	20.57 (17.58, 27.03)
T_{last} (h)	72.00 (48.00, 96.00)	72.00 (72.00, 72.00)
T_{max} (h)	1.00 (1.00, 1.01)	2.00 (1.50, 2.00)

a Data are mean (%CV), except $t_{½}$, T_{last}, and T_{max} that are reported as median (Q1, Q3).
b Subjects 1020 and 1037 did not have FTC PK concentrations with Treatment B.

Table 22. Statistical comparison of FTC PK parameters between study treatments.

FTC PK Parameter (Test/Reference)	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	Test Treatment B: (F/TAF Fed) (N = 38)	Reference Treatment A: (F/TAF Fasted) (N = 40)		
AUC_{inf} (h•ng/mL)	9114.01	10,002.77	91.11	(88.84, 93.44)
AUC_{last} (h•ng/mL)	8901.52	9758.42	91.22	(88.90, 93.60)
C_{max} (ng/mL)	1513.12	2058.61	73.50	(69.26, 78.00)

Safety

The most common AEs in both the fed and fasted groups were nausea and headache. No deaths were reported. Two subjects discontinued study drug, one due to an AE (neutropenia in subject 4534-1037 considered related to study drug) and one due to pregnancy (subject 4534-1020 who subsequently had an SAE of spontaneous abortion considered related to study drug). Exposures were less than the study mean for subject 4534-1037 (Table 23).

Table 23. PK in subject 4534-1037 who discontinued due to neutropenia.

Subject	Analyte	PK parameter	Treatment	Exposure in subject	Mean (range) in study
4534-1037	TAF	Cmax (ng/mL)	Fasted	174	230 (67, 465)
4534-1037	TAF	AUC (ng*h/mL)	Fasted	115	147 (40, 311)
4534-1037	FTC	Cmax (ng/mL)	Fasted	1460	2098 (1310, 2950)
4534-1037	FTC	AUC (ng*h/mL)	Fasted	8613	10114 (6806, 13425)

Source: prepared by reviewer.

REVIEWER'S COMMENTS

The washout period was sufficient as TAF and FTC predose concentrations were all below the limit of quantification. One subject used a disallowed medication (Adderall on day -36) and thus use of concomitant medications did not affect the study. TAF Cmax and AUC were variable in the fed state (CV = ~40%); TAF Cmax variability (CV%) increased to 63% in the fed state while AUC variability was unchanged. FTC Cmax and AUC variability was low (CV% = 15-20%) and did not change between the fasted and fed states.

The effect of food on TAF exposure is larger for F/TAF versus E/C/F/TAF. As both products are immediate release formulations with rapid dissolution and manufactured using standard excipients, the difference in food effect is likely not due to formulation differences. It is hypothesized that TAF bioavailability (estimated to be ~40% in humans) is significantly increased when coadministered with a Pgp inhibitor such as COBI in E/C/F/TAF, thus food does not lead to a further substantial increase in TAF bioavailability (NDA 208215, SN 0012). Whereas in the case of F/TAF alone, no Pgp inhibitor is present, and thus food leads to a substantial increase in bioavailability.

The sponsor's proposed labeling states that F/TAF should be administered with or without food. As there is a larger TAF food effect for F/TAF versus E/C/F/TAF, it is expected that TAF exposures from F/TAF would be lower in the fasted state versus TAF exposures from E/C/F/TAF in the fasted state. However, pharmacologic evidence suggests TAF exposures from F/TAF are adequate in the fasted state: 1) the lower TAF exposures from F/TAF in the fasted state are predicted to be efficacious based on a TAF monotherapy study (Figure 3); in study 311-1089, F/TAF- and FTC/TDF-containing regimens were administered without regard to food, and regardless of 3rd agent, TFV-DP concentrations were higher in the TAF-containing arm relative to the TDF-containing arm (Table 5).

LABEL RECOMMENDATIONS

We agree with the sponsor's labeling recommendation to administered F/TAF with or without food.

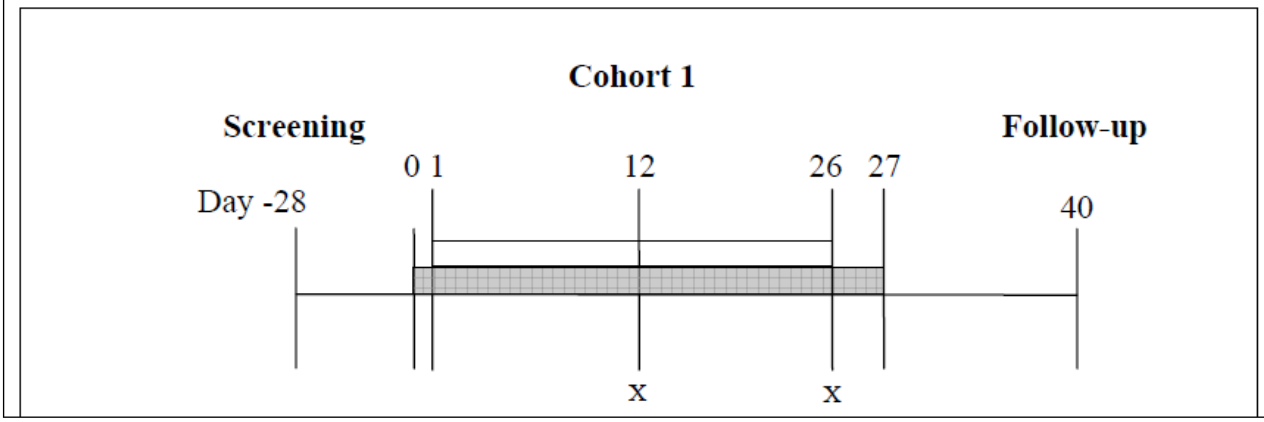
3.4 GS-US-311-0101 – Drug interaction study between F/TAF and EFV or DRV/c

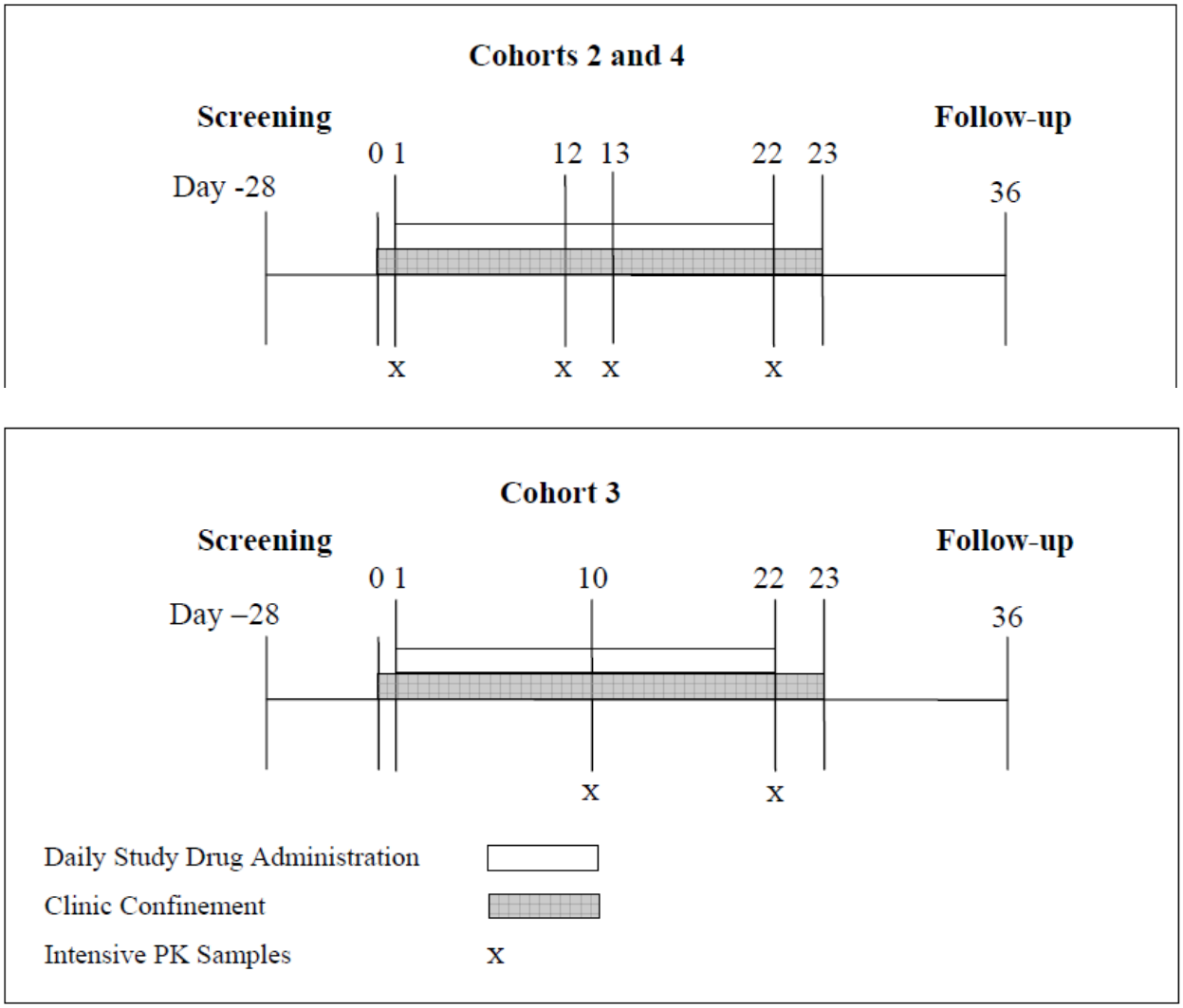
A Phase 1 Study Evaluating the Drug Interaction Potential Between Once-Daily FTC/GS-7340 Fixed Dose Combination and Efavirenz or Cobicistat-Boosted Darunavir	
Study Period	6/6/2011 – 8/31/2011
Link	\\cdsesub1\evsprod\nda207561\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-0101\report-body.pdf

STUDY DESIGN

Open-label, crossover study.

Cohort 1	**Day 1 to 12** Treatment A: FDC oral tablet containing FTC 200 mg and GS-7340 40 mg once daily in the morning, fasted	**Day 13 to 26** Treatment B: FDC oral tablet containing FTC 200 mg and GS-7340 40 mg plus EFV 600-mg oral tablet once daily in the morning, fasted
Cohort 2	**Day 1 to 12** Treatment C: FDC oral tablet containing FTC 200 mg and GS-7340 25 mg once daily in the morning, fed	**Day 13 to 22** Treatment D: FDC oral tablet containing FTC 200 mg and GS-7340 25 mg plus DRV/co 2 × 400/1 × 150-mg oral tablets once daily in the morning, fed
Cohort 3	**Day 1 to 10** Treatment E: DRV/co 2 × 400/1 × 150-mg oral tablets once daily in the morning, fed	**Day 11 to 22** Treatment F: FDC oral tablet containing FTC 200 mg and GS-7340 25 mg plus DRV/co 2 × 400/1 × 150-mg oral tablets once daily in the morning, fed
Cohort 4	**Day 1 to 12** Treatment G: Oral tablet containing single-agent GS-7340 8 mg once daily in the morning, fed	**Day 13 to 22** 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 subjects
Study Rationale	Drug-drug interaction between TAF and EFV, DRV/c, and COBI
Dose Selection Rationale	One of the commercial doses were used (F/TAF 200/25 mg) in cohorts 2-3. The other doses used (F/TAF 200/40 mg and TAF 8 mg), in cohorts 1 and 4, were not among the commercial doses.
Formulation	F/TAF 200/25 mg tablets (lot # CR1106B1 F/TAF 200/40 mg tablets (lot # CR1107B1 TAF 8 mg (lot # CM1002B1)
Interfering Substances Excluded	Any prescription and over-the-counter medications except acetaminophen, ibuprofen, hormonal contraceptives, and topical hydrocortisone. Subject to sponsor approval, other medications can be used to treat a short term minor illness.

Sampling Times	**Cohort 1** Days 12 and 26: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours postdose. **Cohorts 2 and 4** 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. **Cohort 3** Days 10 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.

RESULTS

Bioanalytical methods

Concentrations of FTC, TAF, TFV, COBI, DRV, and EFV were determined using LC/MS/MS. Full validation assessments were conducted and samples were reported to have been measured within their respective durations of stability (Table 24).

Table 24. Summary of bioanalytical methods.

Parameter	GS-7340	TFV	COBI	FTC	EFV	DRV
Linear range (ng/mL)	1–1,000	0.3–300	5–2,500	5–3,000	5–5,000	20–10,000
Lower limit of quantitation (ng/mL)	1	0.3	5	5	5	20
Interassay precision range (%CV)[a]	1.8 to 7.3	2.7 to 8.4	3.9 to 8.3	1.4 to 5.7	5.0 to 11.4	2.8 to 10.6
Interassay accuracy range (%RE)[a]	–3.7 to 6.5	0.0 to 3.0	–0.3 to 9.7	–7.8 to 2.4	–3.3 to 0.5	–3.9 to –1.0
Stability in frozen matrix (days)	72 Days at –70°C	110 Days at –70°C	121 Days at –10°C to –30°C 365 Days at –60°C to –80°C	190 Days at –20°C and –70°C	127 Days at –20°C and –70°C	301 Days at –20°C and –70°C

a CV = coefficient of variation, RE = relative error

Protocol deviations

None reported.

Study population

50 subjects were enrolled; 48 completed the study and two terminated the study early due to AEs. Subject demographics are summarized below (Table 25).

Table 25. 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/m^2)					
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).

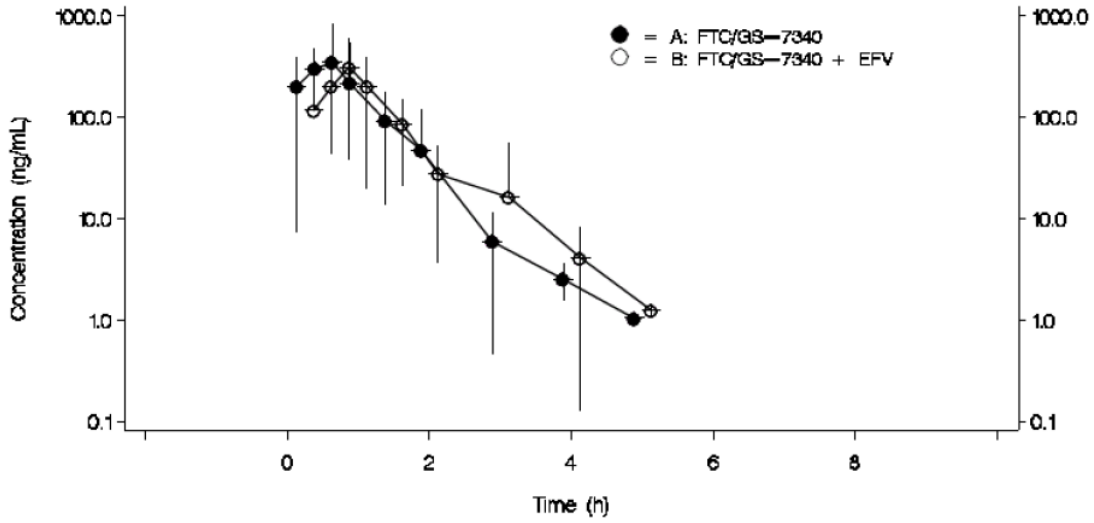
Concomitant medications

Use of concomitant medications not pre-specified as allowed included antibiotics (n=3 subjects), diphenhydramine (n=1), and omeprazole (n=1).

Pharmacokinetics

TAF

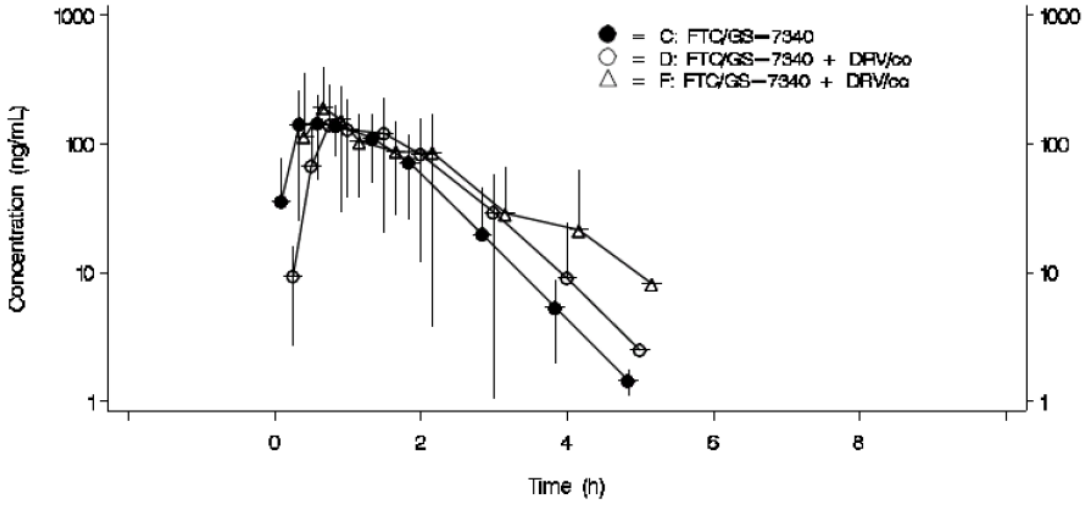
Figure 21. Cohort 1 multiple-dose mean (SD) TAF plasma concentrations.



Note: Plasma concentrations below limit of quantitation (BLQ) were treated as zero for summary purposes and were treated as missing for log-transformed data.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for GS-7340 and were excluded from summaries and paired comparisons.

Figure 22. Cohort 2-3 multiple-dose mean (SD) TAF plasma concentrations.

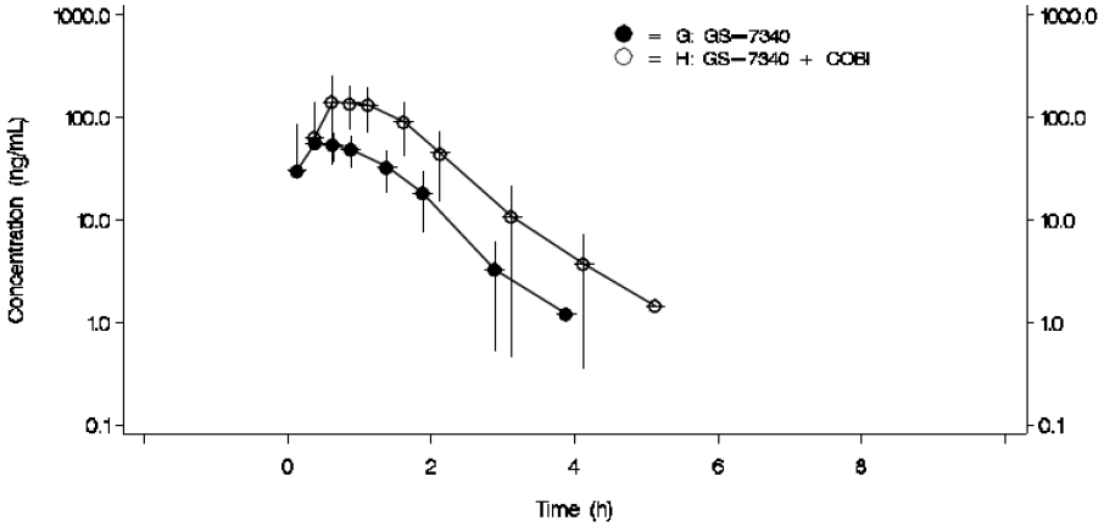


C: FTC/GS-7340 (n=):	11	4
D: FTC/GS-7340 + DRV/co (n=):	11	6
F: FTC/GS-7340 + DRV/co (n=):	14	5

Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for GS-7340 and were excluded from summaries and paired comparisons.

Figure 23. Cohort 4 multiple-dose mean (SD) TAF plasma concentrations.



G: GS-7340 (n=):	12	1
H: GS-7340 + COBI (n=):	12	8

Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for GS-7340 and were excluded from summaries and paired comparisons.

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Table 26. Cohort 1 TAF PK parameters.

GS-7340 PK Parameter	FTC/GS-7340 200/40 mg Cohort 1[a] Day 12 (N = 11)	FTC/GS-7340 200/40 mg + EFV Cohort 1[a] Day 26 (N = 11)
AUC_{last} (ng·h/mL), mean (%CV)	344.0 (60.9)	285.8 (46.4)
C_{max} (ng/mL), mean (%CV)	499.4 (82.8)	390.8 (62.2)
T_{max} (h), median (Q1, Q3)	0.50 (0.50, 0.75)	0.75 (0.50, 1.00)
$T_{1/2}$ (h), median (Q1, Q3)	0.32 (0.28, 0.39)	0.35 (0.31, 0.44)

a Cohort 1 was under fed conditions

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for GS-7340 and were excluded from summaries and paired comparisons.

Table 27. Cohort 2-3 TAF PK parameters.

GS-7340 PK Parameter	FTC/ GS-7340 200/25 mg Cohort 2[a] Day 1 (N = 11)	FTC/ GS-7340 200/25 mg Cohort 2[a] Day 12 (N = 11)	FTC/ GS-7340 200/25 mg + DRV/co Cohort 2[a] Day 13 (N = 11)	FTC/ GS-7340 200/25 mg + DRV/co Cohort 2[a] Day 22 (N = 11)	FTC/ GS-7340 200/25 mg + DRV/co Cohort 3[a] Day 22 (N = 14)
AUC_{last} (ng·h/mL), mean (%CV)	214.9 (51.6)	245.6 (41.9)	350.3 (47.1)	239.3 (41.0)	271.2 (38.6)
C_{max} (ng/mL), mean (%CV)	156.9 (45.1)	208.3 (40.2)	287.7 (45.9)	215.0 (59.2)	287.4 (72.6)
T_{max} (h), median (Q1, Q3)	1.00 (0.50, 1.00)	0.75 (0.50, 1.50)	1.00 (1.00, 2.00)	1.00 (0.75, 1.50)	0.75 (0.50, 2.00)
$T_{1/2}$ (h), median (Q1, Q3)	0.40 (0.33, 0.45)	0.36 (0.30, 0.44)	0.30 (0.28, 0.38)	0.35 (0.27, 0.56)	0.35[b] (0.30, 0.44)

a Cohorts 2 and 3 were under fed conditions

b N = 12

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for GS-7340 and were excluded from summaries and paired comparisons.

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

Table 28. Cohort 4 TAF PK parameters.

GS-7340 PK Parameter	GS-7340 8 mg Cohort 4[a] Day 1 (N = 12)	GS-7340 8 mg Cohort 4[a] Day 12 (N = 12)	GS-7340 + COBI 8/150 mg Cohort 4[a] Day 13 (N = 12)	GS-7340 + COBI 8/150 mg Cohort 4[a] Day 22 (N = 12)
AUC_{last} (ng·h/mL), mean (%CV)	64.7 (33.5)	81.2 (43.9)	188.3 (26.8)	213.3 (37.7)
C_{max} (ng/mL), mean (%CV)	49.9 (37.9)	71.0 (72.9)	141.5 (32.7)	189.9 (45.6)
T_{max} (h), median (Q1, Q3)	1.00 (0.5, 1.25)	0.75 (0.63, 0.88)	1.00 (0.75, 1.00)	0.75 (0.50, 1.00)
$T_{½}$ (h), median (Q1, Q3)	0.45[b] (0.34, 0.57)	0.42 (0.36, 0.47)	0.39 (0.35, 0.46)	0.39 (0.33, 0.48)

a Cohort 4 was under fed conditions
b N = 11

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for GS-7340 and were excluded from summaries and paired comparisons.

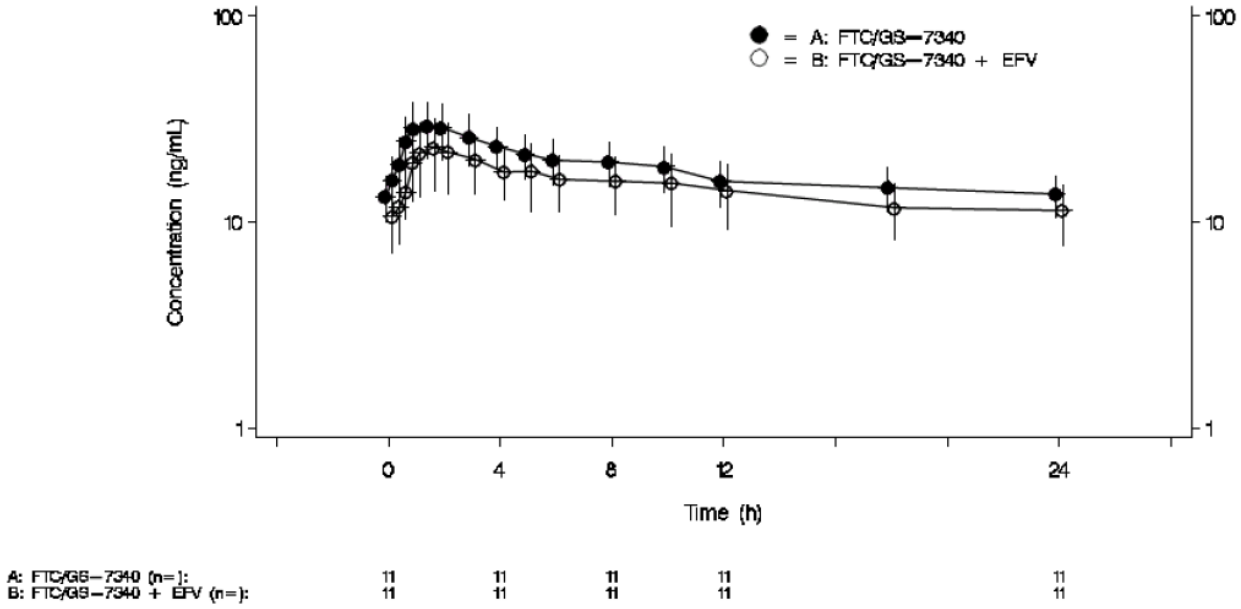
Table 29. Statistical comparison of TAF PK parameters.

GS-7340 PK Parameter	Geometric Least-Squares Means: Test Treatment	Geometric Least-Squares Means: Reference Treatment	Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
Cohort 1: FTC/GS-7340 200/40 mg + EFV (Test) vs FTC/GS-7340 200/40 mg (Reference), (N = 11)				
AUC_{last} (ng·h/mL)	264.79	309.54	85.54	(72.08, 101.52)
C_{max} (ng/mL)	328.21	421.21	77.92	(57.68, 105.25)
Cohort 2: FTC/GS-7340 200/25 + DRV/co (Test) vs FTC/GS-7340 200/25 mg (Reference), (N = 11)				
AUC_{last} (ng·h/mL)	221.95	227.30	97.64	(80.38, 118.62)
C_{max} (ng/mL)	181.36	194.11	93.43	(72.16, 120.98)
Cohort 4: 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)

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

TFV

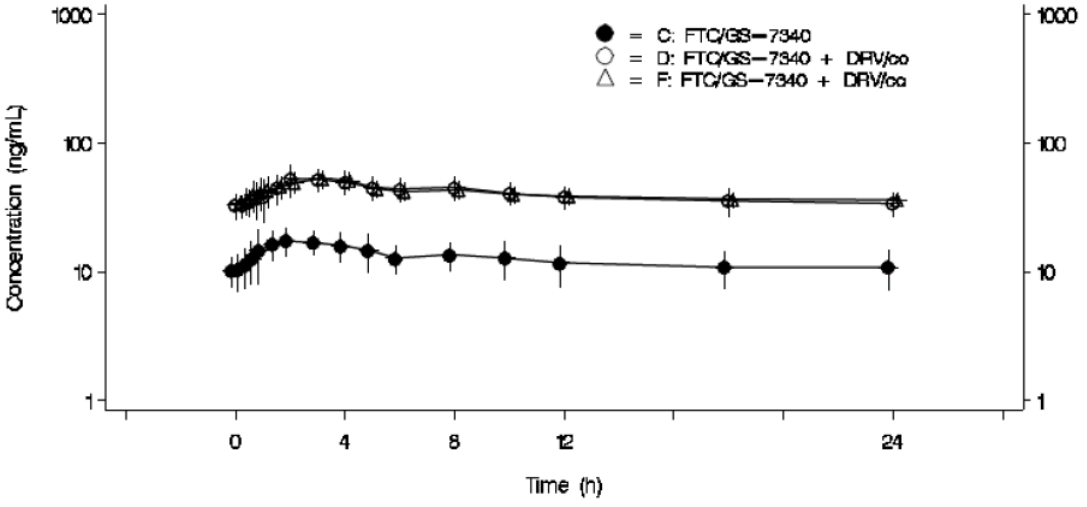
Figure 24. Cohort 1 multiple dose mean (SD) TFV plasma concentrations.



Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for TFV and were excluded from summaries and paired comparisons.

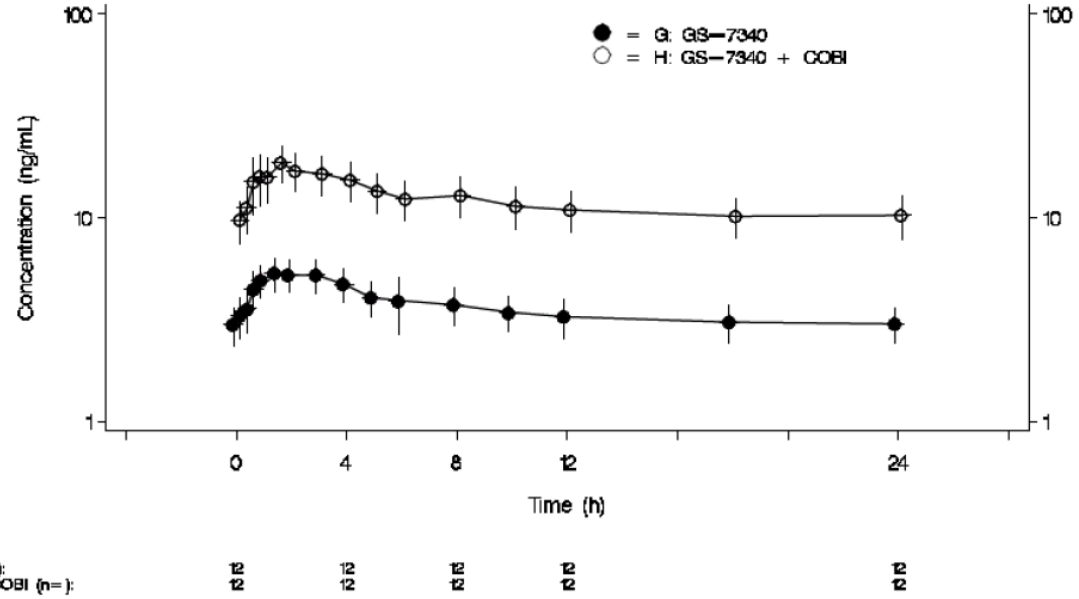
Figure 25. Cohort 2-3 multiple dose mean (SD) TFV plasma concentrations.



Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for TFV and were excluded from summaries and paired comparisons.

Figure 26. Cohort 4 multiple dose mean (SD) TFV plasma concentrations.



Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for TFV and were excluded from summaries and paired comparisons.

Table 30. Cohort 1 TFV PK parameters.

TFV PK Parameter	FTC/GS-7340 200/40 mg Cohort 1[a] Day 12 (N = 11)	FTC/GS-7340 200/40 mg + EFV Cohort 1[a] Day 26 (N = 11)
AUC_{tau} (ng·h/mL), mean (%CV)	430.9 (24.0)	350.2 (31.7)
C_{max} (ng/mL), mean (%CV)	31.1 (26.2)	24.0 (34.7)
C_{tau} (ng/mL), mean (%CV)	13.6 (22.5)	11.4 (32.4)
T_{max} (h), median (Q1, Q3)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)

a Cohort 1 was under fasted conditions

b n = 9

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for TFV and were excluded from summaries and paired comparisons.

Table 31. Cohort 2-3 TFV PK parameters.

TFV PK Parameter	FTC/ GS-7340 200/25 mg Cohort 2[a] Day 1 (N = 11)[b]	FTC/ GS-7340 200/25 mg Cohort 2[a] Day 12 (N = 11)	FTC/ GS-7340 200/25 mg + DRV/co Cohort 2[a] Day 13 (N = 11)[b]	FTC/ GS-7340 200/25 mg + DRV/co Cohort 2[a] Day 22 (N = 11)	FTC/ GS-7340 200/25 mg + DRV/co Cohort 3[a] Day 22 (N = 14)
AUC_{tau} (ng·h/mL), mean (%CV)	na	299.3 (29.3)	na	953.4 (20.0)	967.7 (12.7)
C_{max} (ng/mL), mean (%CV)	7.0 (22.4)	18.3 (27.8)	32.7 (18.0)	57.4 (23.2)	57.7 (14.8)
C_{tau} (ng/mL), mean (%CV)	na	10.8 (33.2)	na	33.7 (19.7)	36.2 (13.1)
T_{max} (h), median (Q1, Q3)	2.00 (1.50, 3.00)	2.00 (1.50, 2.00)	3.00 (2.00, 4.00)	3.00 (2.00, 3.00)	2.00 (1.00, 3.00)

na = not applicable

a Cohorts 2 and 3 were under fed conditions

b AUC_{tau} and C_{tau}, are not presented, due to PK sampling occurring only through 5 hours postdose on Days 1 and 13.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for TFV and were excluded from summaries and paired comparisons.

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

Table 32. Cohort 4 TFV PK parameters.

TFV PK Parameter	GS-7340 8 mg Cohort 4[a] Day 1 (N = 12)[b]	GS-7340 8 mg Cohort 4[a] Day 12 (N = 12)	GS-7340 + COBI 8/150 mg Cohort 4[a] Day 13 (N = 12)	GS-7340 + COBI 8/150 mg Cohort 4[a] Day 22 (N = 12)
AUC_{tau} (ng·h/mL), mean (%CV)	na	86.1 (19.4)	na	286.9 (21.9)
C_{max} (ng/mL), mean (%CV)	2.4 (18.3)	5.8 (19.5)	10.4 (21.5)	19.3 (20.5)
C_{tau} (ng/mL), mean (%CV)	na	3.0 (19.9)	na	10.3 (24.4)
T_{max} (h), median (Q1, Q3)	2.00 (2.00, 2.00)	1.75 (1.50, 3.00)	2.00 (1.25, 2.02)	1.50 (1.13, 1.75)

na = not applicable

a Cohort 4 was under fed conditions

b AUC_{tau} and C_{tau}, are not presented, due to PK sampling occurring only through 5 hours postdose on Days 1 and 13.

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for TFV and were excluded from summaries and paired comparisons.

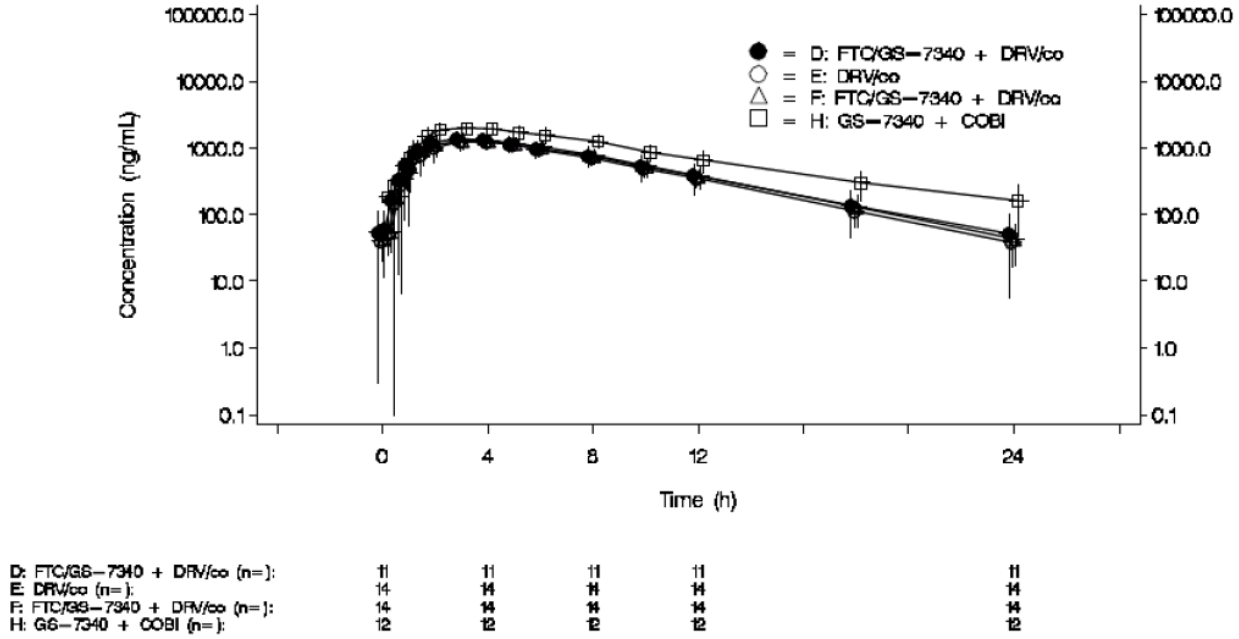
Table 33. Statistical comparison of TFV PK parameters.

TFV PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
Cohort 1: FTC/GS-7340 200/40 mg + EFV (Test) vs FTC/GS-7340 200/40 mg (Reference), (N = 11)				
AUC_{tau} (ng·h/mL)	335.32	420.64	79.72	(73.34, 86.65)
C_{max} (ng/mL)	22.80	30.20	75.49	(66.65, 85.50)
C_{tau} (ng/mL)	10.88	13.34	81.61	(74.74, 89.10)
Cohort 2: FTC/GS-7340 200/25 + DRV/co (Test) vs FTC/GS-7340 200/25 mg (Reference), (N = 11)				
AUC_{tau} (ng·h/mL)	937.35	289.42	323.88	(302.11, 347.21)
C_{max} (ng/mL)	56.14	17.77	316.03	(300.13, 332.76)
C_{tau} (ng/mL)	33.20	10.36	320.56	(290.05, 354.27)
Cohort 4: 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)

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

COBI

Figure 27. Cohort 2-4 mean (SD) COBI plasma concentrations.



Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Table 34. Cohort 2-4 COBI PK parameters.

COBI PK Parameter	FTC/GS-7340 200/25 mg + DRV/co Cohort 2 [a] Day 22 (N = 11)	DRV/co Cohort 3 [a] Day 10 (N = 14)	FTC/GS-7340 200/25 mg + DRV/co Cohort 3 [a] Day 22 (N = 14)	GS-7340 8 mg + COBI 150 mg Cohort 4 [a] Day 22 (N = 12)
AUC_{tau} (ng·h/mL), mean (%CV)	11,971.2 (31.3)	10,797.0 (18.6)	11,786.9 (21.9)	19,610.7 (25.4)
C_{max} (ng/mL), mean (%CV)	1444.5 (15.6)	1356.7 (16.5)	1428.4 (12.8)	2090.8 (16.2)
C_{tau} (ng/mL), mean (%CV)	52.6 (89.2)	38.1 (56.2)	43.6 (61.0)	160.8 (70.8)
T_{max} (h), median (Q1, Q3)	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	3.00 (3.00, 3.00)	3.00 (2.00, 3.50)
$T_{1/2}$ (h), median (Q1, Q3)	3.54 (3.31, 4.41)	3.67 (3.14, 4.12)	3.84 (3.16, 4.18)	5.40 (4.19, 6.37)

a All treatments administered under fed conditions

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

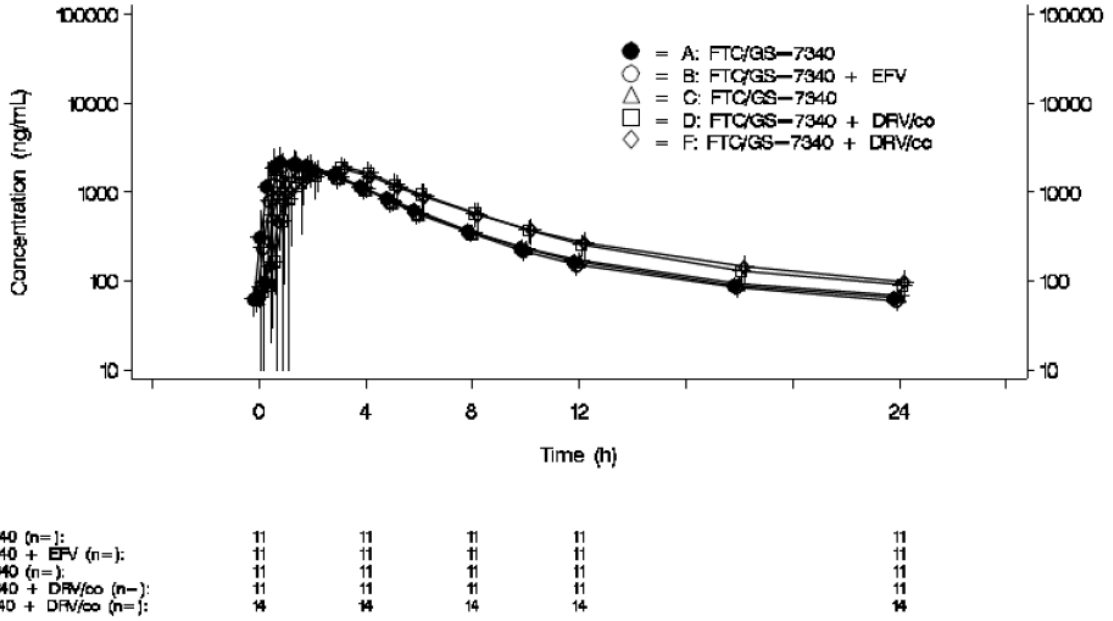
Table 35. Cohort 3 statistical comparison of COBI PK parameters.

COBI PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
Cohort 3: FTC/GS-7340 200/25 mg + DRV/co (Test) vs DRV/co (Reference), (N = 14)				
AUC_{tau} (ng·h/mL)	11,532.94	10,616.30	108.63	(102.75, 114.85)
C_{max} (ng/mL)	1417.94	1339.79	105.83	(100.12, 111.87)
C_{tau} (ng/mL)	36.88	33.31	110.71	(98.01, 125.06)

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

FTC

Figure 28. Cohort 1-3 mean (SD) FTC plasma concentrations.



Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.
Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for FTC and were excluded from summaries and paired comparisons.

Table 36. Cohort 1-3 FTC PK parameters.

FTC PK Parameter	FTC/ GS-7340 200/40 mg Cohort 1[a] Day 12 (N = 11)	FTC/ GS-7340 200/40 mg + EFV Cohort 1[a] Day 26 (N = 11)	FTC/ GS-7340 200/25 mg Cohort 2[a] Day 12 (N = 11)	FTC/ GS-7340 200/25 mg + DRV/co Cohort 2[a] Day 22 (N = 11)	FTC/ GS-7340 200/25 mg + DRV/co Cohort 3[a] Day 22 (N = 14)
AUC_{tau} (ng·h/mL), mean (%CV)	11,251.2 (14.7)	10,339.5 (16.8)	9861.8 (16.9)	12,308.7 (20.1)	12,395.8 (20.6)
C_{max} (ng/mL), mean (%CV)	2643.7 (26.7)	2344.7 (22.5)	2023.7 (24.1)	2268.9 (20.6)	2195.2 (16.6)
C_{tau} (ng/mL), mean (%CV)	64.7 (20.1)	59.5 (20.6)	68.2 (14.6)	90.1 (21.9)	97.9 (34.3)
T_{max} (h), median (Q1, Q3)	1.00 (0.75, 1.52)	1.50 (1.00, 2.00)	2.00 (1.50, 2.00)	3.00 (1.50, 3.00)	2.00 (1.50, 3.00)
$T_{1/2}$ (h), median (Q1, Q3)	8.50 (7.34, 9.20)	8.68 (8.40, 9.32)	8.54 (7.17, 9.83)	7.57 (6.99, 8.02)	7.63 (7.37, 8.29)

a Cohort 1 was under fasted conditions, while all other Cohorts were under fed conditions

Note: Subjects 3648-1011 and 3648-2004 did not have evaluable paired PK profiles for FTC and were excluded from summaries and paired comparisons.
Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

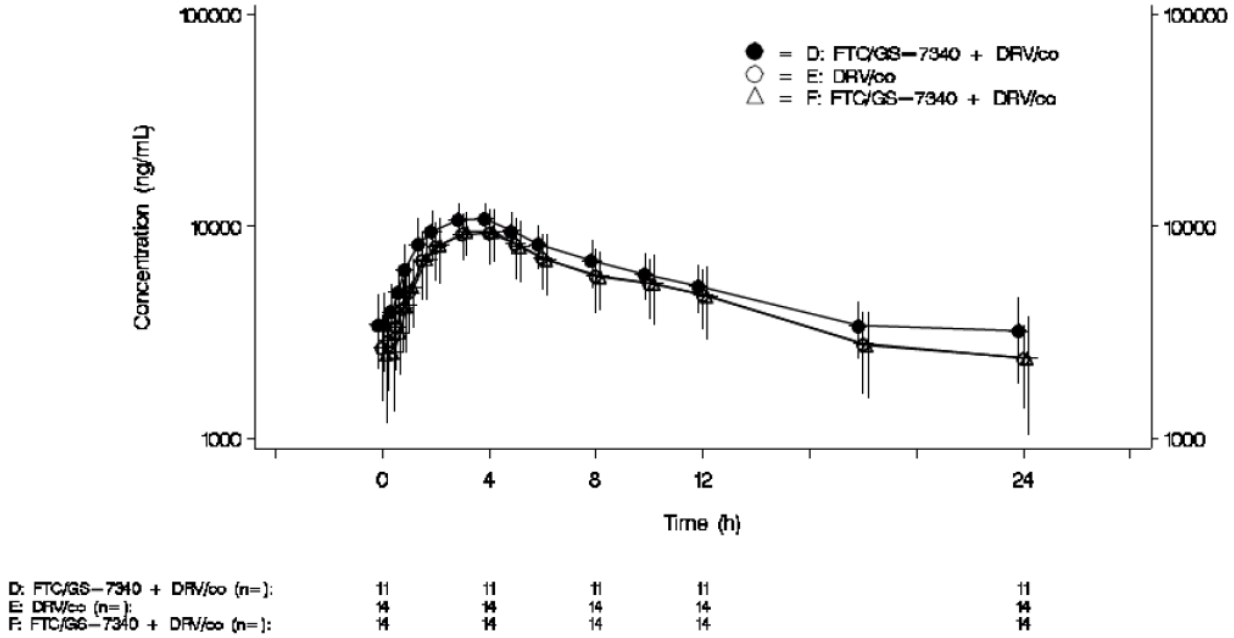
Table 37. Cohort 1-2 statistical comparison of FTC PK parameters.

FTC PK Parameter	Geometric Least Squares Means		Geometric Least Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
Cohort 1: FTC/GS-7340 200/40 mg + EFV (Test) vs FTC/GS-7340 200/40 mg (Reference), (N = 11)				
AUC_{tau} (ng·h/mL)	10,209.89	11,142.37	91.63	(87.38, 96.09)
C_{max} (ng/mL)	2292.03	2556.50	89.66	(81.30, 98.86)
C_{tau} (ng/mL)	58.28	63.39	91.94	(86.05, 98.22)
Cohort 2: FTC/GS-7340 200/25 + DRV/co (Test) vs FTC/GS-7340 200/25 mg (Reference), (N = 11)				
AUC_{tau} (ng·h/mL)	12,089.49	9736.39	124.17	(117.26, 131.49)
C_{max} (ng/mL)	2228.93	1977.02	112.74	(102.27, 124.29)
C_{tau} (ng/mL)	88.35	67.54	130.81	(123.95, 138.06)

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

DRV

Figure 29. Cohort 2-3 mean (SD) DRV plasma concentrations.



Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Table 38. Cohort 2-3 DRV PK parameters.

DRV PK Parameter	FTC/GS-7340 200/25 mg + DRV/co Cohort 2[a] Day 22 (N = 11)	DRV/co Cohort 3[a] Day 10 (N = 14)	FTC/GS-7340 200/25 mg + DRV/co Cohort 3[a] Day 22 (N = 14)
AUC_{tau} (ng·h/mL), mean (%CV)	136,773.5 (21.2)	116,150.0 (28.3)	115,736.3 (31.2)
C_{max} (ng/mL), mean (%CV)	11,701.1 (14.0)	10,023.8 (22.8)	10,215.2 (21.2)
C_{tau} (ng/mL), mean (%CV)	3227.1 (44.0)	2380.0 (41.6)	2401.0 (56.1)
T_{max} (h), median (Q1, Q3)	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)
$T_{1/2}$ (h), median (Q1, Q3)	15.78 (10.60, 18.16)	11.18[b] (8.33, 13.54)	11.34[c] (7.74, 13.23)

a All treatments administered under fed conditions

b n = 13

c n = 12

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

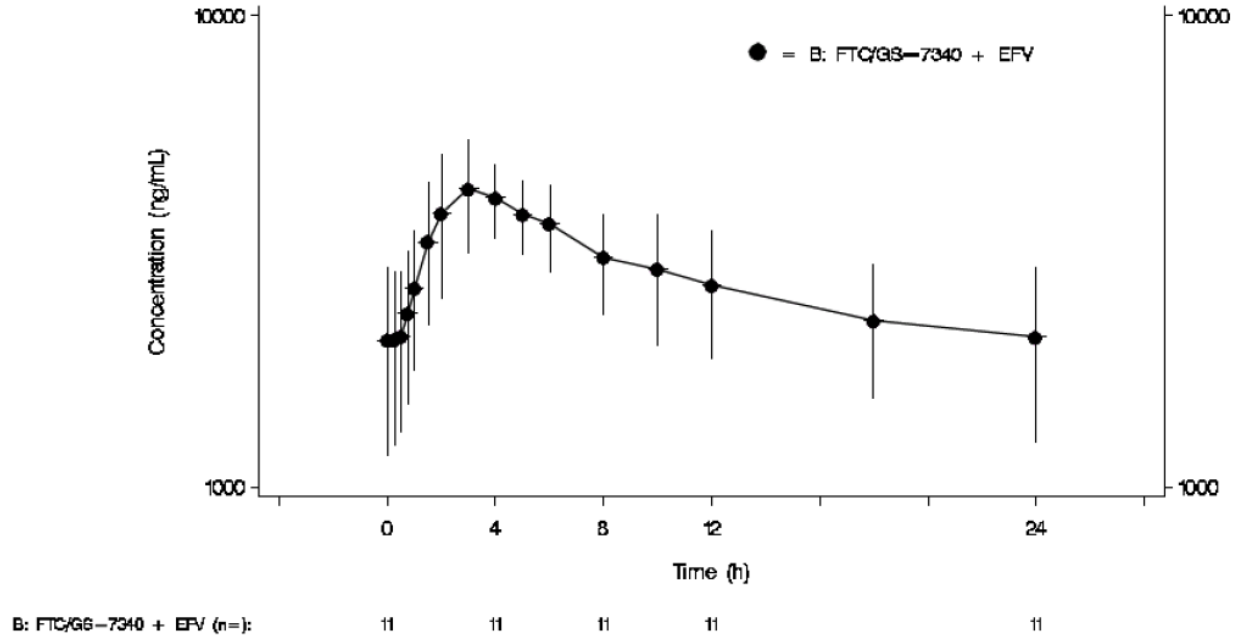
Table 39. Cohort 3 statistical comparison of DRV PK parameters.

DRV PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
Cohort 3: FTC/GS-7340 200/25 mg + DRV/co (Test) vs DRV/co (Reference), (N = 14)				
AUC_{tau} (ng·h/mL)	110,964.08	111,964.94	99.11	(91.54, 107.30)
C_{max} (ng/mL)	10,019.86	9799.10	102.25	(95.61, 109.36)
C_{tau} (ng/mL)	2099.28	2168.43	96.81	(81.51, 114.98)

Note: DRV/co was administered as DRV 800 mg (two 400 mg tablets) plus COBI 150 mg tablet.

EFV

Figure 30. Cohort 1 mean (SD) EFV plasma concentrations.



Note: Plasma concentrations BLQ were treated as zero for summary purposes and were treated as missing for log-transformed data.

Table 40. Cohort 1 EFV PK parameters.

EFV PK Parameter	FTC/GS-7340 200/40 mg + EFV Cohort 1 Day 26[a] (N = 11)
AUC_{tau} (ng·h/mL), mean (%CV)	67,155.1 (26.0)
C_{max} (ng/mL), mean (%CV)	4484.1 (24.1)
C_{tau} (ng/mL), mean (%CV)	2075.2 (40.2)
T_{max} (h), median (Q1, Q3)	3.00 (3.00, 4.00)

a Administered under fasted conditions

Safety

All AEs were reported in a maximum of one subject with the exception of headache (n=4), urinary tract infection (n=2), constipation (n=2), and vessel puncture site pain (n=2). Two subjects discontinued study treatment due to AEs, one due to anxiety and one due to join abscess. No deaths or SAEs occurred during the study. No clinically relevant changes in laboratory values or vital signs were reported.

DISCUSSION

All bioanalytical methods were validated and samples were analyzed within the respective durations of stability. Few subjects took non-study medications and thus drug interactions due to non-study medications did not affect the results.

In cohort 1, TAF AUC was reduced 14% and TFV AUC reduced 20% when coadministered with EFV. TAF is minimally metabolized by CYP3A4 and EFV is a CYP3A4 inducer. A 14% reduction in TAF exposure is not clinically relevant.

In cohort 2, TAF AUC was unaffected when coadministered with DRV/c while TFV AUC was increased 3-fold. Protease inhibitors other than DRV have been reported to be Pgp inducers (Perloff et all, AIDS, 2000), and DRV is hypothesized to be a Pgp inducer. It is unclear how TFV exposures are increased by DRV while TAF exposures are unchanged. A TAF dose of (b) (4) mg was found to be acceptable when coadministered with DRV/CYP3A inhibitor (section 2.1.2).

In cohort 4, TAF AUC was increased 2.65-fold and TFV AUC increased 3.3-fold when coadministered with COBI. The mechanism is attributed to Pgp, BCRP, and/or OATP inhibition by COBI as TAF is a substrate of these transporters. Based on this drug interaction, (b) (4) F/TAF (b) (4) coadministration without RTV or COBI (F/TAF 200/25 mg).

The effect of EFV on FTC (FTC AUC decreased 8%) and the effect of DRV/c on FTC (FTC AUC increased 24%) are not clinically relevant. EFV AUC in cohort 1 was similar to historical data (AUCtau of ~67000 ng*h/mL in this study and ~59000 ng*h/mL in the SUSTIVA label).

LABEL RECOMMENDATIONS

We agree with the sponsor's labeling recommendations that no F/TAF 200/25 mg should be given with EFV (b) (4)

3.5 GS-US-120-0118 – Drug interaction study between TAF and protease inhibitors given with ritonavir or DTG

A Pharmacokinetic Study Evaluating the Drug Interaction Potential of Tenofovir Alafenamide with a Boosted Protease Inhibitor or Unboosted Integrase Inhibitor in Healthy Subjects	
Study Period	8/5/2013-10/7/2013
Link to original study report	\\cdsesub1\evsprod\nda208215\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-120-0118\report-body.pdf
Link to study report amendment	\\cdsesub1\evsprod\nda208215\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-120-0118\report-body-amend-1.pdf

STUDY DESIGN

Multiple-dose, crossover study.

Treatment A = Treatment F: FTC 200 mg + TAF 10 mg once daily (QD), administered in the morning with food

Treatment B: ATV 300 mg + RTV 100 mg QD, administered in the morning with food

Treatment C: DRV 800 mg + RTV 100 mg QD, administered in the morning with food

Treatment D: LPV/r 4 × 200/50 mg QD, administered in the morning with food

Treatment E: DTG 50 mg QD, administered in the morning with food

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

Population	Healthy subjects
Study Rationale	Evaluate the effect of ATV/r, DRV/r, LPV/r, and DTG on the PK of TAF and TFV
Dose Selection Rationale	Approved doses of FTC, ATV/r, DRV/r, LPV/r, and DTG were used. (b) (4) [redacted]

Formulations

Drug	Dosage form	Strength (mg)	Lot #
(b) (4) [redacted]	[redacted]	[redacted]	[redacted]
FTC	Capsule	200	21005AFA
ATV	Capsule	300	3D5104A

	RTV	Tablet	100	1005003
	DRV	Tablet	800	13GG151
	LPV/r	Tablet	200/50	29203AA
	DTG	Tablet	50	3ZP6428
Interfering Substances Excluded	Any prescription and over-the-counter medications except acetaminophen, ibuprofen, hormonal contraceptives, and topical hydrocortisone. Subject to sponsor approval, other medications can be used to treat a short term minor illness.			
Sampling Times	Day 1 Cohorts 1-4: predose, 5 minutes, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, and 24 hours postdose Day 14 Cohort 1: predose and 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose Cohort 2: predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose Cohort 3: predose and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose Cohort 4: predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours postdose Day 15 Cohort 1: predose, 5 minutes, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose Cohort 2: predose, 5 minutes, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose Cohort 3: predose, 5 minutes, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose Cohort 4: predose, 5 minutes, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours postdose			

RESULTS

Bioanalytical methods

Concentrations of study drugs were reported to have been measured using fully validated LC/MS/MS methods. Samples were reported to have been measured within their respective durations of stability (Table 41).

Table 41. Bioanalytical methods.

Parameter	Tenofovir Alafenamide	Atazanavir	Darunavir	Lopinavir	Dolutegravir
Linear range (ng/mL)	1 to 1000	10 to 5000	20 to 10,000	100 to 20,000	20 to 20,000
Lower limit of quantitation (ng/mL)	1	10	20	100	20
Interday precision range (%CV)	1.8 to 7.3	3.8 to 5.5	2.8 to 10.6	1.2 to 1.4	2.1 to 4.6
Interday accuracy range (%RE)	–3.7 to 6.5	–2.4 to –0.1	–3.9 to –1.0	–6.3 to –3.3	–2.7 to 1.1
Stability in frozen matrix (day)	520 days at –70°C	721 days at –70°C	1635 days at –70°C and –20°C	43 days at –70°C and –20°C	77 days at –70°C and –20°C

CV = coefficient of variation; RE = relative error

Protocol deviations

None reported.

Study population

40 subjects were enrolled; 39 completed the study and one subject withdrew consent. Subject demographics are summarized below (Table 42).

Table 42. Subject demographics.

Characteristic	Cohort 1 (N = 10)	Cohort 2 (N = 10)	Cohort 3 (N = 10)	Cohort 4 (N = 10)
Sex (n, %)				
Male	6 (60%)	8 (80%)	6 (60%)	7 (70%)
Female	4 (40%)	2 (20%)	4 (40%)	3 (30%)
Age (year)				
Mean (SD)	34 (7.0)	34 (6.8)	33 (6.0)	37 (6.4)
Median	32	35	34	36
Min, Max	24, 43	23, 43	23, 42	27, 45
Race (n, %)				
White	6 (60%)	10 (100%)	9 (90%)	5 (50%)
Black or African American	4 (40%)	0	1 (10%)	5 (50%)
Ethnicity (n, %)				
Hispanic/Latino	7 (70%)	10 (100%)	10 (100%)	7 (70%)
Non-Hispanic/Latino	3 (30%)	0	0	3 (30%)

Concomitant medications

Reported use of non-study drugs included hormonal contraception (n=1 subject) and acetaminophen (n=1).

Pharmacokinetics

TAF

Figure 31. Cohort 1 mean (SD) TAF plasma concentrations.

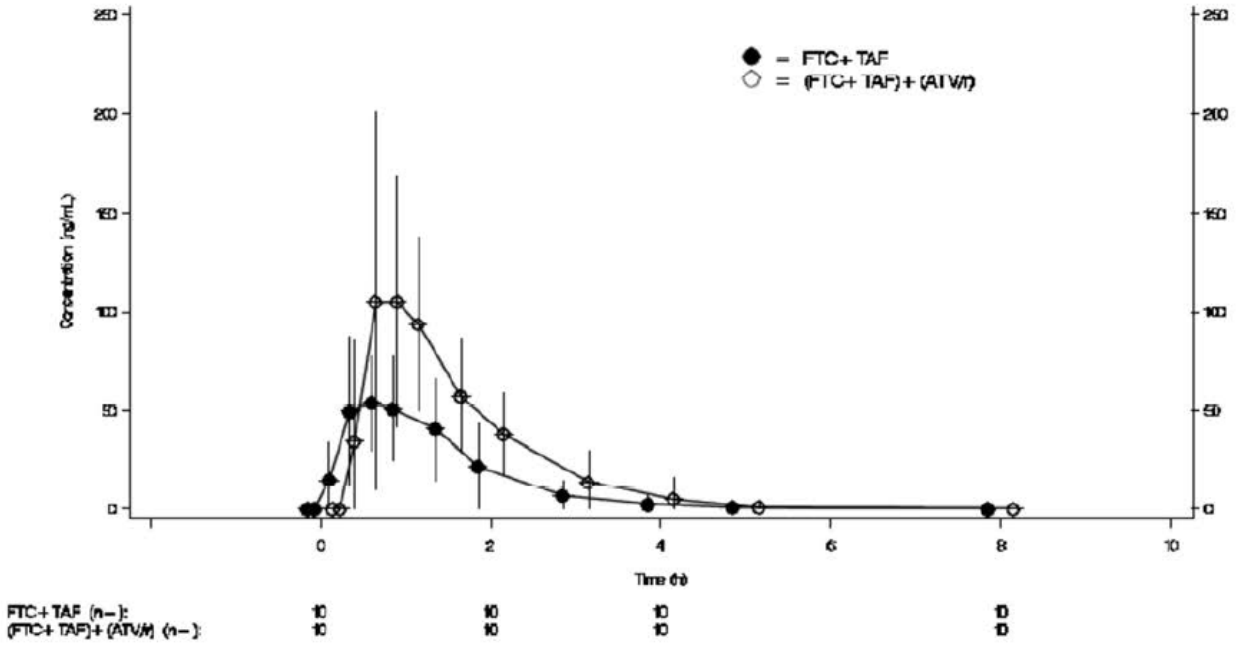


Figure 32. Cohort 2 mean (SD) TAF plasma concentrations.

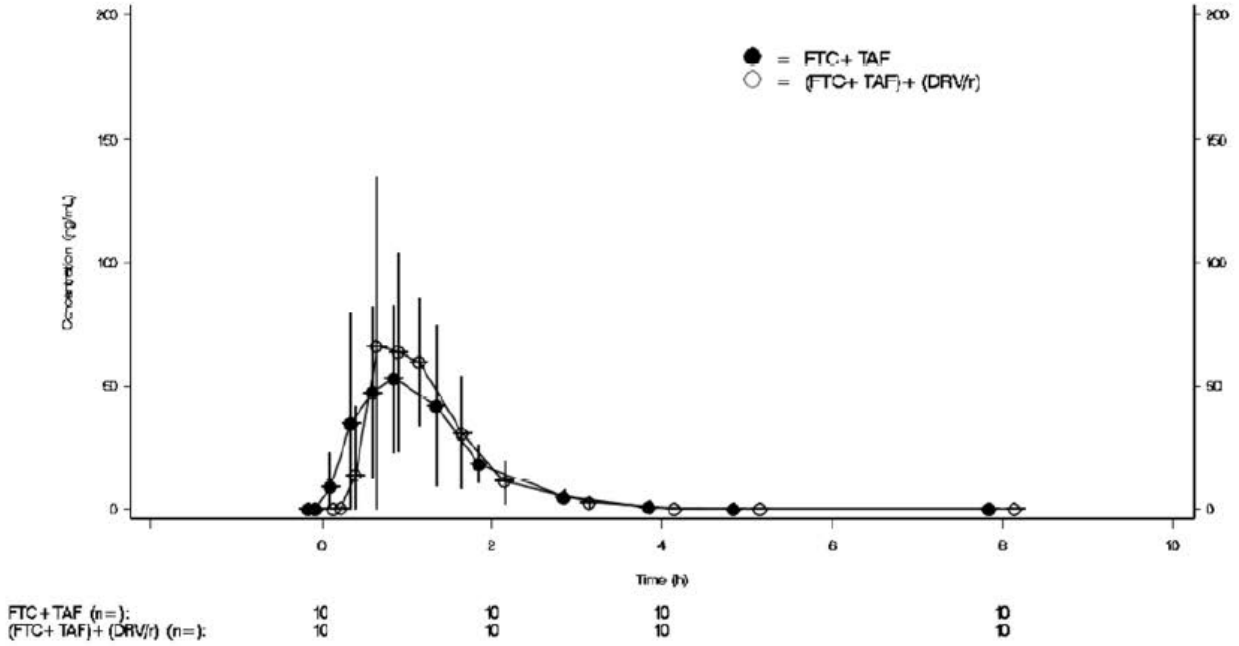


Figure 33. Cohort 3 mean (SD) TAF plasma concentrations.

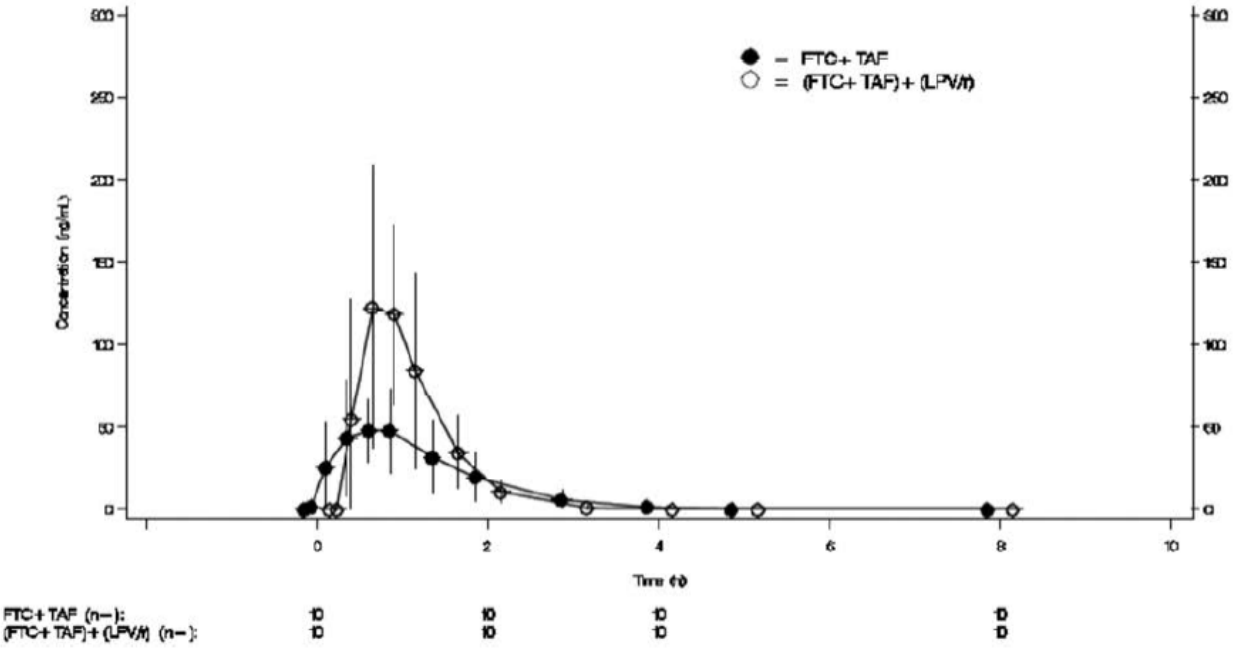


Figure 34. Cohort 4 mean (SD) TAF plasma concentrations.

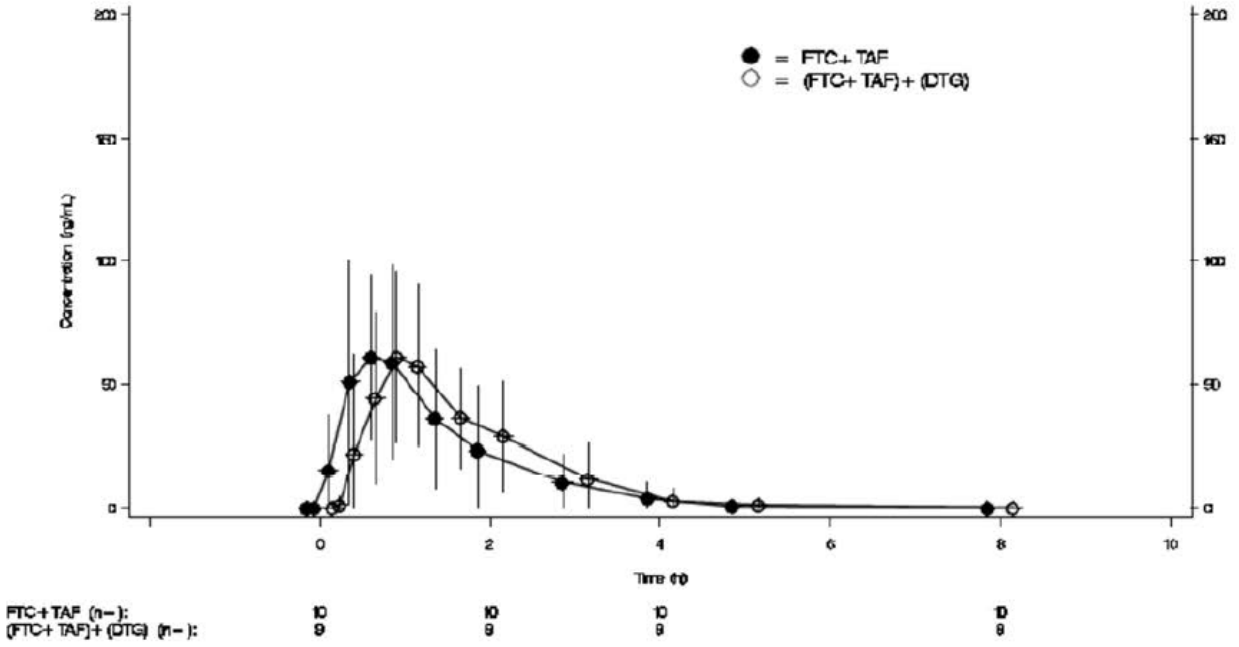


Table 43. Cohort 1 TAF PK parameters.

TAF PK Parameter	FTC+TAF (N = 10)	FTC+TAF+ATV/r (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	91.6 (39.9)	164.8 (18.1)
AUC_{exp} (%) Mean (%CV)	2.53 (102.5)	1.42 (94.7)
AUC_{last} (ng•h/mL) Mean (%CV)	89.5 (40.8)	162.6 (18.8)
C_{last} (ng/mL) Mean (%CV)	2.5 (59.1)	3.0 (64.3)
C_{max} (ng/mL) Mean (%CV)	76.8 (29.4)	146.5 (46.9)
T_{max} (h) Median (Q1, Q3)	0.75 (0.50, 1.00)	0.88 (0.50, 1.00)
T_{last} (h) Median (Q1, Q3)	3 (3, 4)	4 (3, 4)
λ_z (1/h) Median (Q1, Q3)	1.473 (1.138, 1.964)	1.665 (1.202, 1.837)
$t_{1/2}$ (h) Median (Q1, Q3)	0.47 (0.35, 0.61)	0.42 (0.38, 0.58)
CL/F (L/h) Mean (%CV)	122.7 (33.2)	62.2 (15.3)
V_z/F (L) Mean (%CV)	86.9 (47.2)	41.0 (29.2)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 44. Cohort 2 TAF PK parameters.

TAF PK Parameter	FTC+TAF (N = 10)	FTC+TAF+DRV/r (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	80.0 (41.8)	80.5 (30.4)
AUC_{exp} (%) Mean (%CV)	4.24 (117.4)	2.55 (85.8)
AUC_{last} (ng•h/mL) Mean (%CV)	77.4 (43.6)	78.6 (30.9)
C_{last} (ng/mL) Mean (%CV)	3.5 (45.7)	3.1 (61.5)
C_{max} (ng/mL) Mean (%CV)	73.4 (49.4)	102.3 (46.5)
T_{max} (h) Median (Q1, Q3)	0.75 (0.50, 1.50)	0.75 (0.50, 1.00)
T_{last} (h) Median (Q1, Q3)	3 (3, 3)	3 (3, 3)
λ_z (1/h) Median (Q1, Q3)	1.540 (1.134, 1.623)	1.753 (1.413, 2.206)
$t_{1/2}$ (h) Median (Q1, Q3)	0.45 (0.43, 0.61)	0.40 (0.31, 0.49)
CL/F (L/h) Mean (%CV)	148.4 (44.8)	138.1 (39.9)
V_z/F (L) Mean (%CV)	105.0 (57.4)	81.3 (57.5)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 45. Cohort 3 TAF PK parameters.

TAF PK Parameter	FTC+TAF (N = 10)	FTC+TAF+LPV/r (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	82.7 (34.0)	122.5 (42.7)
AUC_{exp} (%) Mean (%CV)	3.25 (56.5)	1.89 (145.7)
AUC_{last} (ng•h/mL) Mean (%CV)	80.0 (34.1)	120.8 (43.9)
C_{last} (ng/mL) Mean (%CV)	3.2 (56.8)	4.2 (123.7)
C_{max} (ng/mL) Mean (%CV)	68.7 (28.7)	157.5 (39.4)
T_{max} (h) Median (Q1, Q3)	0.75 (0.50, 1.00)	0.63 (0.50, 0.75)
T_{last} (h) Median (Q1, Q3)	3 (3, 4)	3 (2, 3)
λ_z (1/h) Median (Q1, Q3)	1.285 (1.132, 1.528)	2.426 (2.311, 2.601)
$t_{1/2}$ (h) Median (Q1, Q3)	0.54 (0.45, 0.61)	0.29 (0.27, 0.30)
CL/F (L/h) Mean (%CV)	135.5 (36.7)	95.2 (40.4)
V_z/F (L) Mean (%CV)	103.2 (28.7)	39.7 (42.5)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 46. Cohort 4 TAF PK parameters.

TAF PK Parameter	FTC+TAF (N = 10)	FTC+TAF+DTG (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	100.9 (51.2)	105.1 (31.7)
AUC_{exp} (%) Mean (%CV)	3.16 (121.5)	1.78 (112.5)
AUC_{last} (ng•h/mL) Mean (%CV)	98.5 (53.3)	103.0 (30.6)
C_{last} (ng/mL) Mean (%CV)	2.6 (45.5)	2.2 (109.0)
C_{max} (ng/mL) Mean (%CV)	79.9 (60.6)	83.4 (30.6)
T_{max} (h) Median (Q1, Q3)	1.00 (0.50, 1.00)	1.00 (0.75, 1.00)
T_{last} (h) Median (Q1, Q3)	4 (3, 4)	4 (3, 4)
λ_z (1/h) Median (Q1, Q3)	1.458 (1.070, 1.948)	1.516 (1.109, 1.648)
$t_{1/2}$ (h) Median (Q1, Q3)	0.49 (0.36, 0.65)	0.46 (0.42, 0.62)
CL/F (L/h) Mean (%CV)	119.4 (42.9)	105.9 (37.7)
V_z/F (L) Mean (%CV)	100.0 (80.6)	80.7 (54.6)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 47. Statistical comparison of TAF PK parameters.

TAF PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	Cohort 1			
	FTC+TAF+ATV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	162.62	86.08	188.92	(155.37, 229.71)
AUC_{last} (ng•h/mL)	160.28	83.89	191.06	(155.08, 235.40)
C_{max} (ng/mL)	130.85	74.04	176.72	(128.19, 243.63)
	Cohort 2			
	FTC+TAF+DRV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	76.73	73.54	104.34	(84.14, 129.39)
AUC_{last} (ng•h/mL)	74.76	70.35	106.27	(83.59, 135.10)
C_{max} (ng/mL)	91.16	64.29	141.80	(96.11, 209.22)
	Cohort 3			
	FTC+TAF+LPV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	113.27	78.25	144.75	(114.15, 183.55)
AUC_{last} (ng•h/mL)	111.07	75.70	146.73	(116.60, 184.65)
C_{max} (ng/mL)	145.42	66.41	218.97	(171.88, 278.97)
	Cohort 4			
	FTC+TAF+DTG (Test) (N = 9)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	106.61	91.42	116.62	(93.49, 145.48)
AUC_{last} (ng•h/mL)	105.29	88.47	119.02	(95.83, 147.82)
C_{max} (ng/mL)	81.74	66.11	123.64	(87.79, 174.13)

GLSM = geometric least-squares mean

TFV

Figure 35. Cohort 1 mean (SD) TFV plasma concentrations.

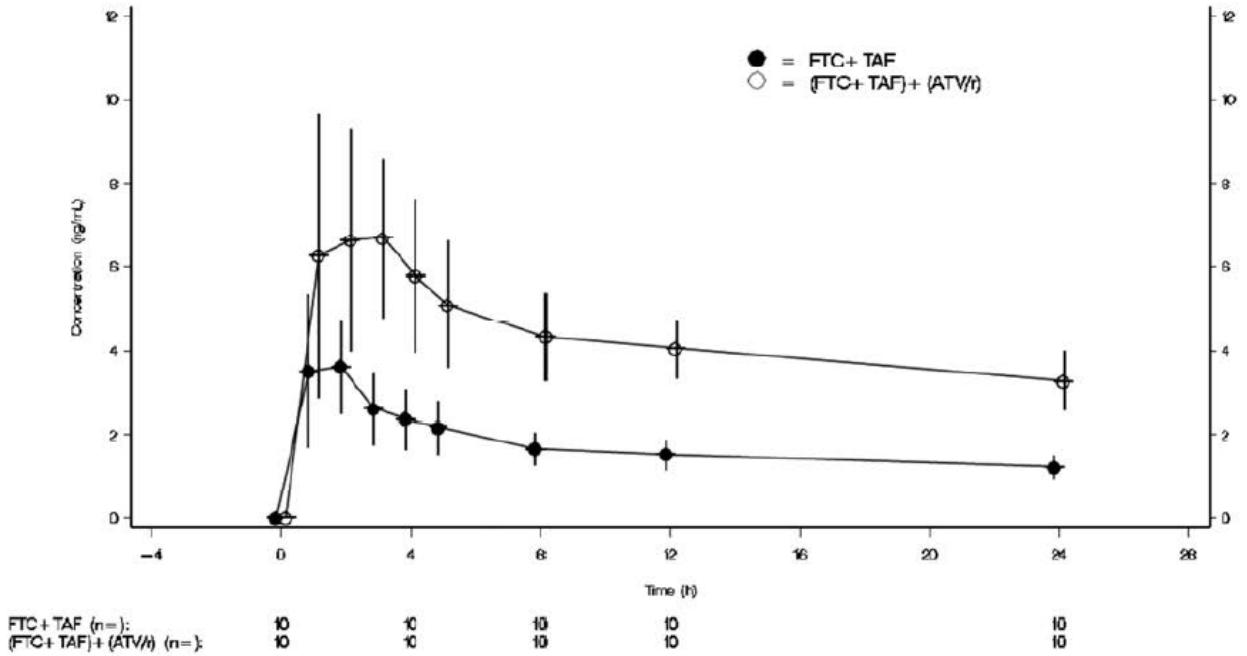


Figure 36. Cohort 2 mean (SD) TFV plasma concentrations.

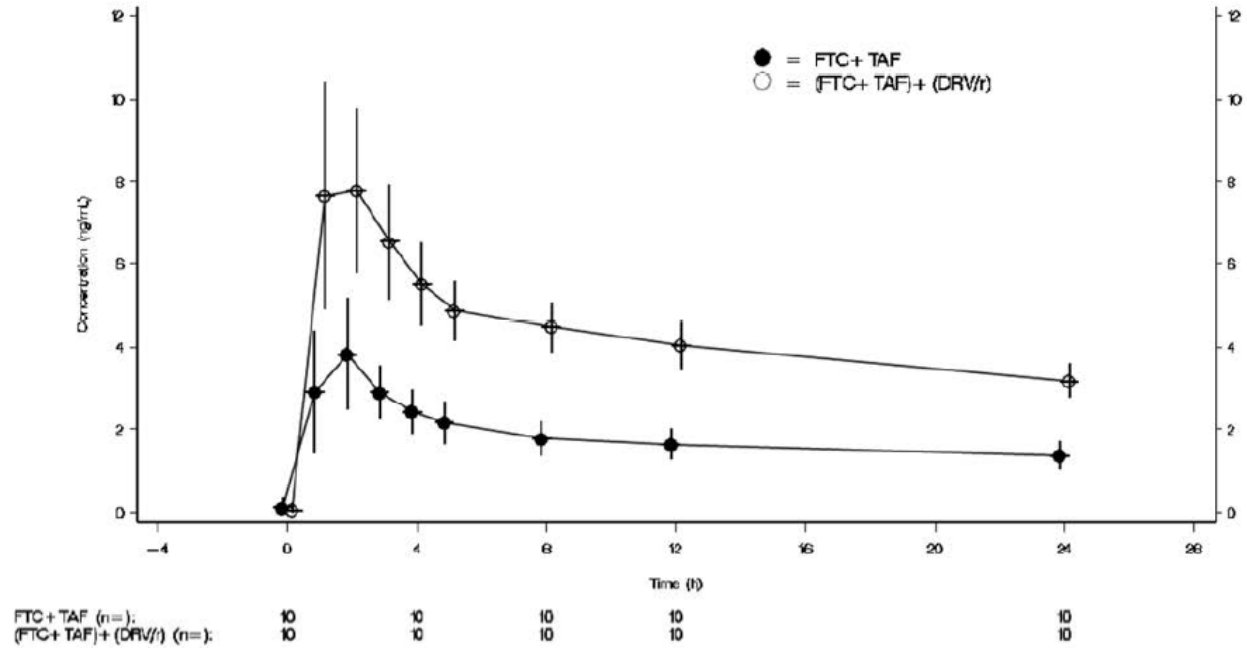


Figure 37. Cohort 3 mean (SD) TFV plasma concentrations.

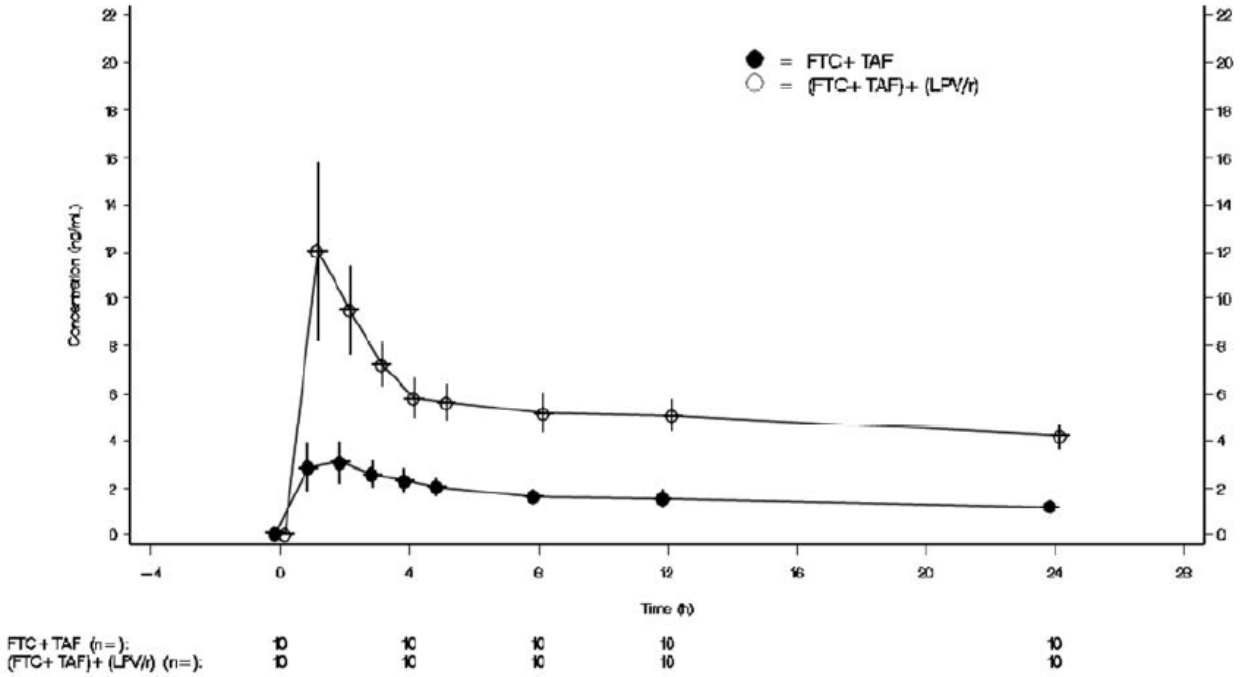


Figure 38. Cohort 4 mean (SD) TFV plasma concentrations.

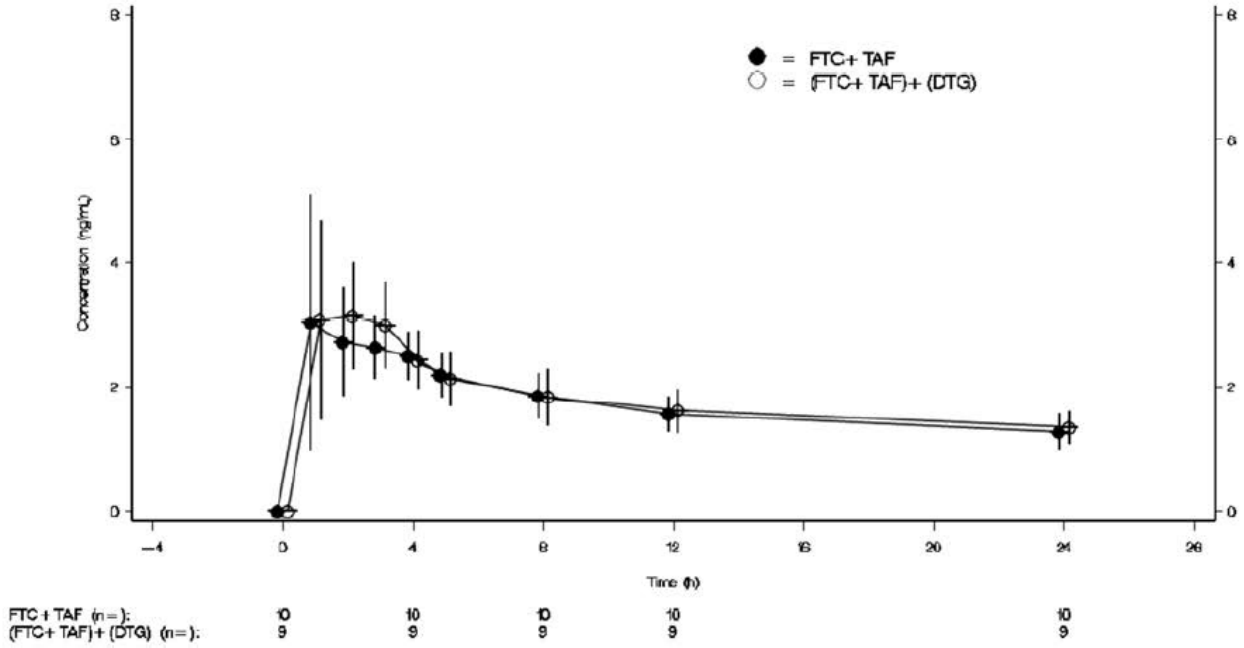


Table 48. Cohort 1 TFV PK parameters.

TFV PK Parameter	FTC+TAF (N = 10)	FTC+TAF+ATV/r (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	113.7 (36.0)	285.9 (22.1)
AUC_{exp} (%) Mean (%CV)	60.98 (13.4)	63.10 (12.4)
AUC_{last} (ng•h/mL) Mean (%CV)	41.7 (22.4)	102.1 (18.0)
C_{last} (ng/mL) Mean (%CV)	1.2 (22.6)	3.3 (22.0)
C_{max} (ng/mL) Mean (%CV)	4.3 (30.7)	8.8 (20.9)
T_{max} (h) Median (Q1, Q3)	1.00 (1.00, 2.00)	1.50 (1.00, 3.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.019 (0.016, 0.024)	0.019 (0.016, 0.022)
$t_{1/2}$ (h) Median (Q1, Q3)	36.72 (28.97, 42.60)	38.13 (32.14, 42.52)
CL/F (L/h) Mean (%CV)	61.1 (43.5)	22.3 (27.4)
V_z/F (L) Mean (%CV)	3059.4 (20.1)	1205.6 (22.2)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 49. Cohort 2 TFV PK parameters.

TFV PK Parameter	FTC+TAF (N = 10)	FTC+TAF+DRV/r (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	137.2 (49.2)	258.9 (21.5)
AUC_{exp} (%) Mean (%CV)	64.28 (16.4)	59.05 (10.8)
AUC_{last} (ng•h/mL) Mean (%CV)	43.5 (24.2)	103.8 (12.7)
C_{last} (ng/mL) Mean (%CV)	1.4 (24.1)	3.2 (12.7)
C_{max} (ng/mL) Mean (%CV)	3.9 (34.1)	9.2 (21.2)
T_{max} (h) Median (Q1, Q3)	2.00 (2.00, 2.00)	2.00 (1.00, 2.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.019 (0.011, 0.021)	0.022 (0.019, 0.026)
$t_{1/2}$ (h) Median (Q1, Q3)	36.87 (32.40, 60.89)	31.82 (26.90, 36.36)
CL/F (L/h) Mean (%CV)	52.9 (39.4)	24.1 (16.8)
V_z/F (L) Mean (%CV)	2957.0 (21.1)	1136.2 (17.1)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 50. Cohort 3 TFV PK parameters.

TFV PK Parameter	FTC+TAF (N = 10)	FTC+TAF+LPV/r (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	98.2 (23.6)	409.8 (22.0)
AUC_{exp} (%) Mean (%CV)	57.74 (15.2)	67.56 (8.9)
AUC_{last} (ng•h/mL) Mean (%CV)	40.3 (16.2)	129.0 (12.5)
C_{last} (ng/mL) Mean (%CV)	1.2 (14.0)	4.2 (12.9)
C_{max} (ng/mL) Mean (%CV)	3.4 (21.1)	12.7 (25.6)
T_{max} (h) Median (Q1, Q3)	2.00 (1.00, 2.00)	1.00 (1.00, 1.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.022 (0.020, 0.029)	0.014 (0.013, 0.019)
$t_{1/2}$ (h) Median (Q1, Q3)	31.74 (24.10, 35.49)	48.77 (36.67, 52.57)
CL/F (L/h) Mean (%CV)	63.8 (17.0)	15.4 (24.5)
V_z/F (L) Mean (%CV)	2972.1 (23.9)	989.0 (13.3)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 51. Cohort 4 TFV PK parameters.

TFV PK Parameter	FTC+TAF (N = 10)	FTC+TAF+DTG (N = 10)
AUC_{inf} (ng•h/mL) Mean (%CV)	94.2 (27.6)	114.9 (16.9)
AUC_{exp} (%) Mean (%CV)	54.84 (8.5)	61.98 (12.9)
AUC_{last} (ng•h/mL) Mean (%CV)	41.7 (20.0)	43.0 (19.8)
C_{last} (ng/mL) Mean (%CV)	1.3 (23.5)	1.3 (19.0)
C_{max} (ng/mL) Mean (%CV)	3.7 (44.3)	3.8 (23.1)
T_{max} (h) Median (Q1, Q3)	1.00 (1.00, 3.00)	1.00 (1.00, 2.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.025 (0.023, 0.028)	0.019 (0.015, 0.020)
$t_{1/2}$ (h) Median (Q1, Q3)	28.30 (24.94, 30.10)	36.76 (33.92, 45.87)
CL/F (L/h) Mean (%CV)	68.3 (25.2)	53.9 (16.3)
V_z/F (L) Mean (%CV)	2662.4 (15.4)	2924.4 (28.1)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 52. Statistical comparison of TFV PK parameters.

TFV PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	Cohort 1			
	FTC+TAF+ATV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	278.69	106.54	261.59	(213.95, 319.84)
AUC_{last} (ng•h/mL)	100.74	40.66	247.77	(216.82, 283.14)
C_{max} (ng/mL)	8.62	4.06	212.35	(185.83, 242.65)
	Cohort 2			
	FTC+TAF+DRV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	254.44	124.35	204.61	(153.78, 272.25)
AUC_{last} (ng•h/mL)	102.99	42.43	242.74	(207.17, 284.41)
C_{max} (ng/mL)	9.03	3.74	241.54	(198.10, 294.51)
	Cohort 3			
	FTC+TAF+LPV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	400.79	96.26	416.36	(349.56, 495.93)
AUC_{last} (ng•h/mL)	128.10	39.78	322.01	(298.02, 347.93)
C_{max} (ng/mL)	12.33	3.29	374.52	(319.28, 439.30)
	Cohort 4			
	FTC+TAF+DTG (Test) (N = 9)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	113.98	91.23	124.94	(106.46, 146.62)
AUC_{last} (ng•h/mL)	42.73	40.99	104.25	(98.74, 110.08)
C_{max} (ng/mL)	3.77	3.43	109.91	(96.39, 125.32)

GLSM = geometric least-squares mean

ATV

Figure 39. Cohort 1 mean (SD) ATV plasma concentrations.

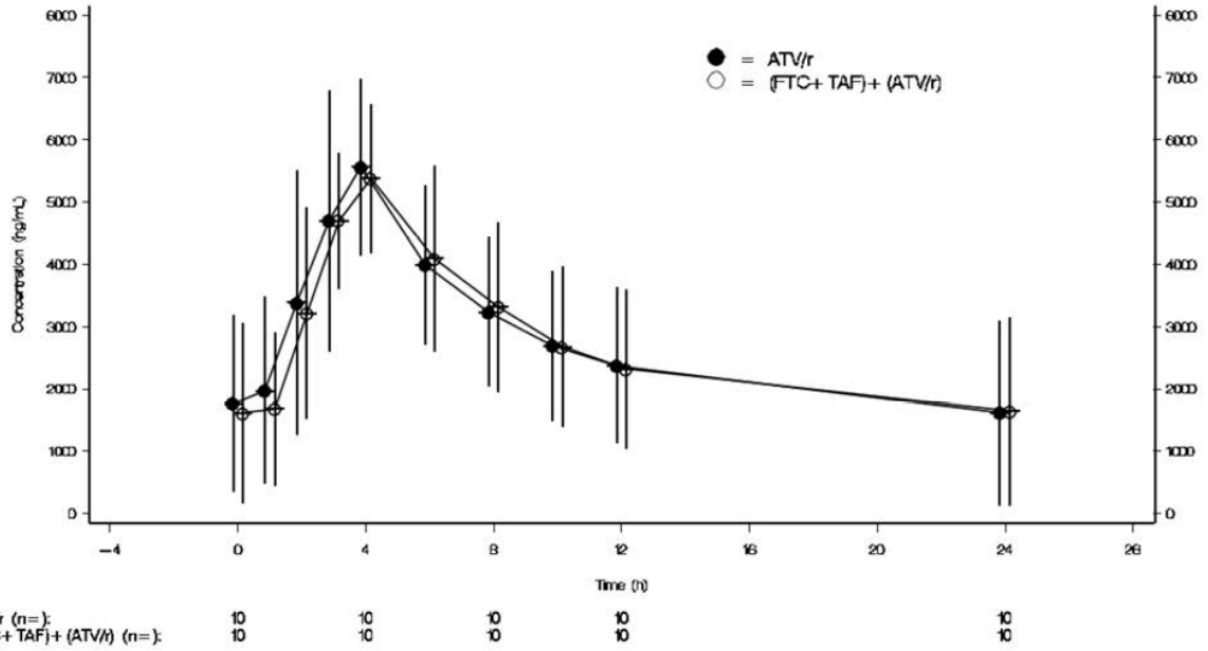


Table 53. Cohort 1 ATV PK parameters.

ATV PK Parameter	FTC+TAF+ATV/r (N = 10)	ATV/r (N = 10)
AUC_{tau} (ng•h/mL) Mean (%CV)	64,035.2 (47.0)	64,692.1 (46.3)
AUC_{last} (ng•h/mL) Mean (%CV)	63,927.1 (46.9)	64,585.9 (46.2)
C_{tau} (ng/mL) Mean (%CV)	1636.9 (91.7)	1619.0 (91.3)
C_{last} (ng/mL) Mean (%CV)	1636.9 (91.7)	1619.0 (91.3)
C_{max} (ng/mL) Mean (%CV)	5730.2 (17.3)	5946.9 (21.7)
T_{max} (h) Median (Q1, Q3)	3.50 (3.00, 4.00)	3.00 (3.00, 4.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.049 (0.027, 0.058)	0.048 (0.032, 0.062)
$t_{1/2}$ (h) Median (Q1, Q3)	14.32 (12.04, 26.08)	14.63 (11.26, 21.76)
CL/F (L/h) Mean (%CV)	3.5 (47.0)	3.5 (43.0)
Vz/F (L) Mean (%CV)	78.1 (29.0)	76.1 (30.1)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 54. Statistical comparison of ATV PK parameters.

	GLSMs by Treatment			
	Cohort 1			
ATV PK Parameter	FTC+TAF+ATV/r (Test) (N = 10)	ATV/r (Reference) (N = 10)	GLSM Ratio (%)	90% CI (%)
AUC_{tau} (ng•h/mL)	59,708.21	60,474.36	98.73	(96.35, 101.18)
C_{tau} (ng/mL)	1308.40	1307.31	100.08	(96.04, 104.29)
C_{max} (ng/mL)	5654.74	5796.77	97.55	(88.98, 106.94)

FTC+TAF +ATV/r (Test: Treatment A+B in Cohort 1); ATV/r alone (Reference: Treatment B in Cohort 1)

DRV

Figure 40. Cohort 2 mean (SD) DRV plasma concentrations.

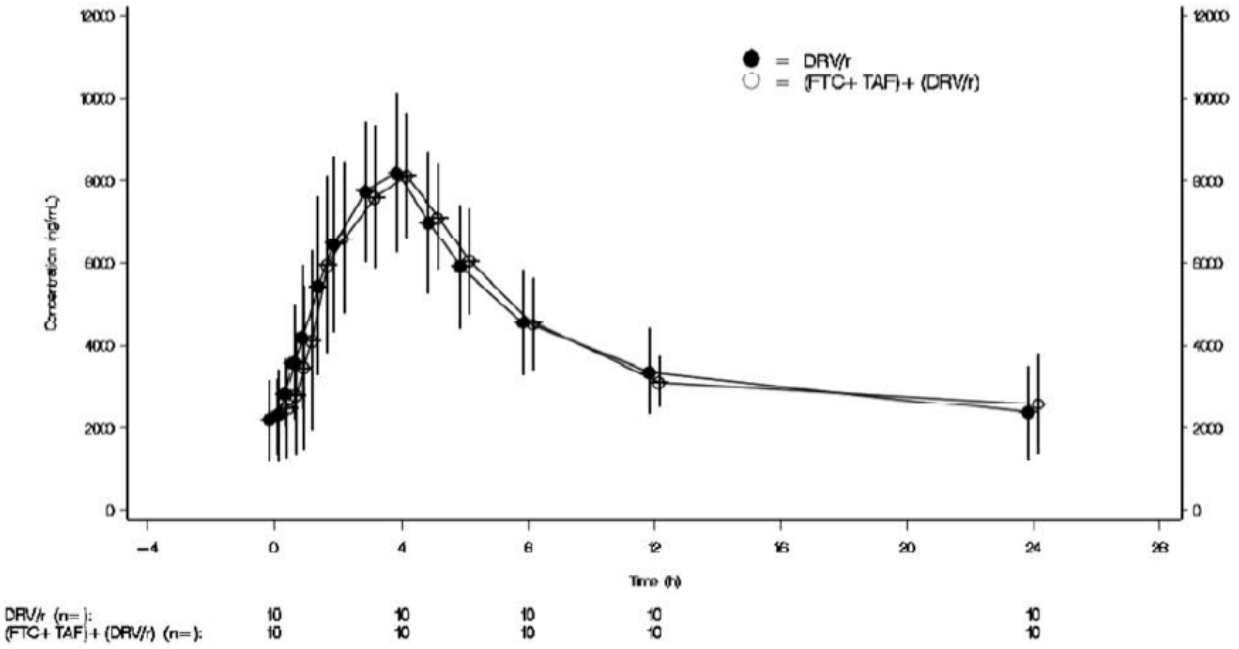


Table 55. Cohort 2 DRV PK parameters.

DRV PK Parameter	FTC+TAF+DRV/r (N = 10)	DRV/r (N = 10)
AUC_{tau} (ng•h/mL) Mean (%CV)	97,486.1 (23.9)	97,646.2 (27.1)
AUC_{last} (ng•h/mL) Mean (%CV)	97,321.3 (23.9)	97,491.3 (27.0)
C_{tau} (ng/mL) Mean (%CV)	2598.0 (45.9)	2374.1 (47.6)
C_{last} (ng/mL) Mean (%CV)	2598.0 (45.9)	2374.1 (47.6)
C_{max} (ng/mL) Mean (%CV)	8472.5 (16.6)	8567.7 (18.7)
T_{max} (h) Median (Q1, Q3)	4.00 (3.00, 4.00)	4.00 (3.00, 4.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.044 (0.038, 0.053)	0.038 (0.034, 0.064)
$t_{1/2}$ (h) Median (Q1, Q3)	15.86 (12.98, 18.16)	18.39 (10.81, 20.35)
CL/F (L/h) Mean (%CV)	5.5 (36.9)	5.9 (45.7)
Vz/F (L) Mean (%CV)	126.6 (26.0)	125.4 (25.5)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 56. Statistical comparison of DRV PK parameters.

	GLSMs by Treatment			
	Cohort 2			
DRV PK Parameter	FTC+TAF+DRV/r (Test) (N = 10)	DRV/r (Reference) (N = 10)	GLSM Ratio (%)	90% CI (%)
AUC_{tau} (ng•h/mL)	95,033.83	94,441.21	100.63	(95.70, 105.81)
C_{tau} (ng/mL)	2369.54	2100.09	112.83	(95.20, 133.73)
C_{max} (ng/mL)	8368.48	8445.36	99.09	(90.85, 108.08)

FTC+TAF +DRV/r (Test: Treatment A+C in Cohort 2); DRV/r alone (Reference: Treatment C in Cohort 2)

Figure 41. Cohort 3 mean (SD) LPV plasma concentrations.

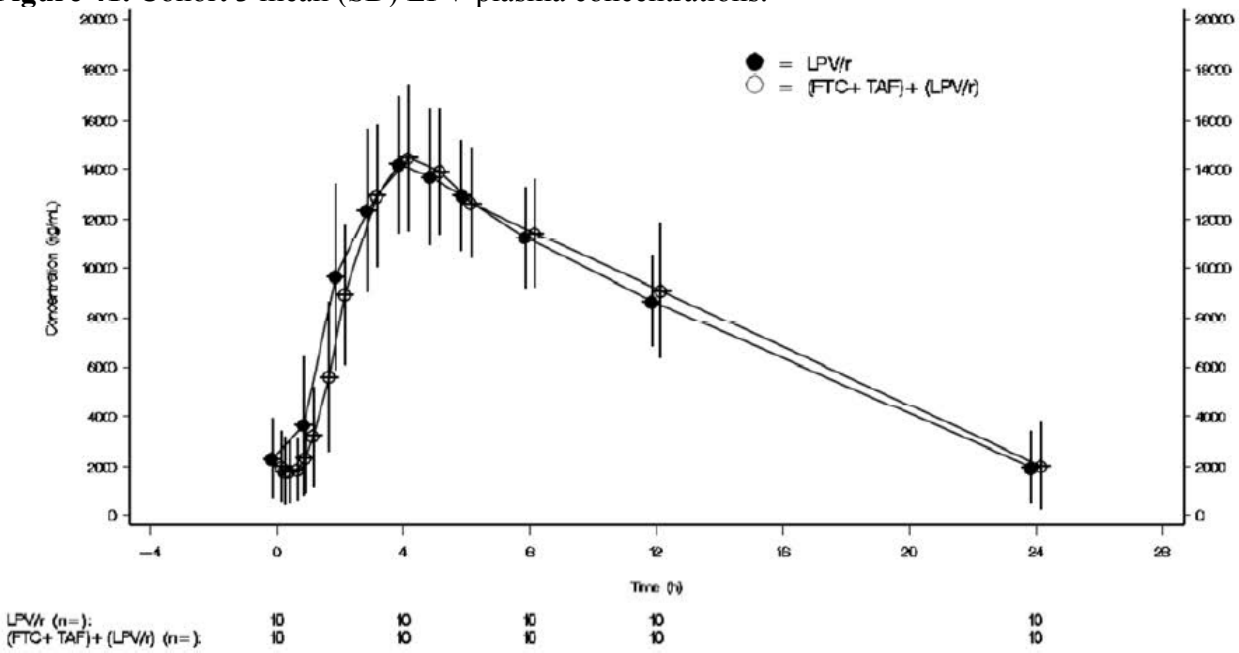


Table 57. Cohort 3 LPV PK parameters.

LPV PK Parameter	FTC+TAF+LPV/r (N = 10)	LPV/r (N = 10)
AUC_{tau} (ng•h/mL) Mean (%CV)	179,207 (30.1)	176,925 (24.3)
AUC_{last} (ng•h/mL) Mean (%CV)	179,207 (30.1)	176,925 (24.3)
C_{tau} (ng/mL) Mean (%CV)	2004.9 (88.2)	1954.4 (73.1)
C_{last} (ng/mL) Mean (%CV)	2004.9 (88.2)	1954.4 (73.1)
C_{max} (ng/mL) Mean (%CV)	14,662.6 (19.2)	14,592.3 (17.4)
T_{max} (h) Median (Q1, Q3)	4.00 (4.00, 5.00)	4.00 (4.00, 5.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.115 (0.104, 0.192)	0.107 (0.091, 0.184)
$t_{1/2}$ (h) Median (Q1, Q3)	6.06 (3.61, 6.69)	6.52 (3.76, 7.65)
CL/F (L/h) Mean (%CV)	4.4 (32.1)	4.4 (32.7)
Vz/F (L) Mean (%CV)	33.9 (19.3)	35.5 (23.8)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 58. Statistical comparison of LPV PK parameters.

LPV PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	Cohort 3			
	FTC+TAF+LPV/r (Test) (N = 10)	LPV/r (Reference) (N = 10)		
AUC_{tau} (ng•h/mL)	172,724.9	172,011.6	100.41	(92.38, 109.15)
C_{tau} (ng/mL)	1346.86	1380.32	97.58	(85.00, 112.02)
C_{max} (ng/mL)	14,430.40	14,388.04	100.29	(95.05, 105.83)

FTC+TAF +LPV/r (Test: Treatment A+D in Cohort 3); LPV/r alone (Reference: Treatment D in Cohort 3)

DTG

Figure 42. Cohort 4 mean (SD) DTG plasma concentrations.

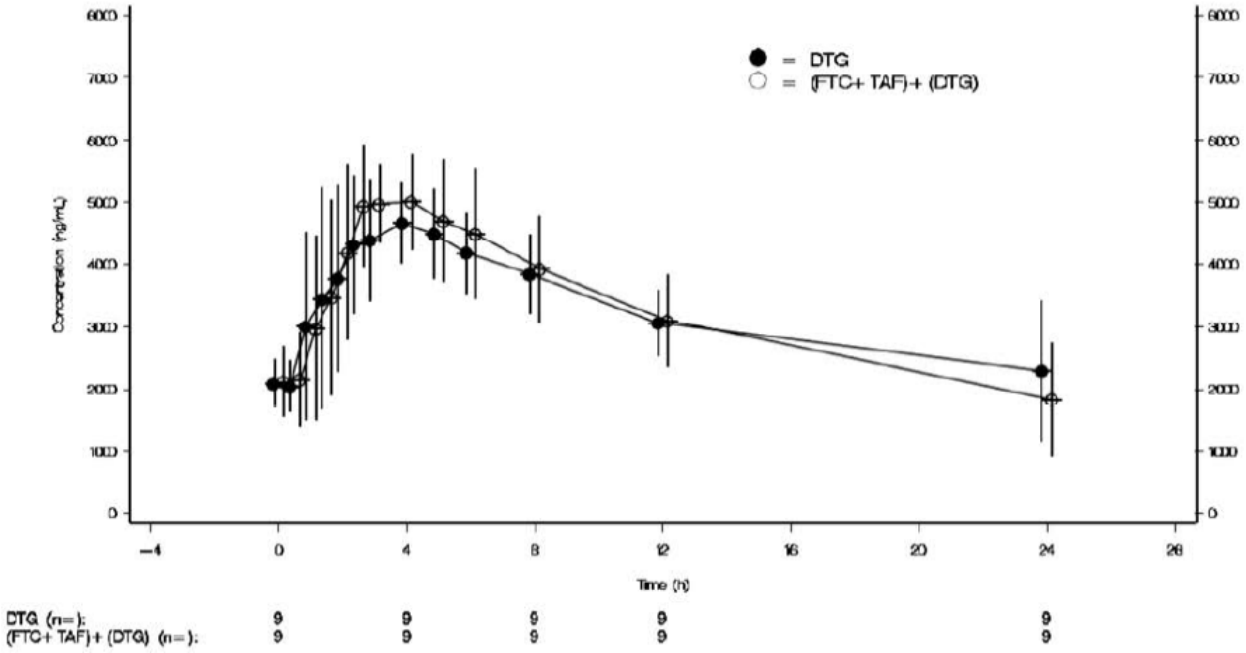


Table 59. Cohort 4 DTG PK parameters.

DTG PK Parameter	FTC+TAF+DTG (N = 9)	DTG (N = 8)
AUC_{tau} (ng•h/mL) Mean (%CV)	77,932.9 (19.3)	74,127.5 (16.0)
AUC_{last} (ng•h/mL) Mean (%CV)	73,806.2 (20.9)	73,998.4 (16.0)
C_{tau} (ng/mL) Mean (%CV)	2063.8 (30.3)	1949.3 (25.1)
C_{last} (ng/mL) Mean (%CV)	2301.6 (40.1)	1949.3 (25.1)
C_{max} (ng/mL) Mean (%CV)	5894.9 (6.7)	5148.0 (17.6)
T_{max} (h) Median (Q1, Q3)	3.00 (2.00, 4.00)	3.25 (1.75, 5.00)
T_{last} (h) Median (Q1, Q3)	24 (24, 24)	24 (24, 24)
λ_z (1/h) Median (Q1, Q3)	0.041 (0.035, 0.043)	0.040 (0.034, 0.046)
$t_{1/2}$ (h) Median (Q1, Q3)	16.99 (16.07, 19.69)	17.38 (15.23, 20.63)
CL/F (L/h) Mean (%CV)	0.4 (28.4)	0.4 (32.7)
Vz/F (L) Mean (%CV)	10.1 (17.9)	10.2 (12.0)

Note: Values are presented as mean (CV%) except where noted—T_{max}, T_{last}, λ_z, and $t_{1/2}$ are presented as median (Q1, Q3).

Table 60. Statistical comparison of DTG PK parameters.

DTG PK Parameter	GLSMs by Treatment Cohort 4 FTC+TAF+DTG (Test) (N = 9)	GLSMs by Treatment Cohort 4 DTG (Reference) (N = 8)	GLSM Ratio (%)	90% CI (%)
AUC_{tau} (ng•h/mL)	76,590.36	74,859.64	(b) (4) **102.31**	(b) (4) **(97.09,107.81)**
C_{tau} (ng/mL)	1983.31[a]	1891.10	(b) (4) **104.88**	(b) (4) **(97.17,113.19)**
C_{max} (ng/mL)	5883.04	5102.93	(b) (4) **115.29**	(b) (4) **(104.48,127.22)**

a N=8

FTC+TAF +DTG (Test: Treatment F+E in Cohort 4); DTG alone (Reference: Treatment E in Cohort 4)

Strikethrough text refers to incorrect data that was submitted in the original CSR.

Safety

No SAEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE. The most common AEs were ocular icterus (10 of 10 subjects in the ATV/r cohort), diarrhea (5 of 10 subjects in the LPV/r cohort), and dry mouth (5 of 10 subjects in the LPV/r cohort). Clinically relevant increases in bilirubin were observed in the ATV/r arm.

DISCUSSION/REVIEWER'S COMMENTS

Bioanalytical methods were acceptable and no study conduct issues were identified.

There was no clinically significant effect of TAF on the PK of LPV, DRV, ATV, or DTG, and no clinically significant effect of DTG on the PK of TAF in this study.

When coadministered with COBI, TAF exposures were increased 2.65-fold. When coadministered with protease inhibitors, TAF exposures were increased not at all (DRV/r) or less than 2.65-fold (LPV/r and ATV/r). The mechanism of the interaction with protease inhibitors is hypothesized to be a combination of Pgp inhibition and induction as TAF is a Pgp substrate, RTV and COBI are Pgp inhibitors, and several protease inhibitors other than DRV, LPV, and ATV have been reported to be Pgp inducers in vitro and in rats (Perloff et al, AIDS, 2000, and Huang et al, DMD, 2001). As discussed in the Executive Summary (2.1.2), based on TAF exposure-response and TFV-DP data, we consider exposures of TAF from (b) (4)

LABEL RECOMMENDATIONS

We agree with the proposed F/TAF labeling which states that the recommended dose of F/TAF is 200/25 mg, [redacted] (b) (4)

3.6 GS-US-120-1554 – Drug interaction study between TAF and RPV

A Fixed-Sequence, Randomized, Open-Label, 2-Cohort, 2-Period, Multiple-Dose Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Rilpivirine in Healthy Subjects	
Study Period	8/18/2014-10/23/2014
Link	\\cdsesub1\evsprod\nda208215\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-120-1554\report-body.pdf

STUDY DESIGN

Treatment A: TAF 25 mg, administered orally once daily in the morning, under fed conditions

Treatment B: RPV 25 mg, administered orally once daily in the morning, under fed conditions

Treatment C: TAF 25 mg+RPV 25 mg, administered orally once daily in the morning, under fed conditions

	Days 1-14	Days 15-28
Cohort 1	Treatment A	Treatment C
Cohort 2	Treatment B	Treatment C

Population	Healthy subjects
Study Rationale	Evaluate two-way drug interactions between TAF and RPV
Dose Selection Rationale	RPV 25 mg is the approved dose TAF 25 mg is one of the doses submitted for approval as part of F/TAF
Formulation	TAF 25 mg tablet (Lot # CM1306B2) RPV 25 mg tablet (Lot # EAL5K00)
Interfering Substances Excluded	Any prescription and over-the-counter medications except acetaminophen, ibuprofen, hormonal contraceptives, and topical hydrocortisone. Subject to sponsor approval, other medications can be used to treat a short term minor illness.

Sampling Times	Intensive PK sampling was performed at the following time points: **Treatment A (TAF 25 mg):** • Analyte TAF (Day 14): predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours postdose • Analyte TFV (Day 14): predose, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours postdose (the 24 hour sample was collected predose on Day 15) **Treatment B (RPV 25 mg):** • Analyte RPV (Day 14): predose, 2, 3, 4, 4.5, 5, 6, 8, 12, 16, and 24 hours postdose (the 24 hour sample was collected predose on Day 15) **Treatment C (TAF 25 mg+RPV 25 mg):** • Analyte TAF (Day 28): predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours postdose • Analyte TFV (Day 28): predose, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours postdose • Analyte RPV (Day 28): predose, 2, 3, 4, 4.5, 5, 6, 8, 12, 16, and 24 hours postdose Trough (predose) PK samples were collected for all treatments prior to the morning dose on Days 2, 11, 12, 13, 16, 25, 26, and 27. A single PK sample was also collected at the early termination visit (as applicable).

RESULTS

Bioanalytical methods

The sponsor reports that concentrations of TAF and RPV in plasma samples were determined using fully validated LC/MS/MS and that samples were analyzed within the duration of stability (Table 61).

Table 61. Bioanalytical methods.

Parameter	TAF	TFV	RPV
Linear Range (ng/mL)	1 to 1000	0.3 to 300	1 to 500
Lower Limit of Quantitation (ng/mL)	1	0.3	1
Interassay Precision Range (%CV)	1.8 to 7.3	1.8 to 4.8	3.4 to 4.9
Interassay Accuracy Range (%RE)	−3.7 to 6.5	−2.7 to 2.7	−3.5 to −2.3
Stability in Frozen Matrix (days)	520 at −70°C	366 at −20°C and 1092 at −70°C	783 at −20°C and −70°C

Protocol deviations

No “important” protocol deviations were reported.

Study population

34 subjects enrolled and 32 completed the study. Two subjects in the RPV -> TAF+RPV arm discontinued early, due to withdrawal of consent (n=1) and AE (n=1).

Concomitant medications

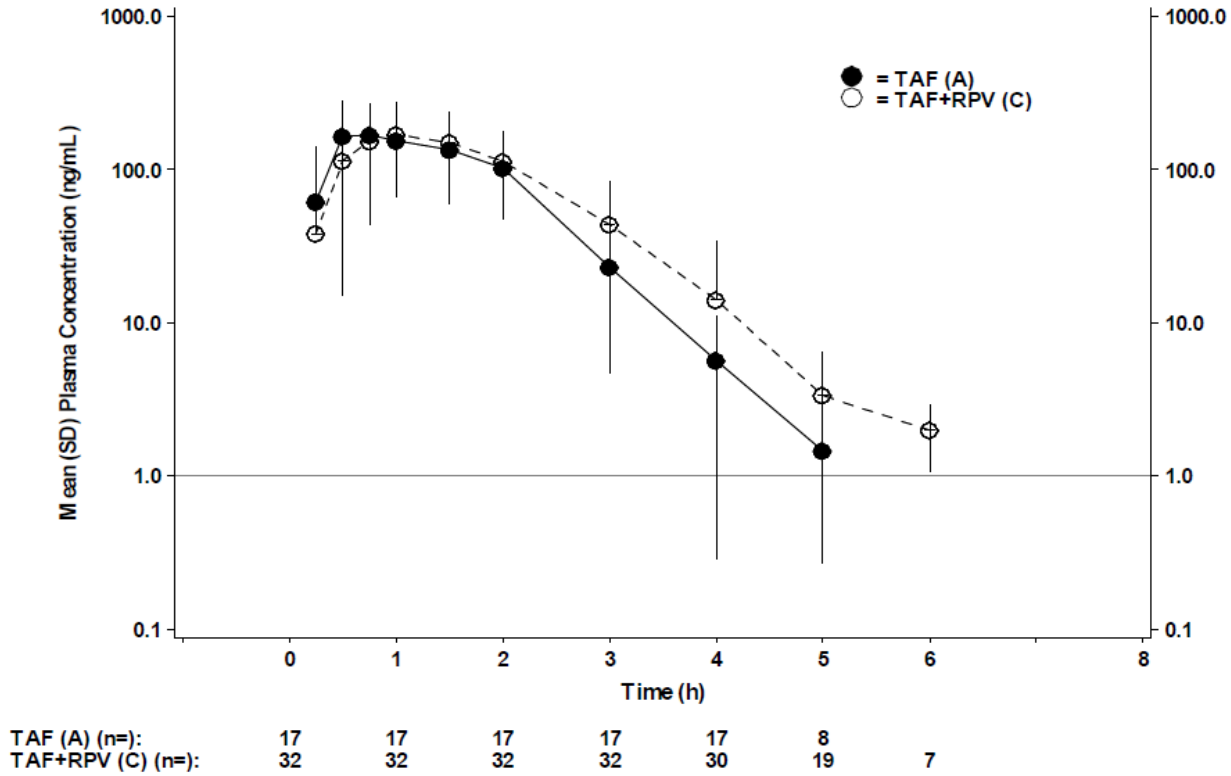
Use of a disallowed concomitant medication was reported for one subject who used aspirin. Use of allowed concomitant medications included acetaminophen (n=3 subjects) and hormonal contraception (n=3 subjects).

Pharmacokinetics

TAF

Plasma concentrations, PK parameters, and statistical comparisons of PK parameters for TAF, TFV, and RPV are shown below.

Figure 43. Mean (SD) TAF plasma concentrations.



Summarized postdose concentration values that were less than or equal to lower limit of quantitation were not displayed in the plot.

Table 62. TAF PK parameters.

TAF PK Parameter, Mean (%CV)[a]	TAF+RPV (N = 32)	TAF (N = 17)
AUC_{tau} (h*ng/mL)	335.6 (29.9)	307.6 (18.4)
AUC_{last} (h*ng/mL)	334.1 (30.0)	306.3 (18.4)
C_{max} (ng/mL)	242.8 (38.2)	238.2 (25.5)
C_{last} (ng/mL)	2.3 (61.3)	2.0 (50.2)
T_{max} (h)	1.00 (0.75, 1.50)	0.75 (0.50, 1.50)
T_{last} (h)	5.00 (4.00, 5.00)	4.00 (4.00, 5.00)
$t_{1/2}$ (h)	0.43 (0.39, 0.49)	0.42 (0.39, 0.48)
CL_{ss}/F (L/h)	81.0 (29.4)	84.1 (19.6)
V_z/F (L)	52.2 (40.5)	53.8 (25.6)

a Data are mean (%CV), except T_{max}, $t_{1/2}$, and T_{last}, which are reported as median (Q1, Q3).

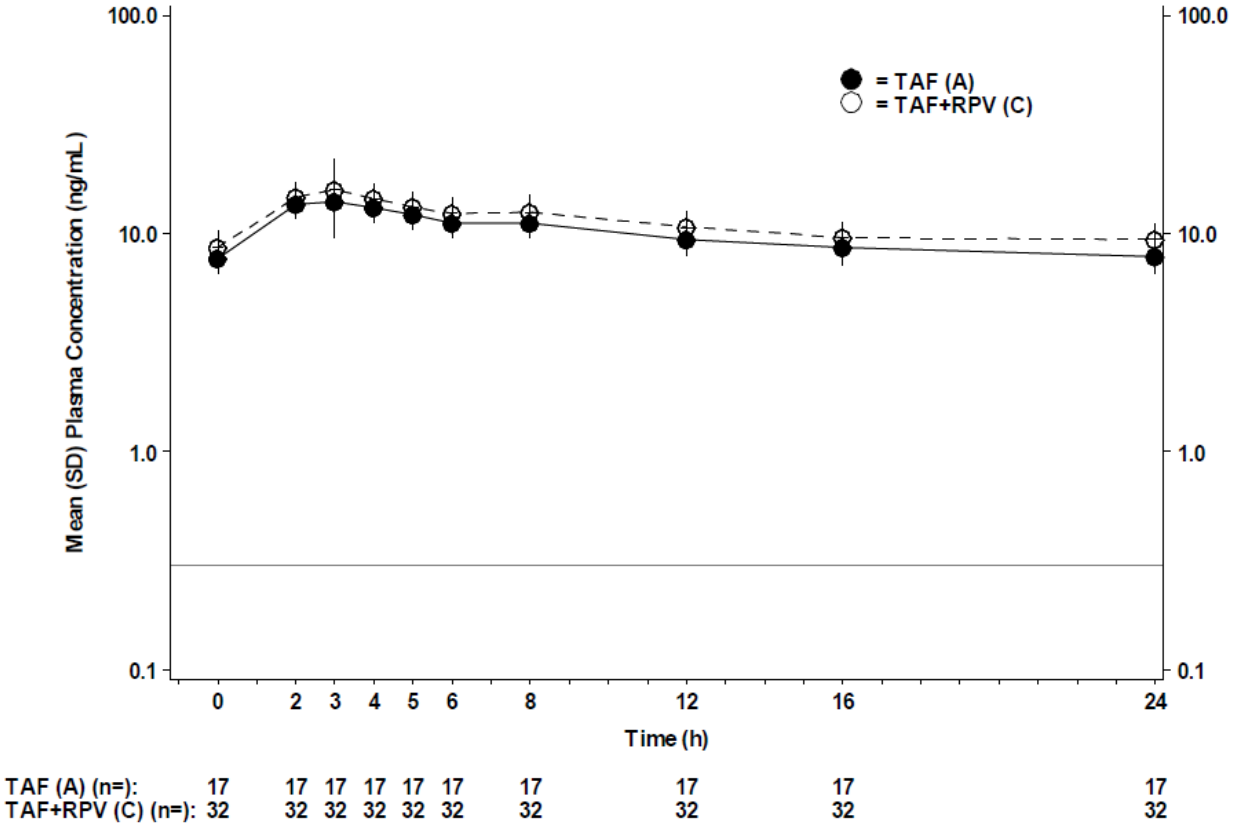
Table 63. Statistical comparison of TAF PK parameters.

TAF PK Parameter	GLSM by Treatment				Statistical Comparison	
	TAF+RPV (Test)		TAF (Reference)		GLSM Ratio (%)	90% CI (%)
	N	GLSM	N	GLSM		
TAF+RPV (Treatment C) vs TAF (Treatment A)						
AUC_{tau} (h*ng/mL)	32	322.75	17	318.21	101.43	93.93, 109.52
AUC_{last} (h*ng/mL)	32	321.22	17	317.06	101.31	93.77, 109.46
C_{max} (ng/mL)	32	223.36	17	220.58	101.26	84.23, 121.73

GLSM = geometric least-squares mean

TFV

Figure 44. Mean (SD) TFV plasma concentrations.



Summarized postdose concentration values that were less than or equal to lower limit of quantitation were not displayed in the plot.

Table 64. TFV PK parameters.

TFV PK Parameter, Mean (%CV)[a]	TAF+RPV (N = 32)	TAF (N = 17)
AUC_{tau} (h*ng/mL)	267.6 (16.9)	237.9 (14.0)
C_{max} (ng/mL)	16.5 (35.9)	14.4 (12.9)
C_{tau} (ng/mL)	9.4 (17.4)	7.9 (16.9)
C_{last} (ng/mL)	9.4 (17.4)	7.9 (16.9)
T_{max} (h)	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)
T_{last} (h)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)
$t_{1/2}$ (h)	45.15 (36.04, 60.34)[b]	33.30 (28.10, 35.75)
CL_{ss}/F (L/h)	18.3 (30.6)[b]	24.5 (32.0)
V_z/F (L)	1132.5 (21.5)[b]	1217.9 (18.4)

a Data are mean (%CV), except T_{max}, $t_{1/2}$, and T_{last}, which are reported as median (Q1, Q3).
b n = 31

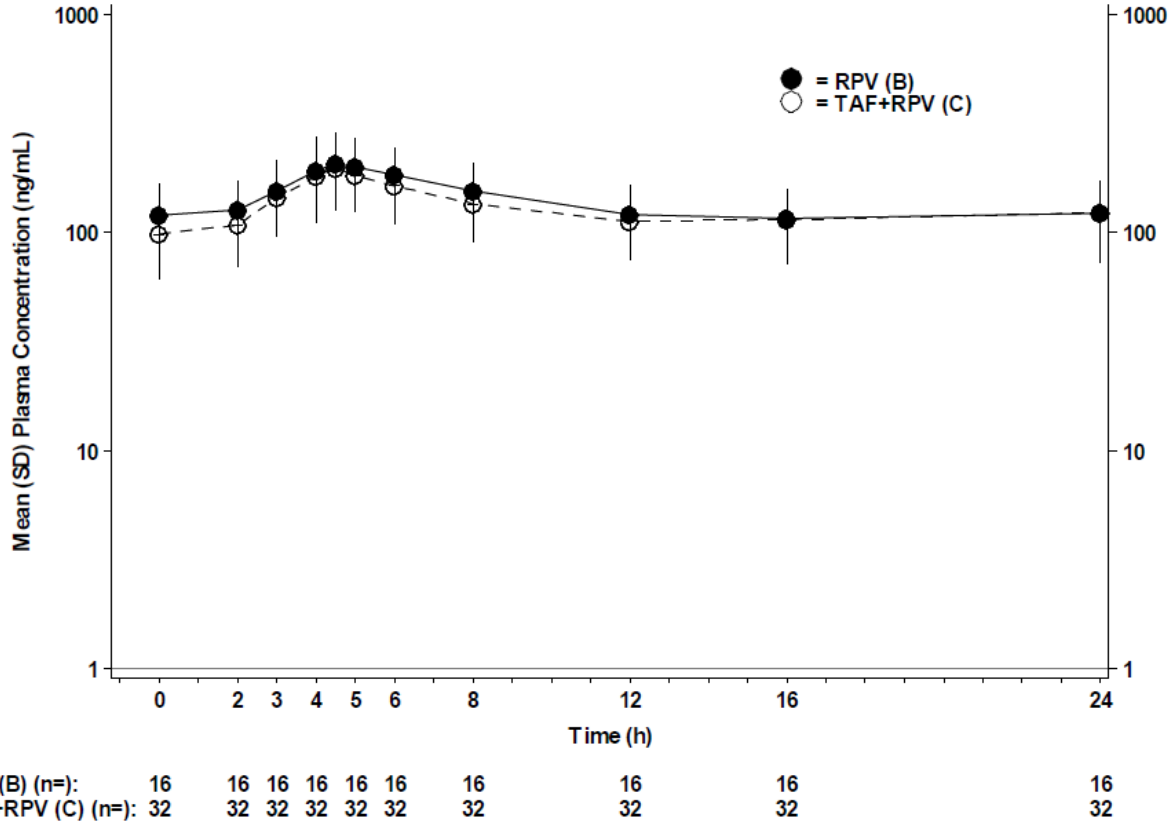
Table 65. Statistical comparison of TFV PK parameters.

TFV PK Parameter	GLSM by Treatment				Statistical Comparison	
	TAF+RPV (Test)		TAF (Reference)		GLSM Ratio (%)	90% CI (%)
	N	GLSM	N	GLSM		
TAF+RPV (Treatment C) vs TAF (Treatment A)						
AUC_{tau} (h*ng/mL)	32	264.00	17	238.56	110.66	107.32, 114.11
C_{max} (ng/mL)	32	15.94	17	14.20	112.27	102.19, 123.33
C_{tau} (ng/mL)	32	9.23	17	7.84	117.72	112.85, 122.80

GLSM = geometric least-squares mean

RPV

Figure 45. Mean (SD) RPV plasma concentrations.



Summarized postdose concentration values that were less than or equal to lower limit of quantitation were not displayed in the plot.

Table 66. RPV PK parameters.

RPV PK Parameter, Mean (%CV)[a]	TAF+RPV (N = 32)	RPV (N = 16)
AUC_{tau} (h*ng/mL)	3052.2 (31.6)	3264.7 (34.3)
C_{max} (ng/mL)	202.6 (31.0)	227.3 (35.3)
C_{tau} (ng/mL)	123.4 (37.7)	122.2 (40.1)
C_{last} (ng/mL)	123.4 (37.7)	122.2 (40.1)
T_{max} (h)	4.50 (4.50, 4.50)	4.50 (4.50, 5.00)
T_{last} (h)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)
$t_{1/2}$ (h)	40.42 (31.95, 59.26)[b]	43.45 (37.55, 72.25)[c]
CL_{ss}/F (L/h)	3.1 (44.3)[b]	2.6 (50.3)[c]
V_z/F (L)	178.7 (29.3)[b]	171.8 (36.3)[c]

a Data are mean (%CV), except T_{max}, $t_{1/2}$, and T_{last}, which are reported as median (Q1, Q3).
b n = 18
c n = 12

Table 67. Statistical comparison of RPV PK parameters.

RPV PK Parameter	GLSM by Treatment				Statistical Comparison	
	TAF+RPV (Test)		RPV (Reference)		GLSM Ratio (%)	90% CI (%)
	N	GLSM	N	GLSM		
TAF+RPV (Treatment C) vs RPV (Treatment B)						
AUC_{tau} (h*ng/mL)	32	2926.33	16	2889.75	101.27	96.42, 106.36
C_{max} (ng/mL)	32	193.24	16	207.98	92.91	87.44, 98.72
C_{tau} (ng/mL)	32	116.44	16	103.25	112.77	103.58, 122.77

GLSM = geometric least-squares mean

Safety

No deaths or SAEs were reported during this study. One AE leading to premature study drug discontinuation (Grade 2 increased hepatic enzymes) was reported for 1 subject assigned to Cohort 2 (RPV->TAF+RPV). Headache was the only AE reported in >1 subject. No clinically relevant changes in laboratory parameters were reported.

DISCUSSION

No study conduct issues were identified. No clinically relevant changes in TAF or TFV PK were observed when coadministered with RPV. RPV exposure is associated with both safety and efficacy; however, when coadministered with TAF, there were clinically insignificant changes in RPV exposures.

LABEL RECOMMENDATIONS

We agree with the proposed F/TAF labeling which states that no clinically significant interaction was observed between TAF and RPV.

3.7 GS-US-120-1538 – Drug interaction study between TAF and MDZ

A Fixed-Sequence, Open-Label, Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Midazolam (Oral and Intravenous) in Healthy Volunteers	
Study Period	8/25/2014-10/04/2014
Link	\\cdsesub1\evsprod\nda208215\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-120-1538\report-body.pdf

STUDY DESIGN

		Study Period									
	Screening		1	Washout	2	3	4	5	6	Discharge	Telephone Follow-Up
Day	−28	−1	1	2	3	4–15	16	17	18	19	25 (± 2)
Treatment	X	X	A MDZ_{oral}	X	B MDZ_{IV}	C TAF	D TAF + MDZ_{oral}	C TAF	E TAF + MDZ_{IV}	X	X

IV = intravenous; MDZ = midazolam; TAF = tenofovir alafenamide; X = no study treatment administered
Shaded area indicates study clinic confinement.

- **Treatment A (Day 1):** MDZ_{oral} 2.5 mg oral syrup
- **Treatment B (Day 3):** MDZ_{IV} 1 mg solution for injection (slow IV push over 1 min)
- **Treatment C (Days 4-15 and 17):** TAF 25-mg tablet
- **Treatment D (Day 16):** TAF 25-mg tablet + MDZ_{oral} 2.5 mg oral syrup coadministered
- **Treatment E (Day 18):** TAF 25 mg tablet + MDZ_{IV} 1 mg solution for injection (slow IV push over 1 minute) administered within 5 min of each other

All study drugs were administered in the morning at approximately the same time each day and within 5 minutes of completion of a standard breakfast.

Population	Healthy volunteers
Study Rationale	Evaluate the effect of TAF on the PK of oral and IV midazolam
Dose Selection Rationale	TAF 25 mg is one of the doses submitted for approval as part of F/TAF. The midazolam doses are commonly used in drug interaction studies.
Formulation	TAF 25 mg tablet (lot # CM1306B2) MDZ 2 mg/mL oral syrup (lot # 460339A) MDZ 1 mg/mL for injection (lot # 39-382-DK)

Interfering Substances Excluded	Any prescription and over-the-counter medications except acetaminophen, ibuprofen, hormonal contraceptives, topical hydrocortisone, and flumazenil (midazolam antidote).
Sampling Times	• **MDZ, 1'-OH-MDZ (oral dose) (Days 1 and 16):** predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose • **MDZ, 1'-OH-MDZ (IV dose) (Days 3 and 18):** predose, 5 min postdose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose • **TFV (Days 5, 12, 13, and 14):** predose • **TAF (Days 15, 16, and 18):** predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours postdose

RESULTS

Bioanalytical methods

Plasma concentrations of TAF, TFV, MDZ, and 1'-OH-MDZ were reported to have been determined using fully validated LC/MS/MS methods and samples were reported to have been measured within the timeframe supported by stability data (Table 68).

Table 68. Bioanalytical methods.

Parameter	TAF	TFV	MDZ	1'-OH-MDZ
Linear Range (ng/mL)	1 to 1000	0.3 to 300	0.1 to 100	0.1 to 100
LLOQ (ng/mL)	1	0.3	0.1	0.1
Interassay Precision Range (%CV)	1.8 to 7.3	1.8 to 4.8	2.4 to 7.1	3.0 to 8.2
Interassay Accuracy Range (%RE)	−3.7 to 6.5	−2.7 to 2.7	−2.7 to −1.0	−3.0 to −1.3
Stability in Frozen Matrix (days)	520 at −70°C	366 at −20°C and 1092 at −70°C	63 at −20°C and 135 at −70°C	63 at −20°C and 135 at −70°C

LLOQ = lower limit of quantitation; CV = coefficient of variation; RE = relative error

Protocol deviations

No "important" protocol deviations were reported.

Study population

Eighteen subjects were enrolled and all completed the study (Table 69).

Table 69. Subject demographics.

Demographic/Characteristic	Treatment Sequence A-B-C-D-C-E (N = 18)
Age (Years)	
N	18
Mean (SD)	38 (5.0)
Median	39
Q1, Q3	34, 41
Min, Max	24, 45
Sex, n (%)	
Male	9 (50.0%)
Female	9 (50.0%)
Race, n (%)	
American Indian or Alaska Native	0
Asian	0
Black or African American	2 (11.1%)
Native Hawaiian or Other Pacific Islander	0
White	16 (88.9%)
Other	0
Ethnicity, n (%)	
Hispanic/Latino	18 (100.0%)
Non-Hispanic/Latino	0
Baseline $eGFR_{CG}$, (mL/min)	
N	18
Mean (SD)	120.1 (14.84)
Median	119.5
Q1, Q3	109.1, 132.8
Min, Max	86.4, 142.9
Baseline Weight (kg)	
N	18
Mean (SD)	73.7 (13.56)
Median	69.8

Demographic/Characteristic	Treatment Sequence A-B-C-D-C-E (N = 18)
Q1, Q3	65.2, 82.1
Min, Max	54.8, 107.0
Baseline Weight (kg): Male	
N	9
Mean (SD)	83.3 (12.41)
Median	82.1
Q1, Q3	71.3, 87.0
Min, Max	69.3, 107.0
Baseline Weight (kg): Female	
N	9
Mean (SD)	64.2 (5.76)
Median	65.2
Q1, Q3	60.4, 68.9
Min, Max	54.8, 71.5
Baseline Height (cm)	
N	18
Mean (SD)	165.1 (9.73)
Median	163.0
Q1, Q3	157.0, 170.5
Min, Max	151.0, 189.5
Baseline Height (cm): Male	
N	9
Mean (SD)	171.8 (9.22)
Median	170.5
Q1, Q3	168.0, 175.5
Min, Max	157.0, 189.5
Baseline Height (cm): Female	
N	9
Mean (SD)	158.4 (4.00)
Median	158.0
Q1, Q3	156.0, 162.0
Min, Max	151.0, 164.0
Baseline BMI (kg/m^2)	
N	18
Mean (SD)	26.8 (2.34)
Median	27.4
Q1, Q3	25.5, 28.6
Min, Max	22.5, 29.9

Note: Treatment Sequence A = MDZ_{oral}; B = MDZ_{IV}; C = TAF; D = TAF + MDZ_{oral}; E = TAF + MDZ_{IV}

Pharmacokinetics

Plasma concentrations, PK parameters, and statistical comparisons of PK parameters for MDZ, 1'-OH-MDZ, and TAF are shown below. In addition, trough TFV concentrations were evaluated to assess attainment of steady-state.

Oral MDZ and 1'-OH-MDZ

Figure 46. Mean (SD) MDZ_{oral} plasma concentrations.

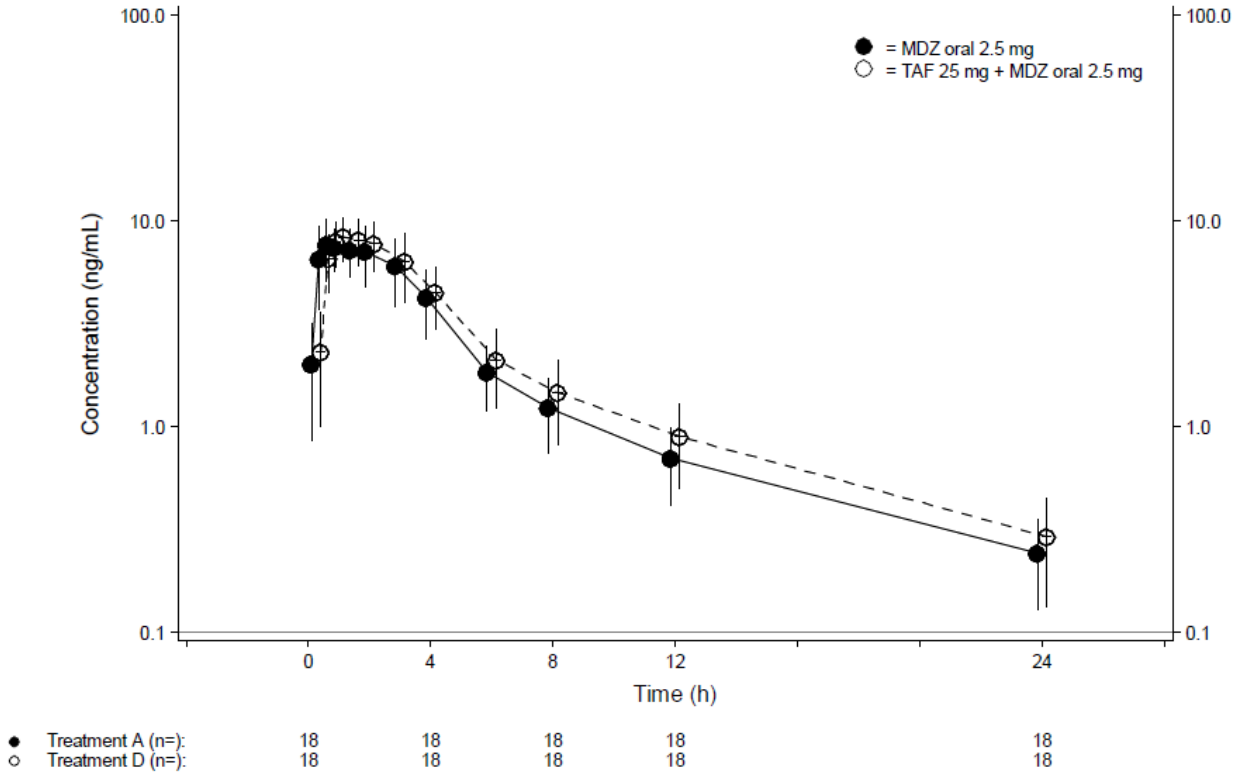


Table 70. MDZ_{oral} PK parameters.

MDZ_{oral} PK Parameter	**TAF+MDZ_{oral} (N = 18)**	**MDZ_{oral} (N = 18)**
AUC_{inf} (h*ng/mL), mean (%CV)	49.4 (32.0)	43.7 (31.4)
AUC_{last} (h*ng/mL), mean (%CV)	46.5 (31.8)	41.3 (30.8)
AUC_{exp} (%), mean (%CV)	5.89 (41.71)	5.36 (41.04)
C_{max} (ng/mL), mean (%CV)	8.9 (22.5)	8.8 (26.9)
$t_{1/2}$ (h), median (Q1, Q3)	6.72 (6.27, 7.13)	6.40 (5.59, 7.60)
T_{max} (h), median (Q1, Q3)	1.00 (0.75, 1.50)	0.88 (0.75, 2.00)

TAF 25 mg was administered as an oral tablet; MDZ 2.5 mg was administered as oral syrup.

Table 71. Statistical comparisons of MDZ_{oral} PK parameters.

MDZ_{oral} PK Parameter	GLSM by Treatment		GLSM Ratio (%) Test/Reference	90% CI
	Test Treatment (TAF+MDZ_{oral}) (N = 18)	Reference Treatment (MDZ_{oral}) (N = 18)		
AUC_{last} (h*ng/mL)	44.17	39.34	112.28	103.05, 122.33
AUC_{inf} (h*ng/mL)	46.95	41.56	112.97	103.61, 123.17
C_{max} (ng/mL)	8.68	8.52	101.87	91.96, 112.84

GLSM = geometric least-squares mean
TAF 25 mg was administered as an oral tablet; MDZ 2.5 mg was administered as oral syrup.

Figure 47. Mean (SD) 1'-OH-MDZ_{oral} plasma concentrations.

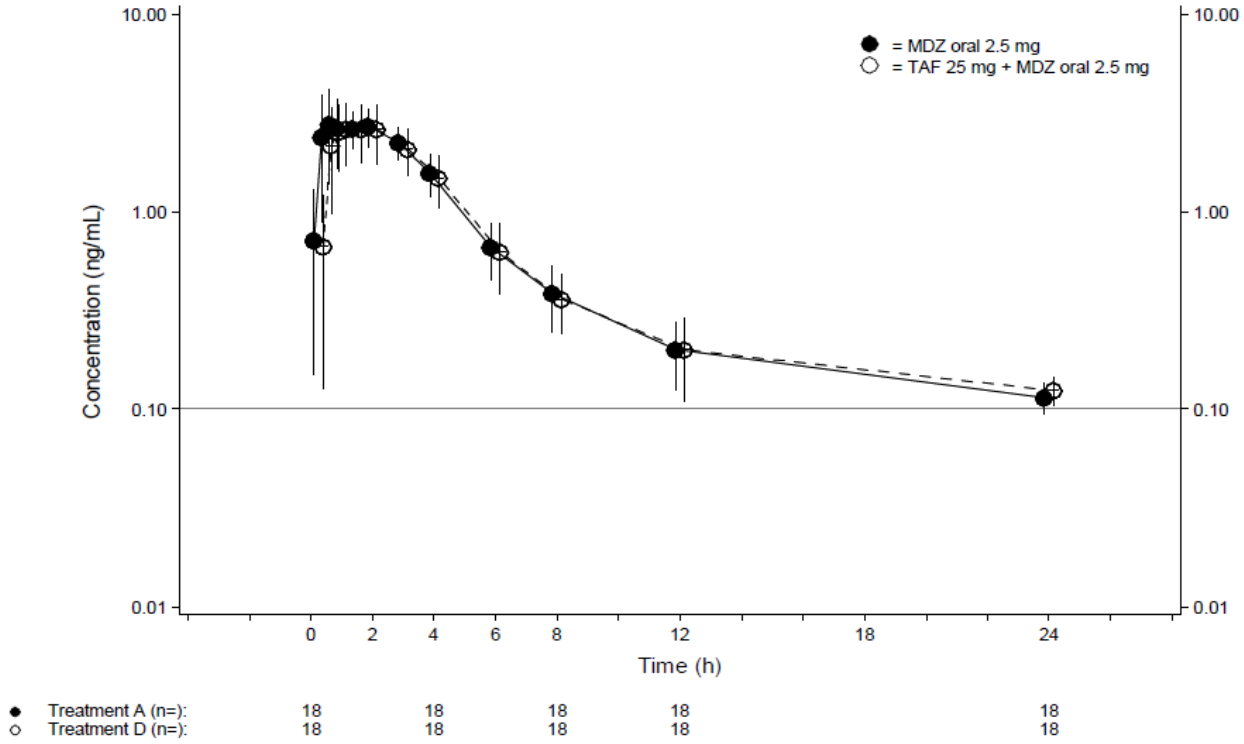


Table 72. 1'-OH-MDZ_{oral} PK parameters.

1'-OH-MDZ_{oral} PK Parameter	TAF+MDZ_{oral} (N = 18)	MDZ_{oral} (N = 18)
AUC_{inf} (h*ng/mL), mean (%CV)	14.3 (34.8)	14.3 (24.9)
AUC_{last} (h*ng/mL), mean (%CV)	12.9 (29.7)	13.4 (26.1)
AUC_{exp} (%), mean (%CV)	8.93 (85.04)	6.95 (29.87)
C_{max} (ng/mL), mean (%CV)	3.0 (32.2)	3.3 (33.4)
$t_{1/2}$ (h), median (Q1, Q3)	3.55 (3.19, 4.59)	3.56 (3.24, 4.42)
T_{max} (h), median (Q1, Q3)	1.50 (0.75, 2.00)	1.25 (0.75, 2.00)

TAF 25 mg was administered as an oral tablet; MDZ 2.5 mg was administered as oral syrup.

Table 73. Statistical comparisons of 1'-OH-MDZ_{oral} PK parameters.

1'-OH-MDZ_{oral} PK Parameter	GLSM by Treatment		GLSM Ratio (%) Test/Reference	90% CI
	Test Treatment (TAF+MDZ_{oral}) (N = 18)	Reference Treatment (MDZ_{oral}) (N = 18)		
AUC_{last} (h*ng/mL)	12.37	13.00	95.13	86.05, 105.16
AUC_{inf} (h*ng/mL)	13.65	13.96	97.75	88.02, 108.56
C_{max} (ng/mL)	2.88	3.18	90.65	76.64, 107.22

GLSM = geometric least-squares mean
TAF 25 mg was administered as an oral tablet; MDZ 2.5 mg was administered as oral syrup.

IV MDZ and 1'-OH-MDZ

Figure 48. Mean (SD) MDZ_{IV} plasma concentrations.

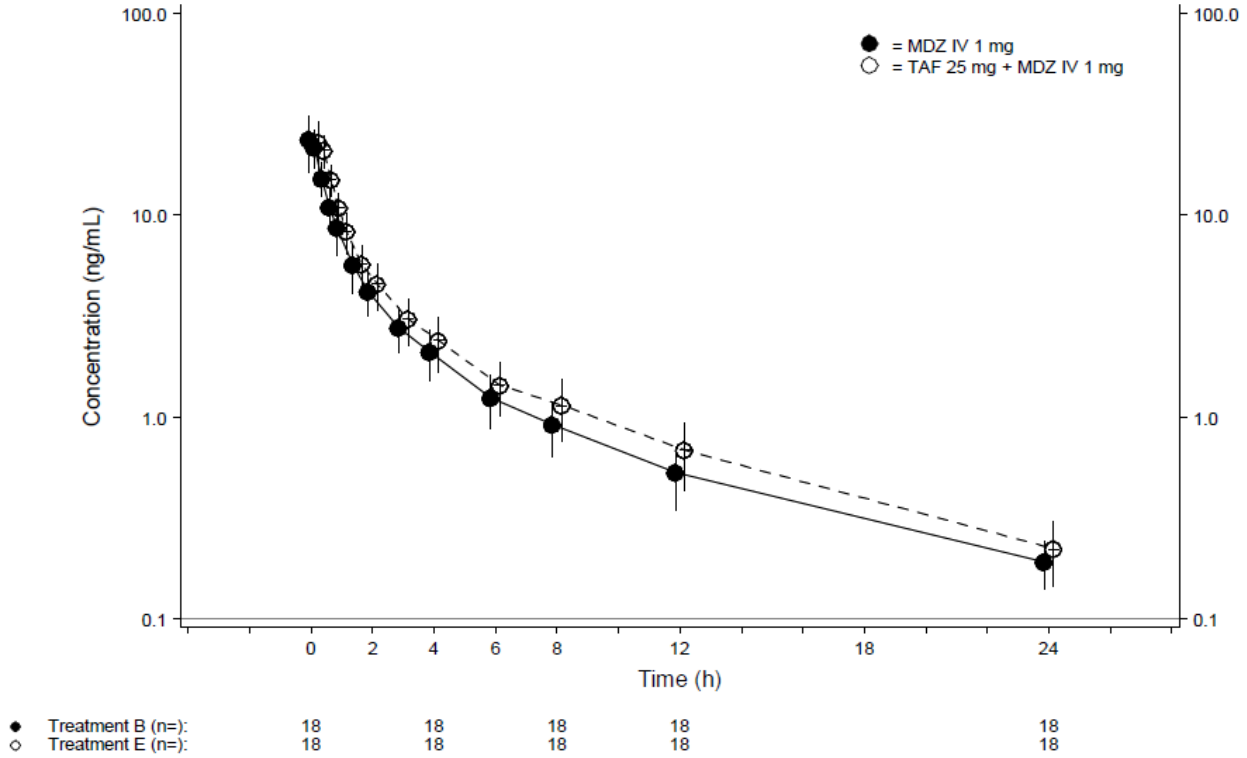


Table 74. MDZ_{IV} PK parameters.

MDZ_{IV} PK Parameter	**TAF+MDZ_{IV} (N = 18)**	**MDZ_{IV} (N = 18)**
AUC_{inf} (h*ng/mL), mean (%CV)	43.8 (21.7)	40.4 (21.9)
AUC_{last} (h*ng/mL), mean (%CV)	41.6 (21.4)	38.4 (22.3)
AUC_{exp} (%), mean (%CV)	4.94 (28.51)	4.97 (30.19)
C_{max} (ng/mL), mean (%CV)	23.8 (21.9)	24.4 (27.8)
$t_{1/2}$ (h), median (Q1, Q3)	6.53 (5.94,6.96)	6.47 (5.35,7.13)

TAF 25 mg was administered as an oral tablet; MDZ 1.0 mg was administered IV.

Table 75. Statistical comparisons of MDZ_{IV} PK parameters.

MDZ_{IV} PK Parameter	GLSM by Treatment		GLSM Ratio (%) Test/Reference	90% CI
	Test Treatment ($TAF+MDZ_{IV}$) (N = 18)	Reference Treatment (MDZ_{IV}) (N = 18)		
AUC_{last} (h*ng/mL)	40.73	37.54	108.47	103.57, 113.61
AUC_{inf} (h*ng/mL)	42.85	39.51	108.45	103.72, 113.40
C_{max} (ng/mL)	23.29	23.48	99.19	88.51, 111.15

GLSM = geometric least-squares mean
TAF 25 mg was administered as an oral tablet; MDZ 1.0 mg was administered IV.

Figure 49. Mean (SD) 1'-OH-MDZ_{IV} plasma concentrations.

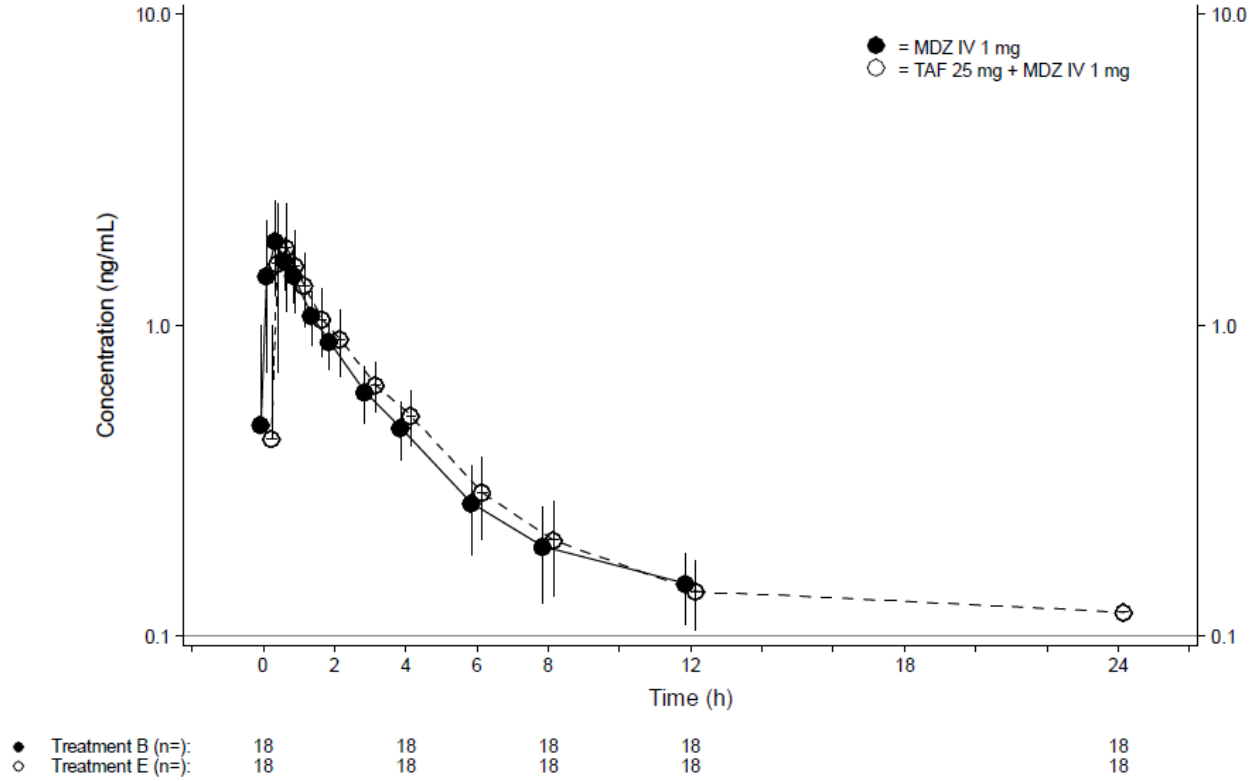


Table 76. 1'-OH-MDZ_{IV} PK parameters.

1'-OH-MDZ_{IV} PK Parameter	TAF+MDZ_{IV} (N = 18)	MDZ_{IV} (N = 18)
AUC_{inf} (h*ng/mL), mean (%CV)	6.8 (27.2)	6.1 (27.9)
AUC_{last} (h*ng/mL), mean (%CV)	5.7 (26.4)	5.3 (25.3)
AUC_{exp} (%), mean (%CV)	15.05 (35.91)	13.28 (42.77)
C_{max} (ng/mL), mean (%CV)	1.9 (39.5)	1.9 (31.6)
$t_{1/2}$ (h), median (Q1, Q3)	4.90 (3.88,7.18)	2.91 (2.66,4.06)
T_{max} (h), median (Q1, Q3)	0.50 (0.25,0.50)	0.50 (0.50,0.75)

TAF 25 mg was administered as an oral tablet; MDZ 1.0 mg was administered IV.

Table 77. Statistical comparisons of 1'-OH-MDZ_{IV} PK parameters.

1'-OH-MDZ_{IV} PK Parameter	GLSM by Treatment		GLSM Ratio (%) Test/Reference	90% CI
	Test Treatment (TAF+MDZ_{IV}) (N = 18)	Reference Treatment (MDZ_{IV}) (N = 18)		
AUC_{last} (h*ng/mL)	5.55	5.12	108.49	100.75, 116.83
AUC_{inf} (h*ng/mL)	6.55	5.91	110.71	102.31, 119.79
C_{max} (ng/mL)	1.80	1.87	96.45	85.67, 108.59

GLSM = geometric least-squares mean
TAF 25 mg was administered as an oral tablet; MDZ 1.0 mg was administered IV.

TAF

Figure 50. Mean (SD) TAF plasma concentrations.

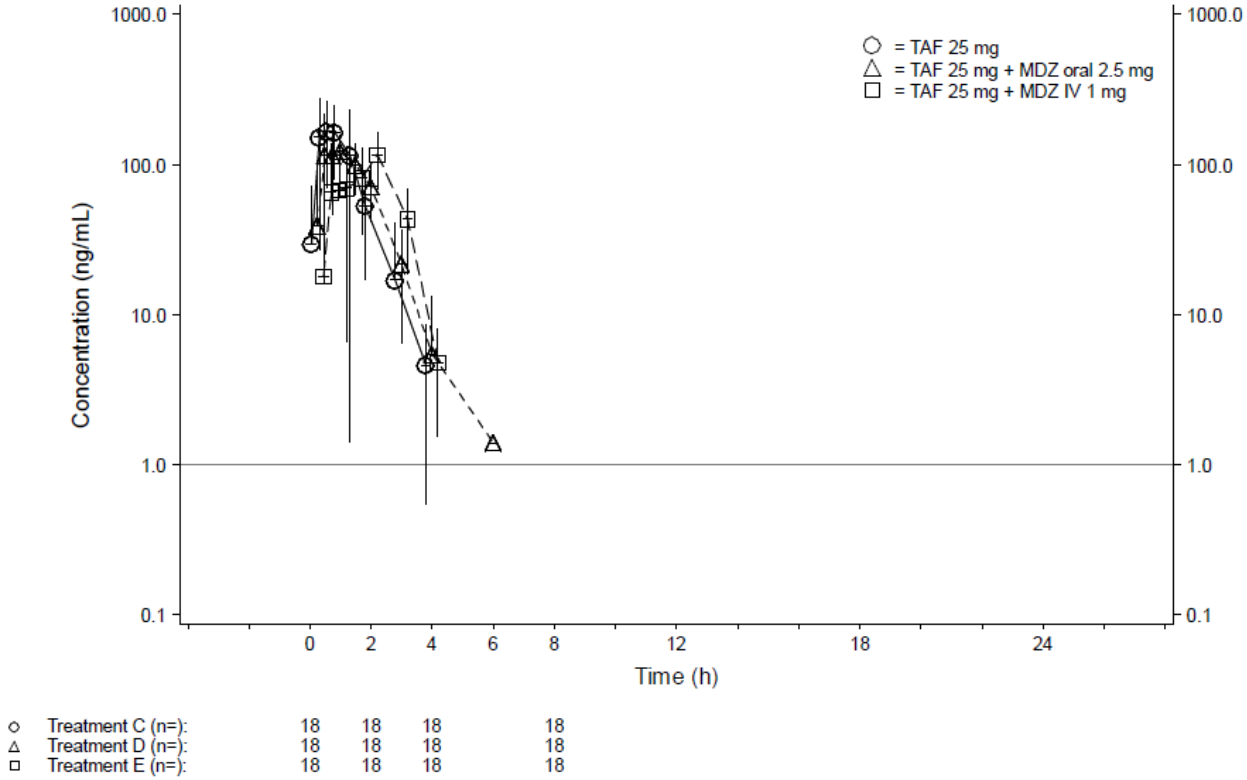


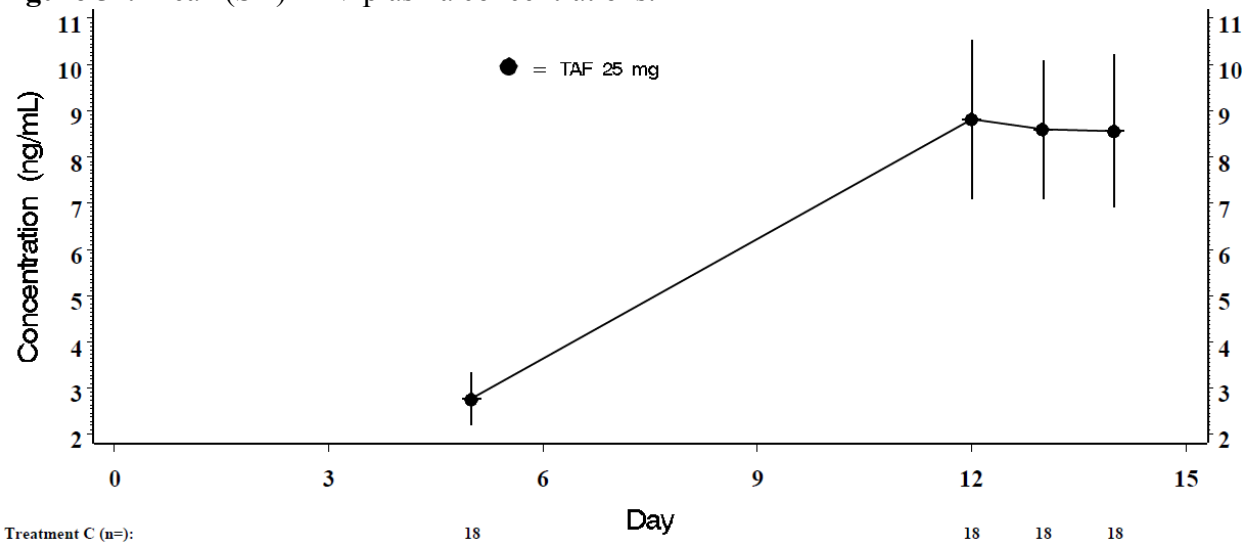
Table 78. TAF PK parameters.

TAF PK Parameter	TAF+MDZ$_{oral}$ (N = 18)	TAF+MDZ$_{IV}$ (N = 18)	TAF (N = 18)
AUC_{last} (h*ng/mL), mean (%CV)	228.7 (20.0)	215.1 (23.2)	249.1 (27.3)
C_{last} (ng/mL), mean (%CV)	4.4 (138.0)	4.7 (67.8)	4.0 (74.5)
C_{max} (ng/mL), mean (%CV)	174.7 (33.4)	149.9 (29.8)	249.8 (47.6)
$t_{1/2}$ (h), median (Q1, Q3)	0.43 (0.39,0.49)	0.41 (0.37,0.43)	0.37 (0.34,0.42)
T_{max} (h), median (Q1, Q3)	0.88 (0.50,1.50)	1.75 (0.75,2.00)	0.88 (0.50,1.50)

TAF 25 mg was administered as an oral tablet; MDZ 2.5 mg was administered as oral syrup, and MDZ 1.0 mg was administered IV.

TFV

Figure 51. Mean (SD) TFV plasma concentrations.



Safety

The most frequently reported AEs by treatment were dizziness (16.7%), vessel puncture site hemorrhage (11.1%), and vessel puncture site pain (11.1%) while subjects were receiving MDZ_{IV}; contact dermatitis (11.1%) while subjects were receiving TAF; and infusion site pain (11.1%), while subjects were receiving TAF+MDZ_{IV}. No SAEs or deaths occurred during the study. Two subjects had graded laboratory abnormalities during the study: 1 subject with Grade 1 decreased bicarbonate and Grade 3 blood in urine (menses confirmed) and 1 (female) subject with Grade 1 blood in urine.

DISCUSSION/REVIEWER'S COMMENTS

No bioanalytical or study conduct issues were identified.

Steady-state TAF and TFV was demonstrated prior to the TAF+MDZ arms (Figure 51). There was no clinically significant effect of TAF on oral or IV MDZ or 1'-OH-MDZ exposures (<13% increase in MDZ exposure), indicating that TAF is not an in vivo intestinal or hepatic CYP3A inhibitor.

FTC was not evaluated in this study but is known to be minimally metabolized and is not a CYP inhibitor.

LABEL RECOMMENDATIONS

We agree with the proposed F/TAF labeling which states that no clinically significant interaction was observed between TAF and midazolam.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIO SAMPSON
12/07/2015

ISLAM R YOUNIS
12/07/2015