CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208351Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA	208351
Submission Type	Non-NME NDA [505(b)(1)]
Applicant Name	Gilead
Submission Date	7/1/2015
Generic Name	Emtricitabine (FTC)/Rilpivirine (RPV)/Tenofovir Alafenamide (TAF) (F/R/TAF or FTC/RPV/TAF)
Dosage Form (Strength)	Tablet (200/25/25 mg)
Indication	Treatment of HIV-1 in (b) (4) virologically suppressed patients aged ≥12 years
Review Team	Mario Sampson, PharmD, Islam Younis, PhD

This is an addendum to the NDA 208351 Clinical Pharmacology review dated 12/1/2015. Included in this review is a summary of clinical pharmacology-related labeling negotiations with the sponsor, which are now complete. A substantial portion of these negotiations occurred after submission of the initial review of this application. As shown below in Table 1, clinical pharmacology-related labeling negotiations were focused on the Drug Interactions (section 7) and Pharmacokinetics (section 12.3) sections, and that FDA and the sponsor reached agreement on all of the issues. Of note are the FDA recommendation to take FTC/RPV/TAF with a meal (versus (b) (4) as was the sponsor's initial proposal) and to remove drug interaction information for the effect of efavirenz on TAF (see Table 1). The recommendation to take FTC/RPV/TAF with a meal was made because the food effect between FTC/RPV/TAF is similar to single agent RPV, which is labeled to be taken with a meal, and in our opinion a meal represents a significant quantity of food (b) (4) (b) (4) The recommendation to remove drug interaction information for the effect of efavirenz on TAF was made because FTC/RPV/TAF is a complete regimen and should not be taken with efavirenz and because we do not consider efavirenz to be representative of worst case Pgp induction.

Table 1. Summary of clinical pharmacology-related labeling negotiations.

Section	Issue	FDA edits 1/14/16	Sponsor edits 1/27/16	FDA edits 2/4/16	Sponsor edits 2/11/16
Dosing and administration	FTC/RPV/TAF should (b) (4)	Replace with "take with a meal"	Replaced with (b) (4) with comment that data in the NDA supports this.	Replaced with "take with a meal". Included rationale: the food effect between F/R/TAF is similar to single agent RPV, which is labeled to be taken with a meal; in our opinion a meal represents a significant quantity of food (b) (4)	Accepted FDA recommendation
Drug interactions	(b) (4)	Deleted paragraph	(b) (4)		Accepted FDA recommendation
Drug interactions	(b) (4)		Accepted FDA recommendation		
Drug interactions	Clinical significance of increased RPV and TAF exposure	For inhibition of 3A resulting in increased RPV exposure and inhibition of Pgp resulting in increased TAF exposure, added that possible adverse events may result	Accepted FDA recommendation		
Drug interactions	Clinical significance of using FTC/RPV/TAF with QT-prolonging drugs	Change from (b) (4) to "consider alternative medications" in order to be more specific	Accepted FDA recommendation		
Specific Populations	Hepatic impairment		Changed from (b) (4)	Accepted sponsor's recommendation	

			(b) (4) severe hepatic impairment"		
Pharmacokinetics	(b) (4)	Requested that sponsor add (b) (4)	Proposed not to do so to be consistent with the E/C/F/TAF label	Accepted sponsor's recommendation	
Pharmacokinetics	(b) (4)		Added back, stating that it is important to prescribers	Deleted statement with initial rationale	Accepted FDA recommendation
Pharmacokinetics	Renal impairment categories	Asked sponsor to replace the ter (b) (4) with the specific GFR values of the enrolled subjects	Did not address comment	Repeated initial comment	Accepted FDA recommendation
Pharmacokinetics	(b) (4)				Accepted FDA recommendation
Pharmacokinetics	Inclusion of ARVs in DDI table for effect of other drugs on TAF PK	Removed COBI because it is an ARV and ODEFSEY is a complete regimen	Added back noting that COBI is a representative strong CYP3A/Pgp inhibitor	Accepted sponsor's recommendation	
Pharmacokinetics	(b) (4)				Accepted FDA recommendation

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/s/

MARIO SAMPSON
03/30/2016

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03/30/2016

CLINICAL PHARMACOLOGY REVIEW

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2 Executive summary

2.1 Background

FTC, RPV, and TAF are approved drugs and their approved doses were used in the FTC/RPV/TAF combination tablet. Relative bioavailability (BA) study 366-1159, which compared the exposures of FTC/RPV/TAF versus RPV and versus E/C/F/TAF, is the basis for approval of FTC/RPV/TAF. Also included in this NDA were a food effect study and two drug interaction studies. The same formulation of FTC/RPV/TAF was used in all clinical studies. No efficacy/safety studies were submitted to this NDA. Clinical pharmacology-related labeling for FTC/RPV/TAF was primarily derived from previously approved products containing the components of FTC/RPV/TAF.

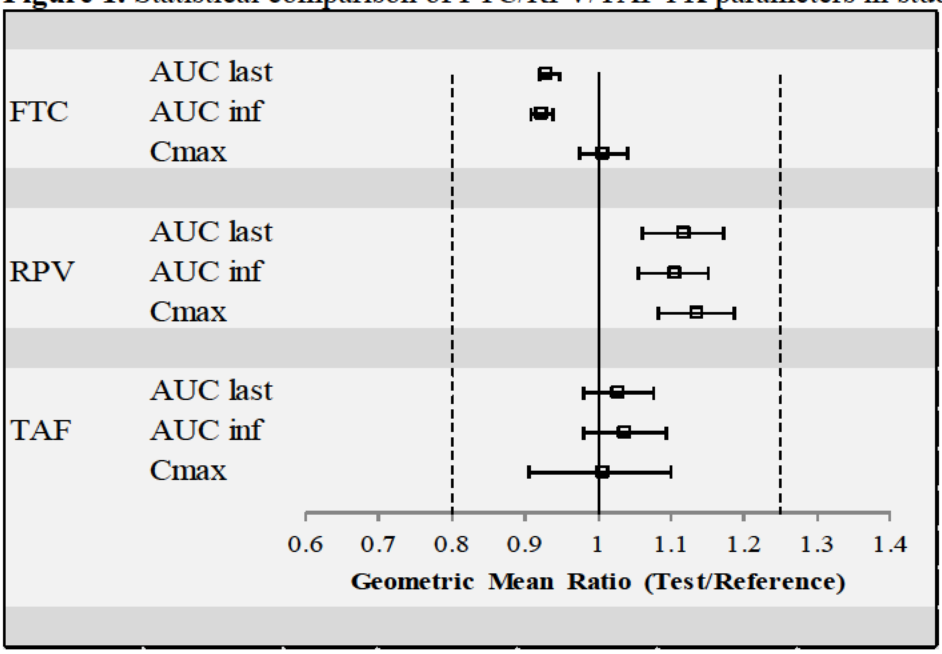
A clinical and analytical site inspection was requested for the pivotal relative BA study 366-1689. Based on the last inspection of the site, the Division of New Drug Bioequivalence Evaluation recommended accepting the analytical data without an on-site inspection (memo dated 8/17/2015). According to the sponsor, the commercial formulation is identical to that used in this study. The results of the clinical inspection are expected by 11/29/2015.

2.2 Summary of clinical pharmacology findings

2.2.1 Relative BA Study

In relative BA study 366-1159, similar exposures of FTC, RPV, and TAF between FTC/RPV/TAF, RPV, and E/C/F/TAF were demonstrated, which supports approval of FTC/RPV/TAF (Figure 1).

Figure 1. Statistical comparison of FTC/RPV/TAF PK parameters in study 366-1159.



Source: Prepared by reviewer. Error bars are 90% confidence intervals.

2.2.2 Food Effect

RPV AUC from FTC/RPV/TAF in the fasted state was decreased ~42% relative to administration with a high fat (800-1000 calories, ~50% fat) meal (Table 1). This is the same magnitude of reduction in RPV AUC observed with single agent RPV in the fasted state relative to a normal caloric and high fat meal. RPV is labeled to be taken with a meal. RPV AUC from Complera® (FTC/RPV/TDF) was decreased 14% in the fasted state relative to a standard meal (400 calories and 13 grams of fat), and was not evaluated with regard to a high fat meal; Complera® is labeled to be taken with food. Because low RPV exposure is associated with virologic failure (NDA 202022 Clinical Pharmacology review dated 9/2/2010), we recommend that FTC/RPV/TAF should be labeled to "be taken with a meal", which differs from the sponsor's recommendation of (b) (4). Our view is that to most people the term "meal" signifies a substantial quantity of food (b) (4).

Table 1. Results of food effect study 366-1651.

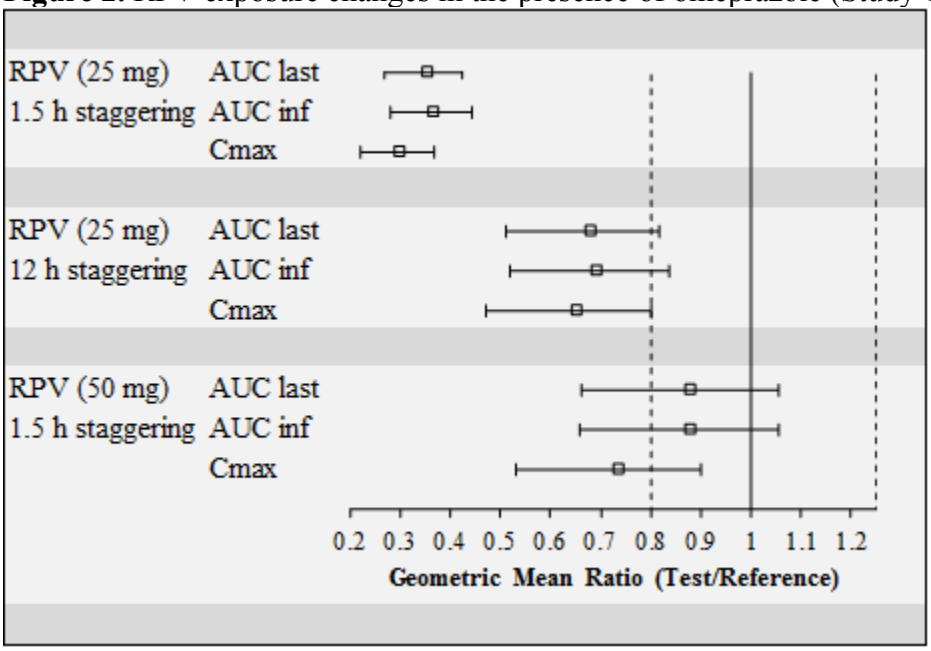
Analyte	Geometric mean AUC ratio	
	Moderate-fat meal relative to fasted (%), (90% CI)	High-fat meal relative to fasted (%), (90% CI)
FTC	91 (89, 93)	88 (85, 90)
RPV	113 (103, 123)	172 (149, 199)*
TAF	145 (133, 158)	153 (139, 169)

Source: prepared by reviewer. The 42% reduction in the fast state was estimated by 1-(100/172)=0.42.

2.2.3 Drug-Drug Interactions

Study TMC278-TiDP6 evaluated drug-drug interactions between RPV and omeprazole at the clinical dose of RPV (25 mg) with RPV given 1.5 hours or 12 hours after omeprazole or with a higher RPV dose of 50 mg given 1.5 hours after omeprazole. When administered 1.5 hours after omeprazole, mean RPV AUC was decreased 63% (RPV 25 mg) and 12% (RPV 50 mg). Also, RPV administered 12 hours after omeprazole resulted in a mean RPV AUC decrease of 32% (Figure 2). Due to the association of low RPV exposure with virologic failure, we agree with the labeling proposal to contraindicate the use of omeprazole with RPV. This is consistent with current RPV single agent labeling, which contraindicates the coadministration of omeprazole and RPV based on the findings of a prior RPV-omeprazole drug-drug interaction study that utilized a supratherapeutic (150 mg) RPV dose.

Figure 2. RPV exposure changes in the presence of omeprazole (Study TMC278-TiDP6-C154).



Source: Prepared by reviewer. Error bars are 90% confidence intervals.

Drug interaction study 366-1689 evaluated two-way drug interactions between the components of FTC/RPV/TAF and ledipasvir/sofosbuvir (LDV/SOF). Clinically insignificant increases in TAF and TFV exposure were observed; other components of the study drugs were unaffected. We agree with the labeling proposal that there are no clinically significant drug interactions between FTC/RPV/TAF and LDV or SOF.

2.3 Recommendations

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

2.4 Labeling recommendations

Internal discussion is ongoing regarding how to label combination products and to what extent labeling from other approved products should be duplicated in the combination label versus referred to. Labeling negotiations have yet to begin. We do not anticipate significant labeling modifications to the clinical pharmacology labeling. As stated above, we recommend changing food effect labeling from FTC/RPV/TAF should be [redacted] (b) (4) to "taken with a meal". Also, FTC/RPV/TAF labeling for renal impairment (no dose adjustment for CrCL ≥ 30 mL/min) and hepatic impairment (no dose adjustment for mild-moderate, not recommended in severe) are consistent with approved products E/C/F/TAF and RPV and are therefore acceptable.

3 Individual study reviews

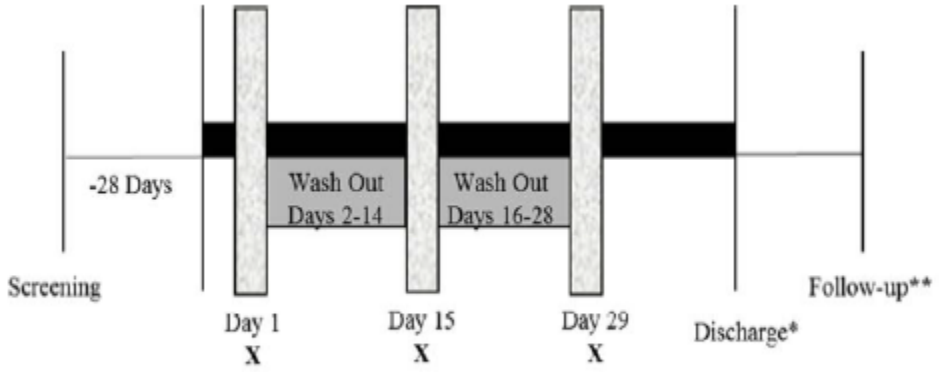
Sources for analyses

Figures and tables in the individual study reviews were from the respective study reports unless otherwise indicated.

3.1 Study 366-1159 – relative BA of FTC/RPV/TAF versus RPV and versus E/C/F/TAF

A Phase 1, Randomized, Open-Label, Single-Dose, Three-Way, Six-Sequence, Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine, Rilpivirine and Tenofovir Alafenamide from a Fixed Dose Combination of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (200/25/25 mg) Relative to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination and Rilpivirine (25 mg)	
Study Period	10/21/2014-12/26/2014
Link	(b) (4)

STUDY DESIGN



Dosing

Clinic Confinement

Wash out

X Intensive PK Draws relative to dosing. Treatment A and B: through 336 hours; Treatment C: through 48 hours

* Discharge: Treatment Sequences 1 and 3: Day 35; Treatment Sequences 2, and 4-6: Day 43

** Follow-up phone call 7 days (+/- 2 days) following discharge

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

The dose was administered within 5 minutes of completing a standardized moderate fat breakfast (~600 kcal, ~27% fat).

Treatment Sequence	Day 1	Days 2-14	Day 15	Days 16-28	Day 29	Discharge
1	A	Washout	B	Washout	C	Discharge after the last PK sample blood draw
2	A		C		B	
3	B		A		C	
4	B		C		A	
5	C		A		B	
6	C		B		A	

Population	Healthy volunteers
Study Rationale	Determine if the components of FTC/RPV/TAF provide similar exposures compared to RPV and E/C/F/TAF
Dose Selection Rationale	The doses of FTC, RPV, and TAF are approved
Formulation	FTC/RPV/TAF: tablet (Lot # EF1401B1) E/C/F/TAF: tablet (Lot # CP1401B1) RPV: tablet (Lot # EFL0I00) The FTC/RPV/TAF formulation in this study is stated to be identical to the commercial formulation.
Interfering Substances Excluded	Prescription, over-the-counter, and herbal medicines excluded with the exception of vitamins, acetaminophen, ibuprofen, hormonal contraceptives, and short-term topical hydrocortisone
Sampling Times on days 1, 15, and 29	All treatments: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours postdose, and for treatments A and B only, every 24 hours after the 144 hour timepoint up to 336 hours postdose
Bioanalysis	• FTC, RPV, TAF, EVG, and COBI were measured using LC/MS/MS • Full method validation assessments were conducted for each analyte • All samples for each analyte were reported to have been measured within the respective duration of stability

RESULTS

Protocol Deviations

No "important" protocol deviations were reported.

Study population

A total of 96 subjects were randomized and received at least 1 dose of study drug. Two subjects did not complete the study: 1 subject did not complete study drug dosing and withdrew consent, and 1 subject completed study drug dosing and withdrew consent.

The majority of subjects were male (71.9%) and white (68.8%). At baseline, the median age was 32 years (range: 19 to 45 years), median (first quartile [Q1], third quartile [Q3]) BMI was 26.4 (23.8, 28.3) kg/m^2, and median (Q1, Q3) $eGFR_{CG}$, ie, creatinine clearance, was 120.5 (106.2, 137.2) mL/min.

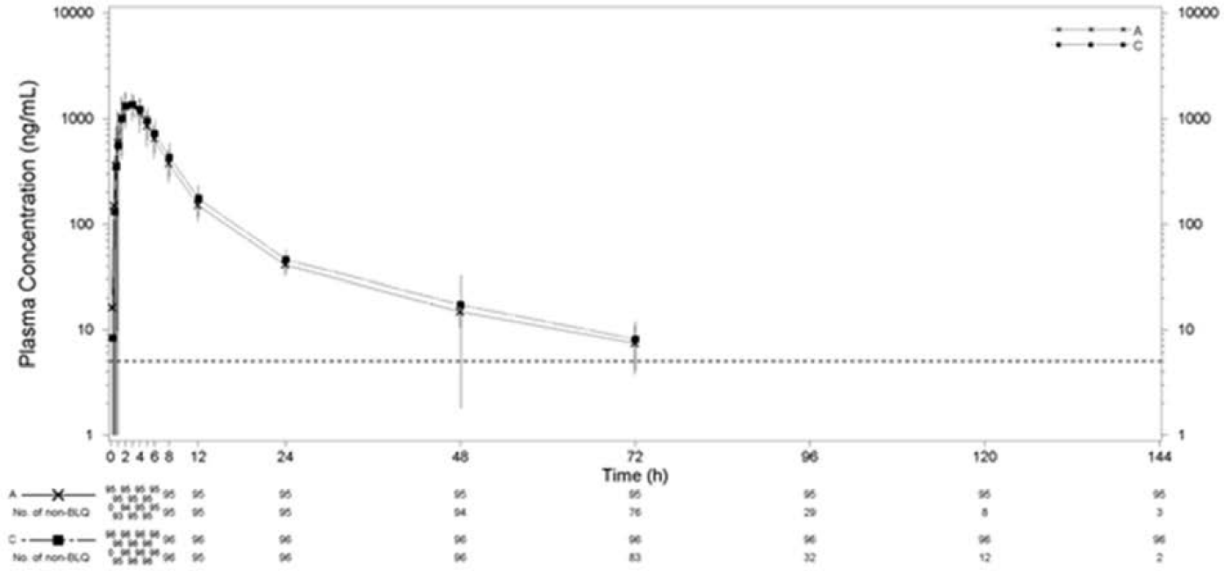
Concomitant medications

Reported use of non-study medications included acetaminophen (n=5 subjects), birth control (n=7), ciprofloxacin (n=1), and topical terbinafine (n=1).

Pharmacokinetics

FTC, RPV, and TAF concentration-time profiles, PK parameters, and statistical comparisons of PK parameters between treatments are shown below. Geometric mean ratios and 90% CIs for Cmax and AUC of FTC, RPV, and TAF were within the noeffect limits of 80% to 125% (Table 3, Table 5, Table 7).

Figure 3. FTC plasma concentration-time profiles.



Treatment A = Single dose FTC/RPV/TAF (200/25/25 mg) FDC tablet; Treatment C = Single dose E/C/F/TAF (150/150/200/10 mg) FDC tablet.
Concentration values BLQ were treated as 0 for predose and one-half LLOQ for postdose summaries.
LLOQ is 5 ng/mL for FTC (dotted reference line indicates LLOQ). Concentration values below LLOQ are not shown.

Table 2. FTC PK parameters.

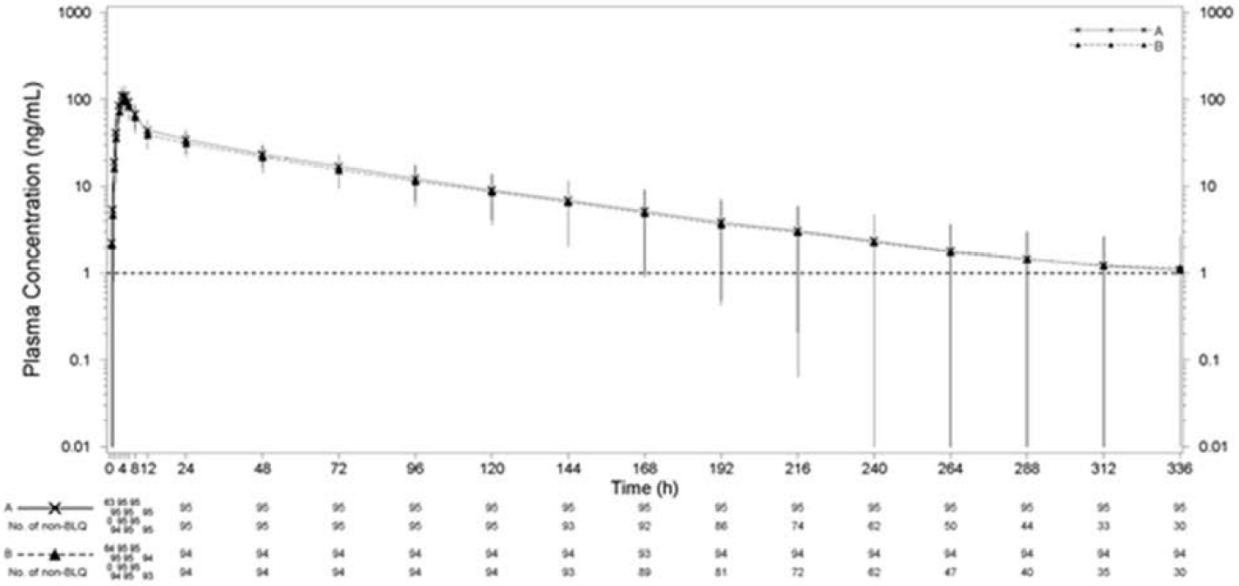
FTC PK Parameter[a]	FTC/RPV/TAF (Treatment A) (N = 95)	E/C/F/TAF (Treatment C) (N = 96)
AUC_{last} (h•ng/mL)	9381.9 (21.7)	10159.4 (21.5)
AUC_{inf} (h•ng/mL)	9603.2 (21.6)	10387.1 (21.5)
C_{max} (ng/mL)	1608.6 (26.5)	1583.8 (23.8)
T_{max} (h)	2.00 (1.50, 3.00)	2.00 (2.00, 3.00)
$t_{1/2}$ (h)	18.71 (15.05, 25.27)	18.90 (15.89, 26.43)
CL/F (L/h)	21.7 (19.8)	20.1 (19.6)
Vz/F (L)	650.0 (43.5)	622.9 (43.5)

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

Table 3. Statistical comparison of FTC PK parameters.

FTC PK Parameter	N	Test GLSM	N	Reference GLSM	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	95	9112.91	96	9879.18	92.24	90.84, 93.67
AUC_{inf} (h•ng/mL)	95	9316.60	96	10085.96	92.37	90.93, 93.83
C_{max} (ng/mL)	95	1534.56	96	1522.22	100.81	97.52, 104.21

Figure 4. RPV plasma concentration-time profiles.



Treatment A = Single dose FTC/RPV/TAF (200/25/25 mg) FDC tablet; Treatment B = Single dose RPV 25-mg tablet.
Concentration values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ for RPV is 1 ng/mL (dotted reference line indicates LLOQ). Concentration values below LLOQ are not shown.

Table 4. RPV PK parameters.

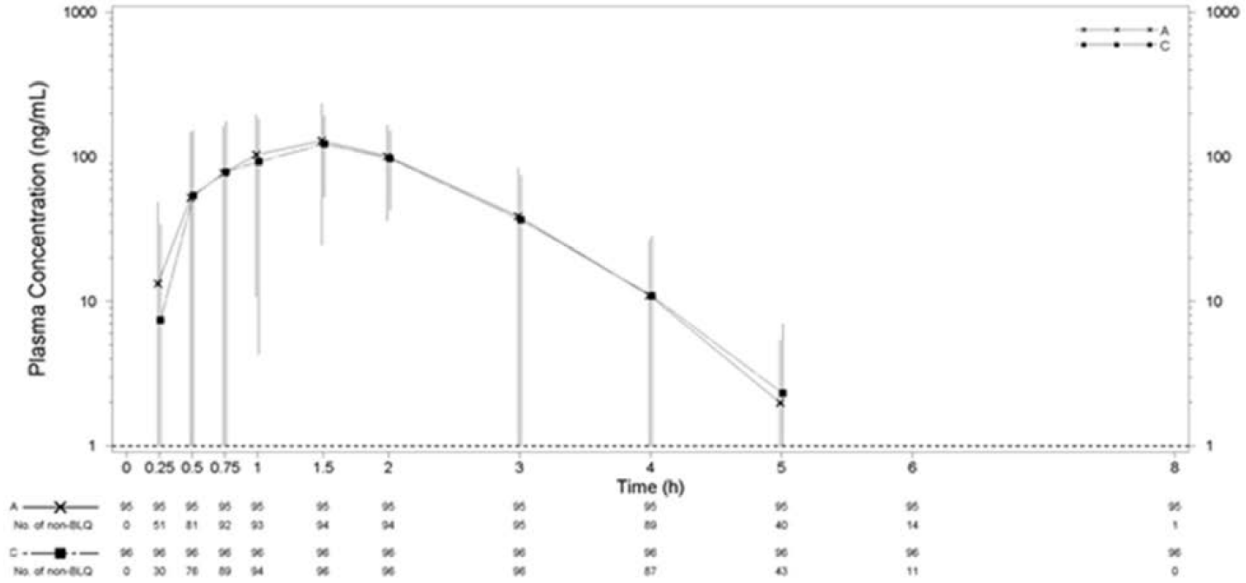
RPV PK Parameter[a]	FTC/RPV/TAF (Treatment A) (N = 95)	RPV (Treatment B) (N = 95)
AUC_{last} (h•ng/mL)	3698.6 (34.9)	3373.4 (40.0)
AUC_{inf} (h•ng/mL)	3843.1 (36.2)	3540.7 (43.0)
C_{max} (ng/mL)	121.4 (26.1)	108.0 (28.7)
T_{max} (h)	4.00 (4.00, 5.00)	4.00 (4.00, 5.00)
$t_{1/2}$ (h)	51.65 (36.83, 66.88)	52.51 (39.29, 66.79)
CL/F (L/h)	7.2 (30.9)	8.1 (36.6)
Vz/F (L)	546.1 (40.5)	600.4 (33.6)

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

Table 5. Statistical comparison of RPV PK parameters.

RPV PK Parameter	N	Test GLSM	N	Reference GLSM	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs RPV (25 mg) (Reference)						
AUC_{last} (h•ng/mL)	95	3510.57	95	3142.72	111.70	106.31, 117.38
AUC_{inf} (h•ng/mL)	95	3637.96	95	3291.86	110.51	105.82, 115.42
C_{max} (ng/mL)	95	117.48	95	103.48	113.52	108.40, 118.89

Figure 5. TAF plasma concentration-time profiles.



Treatment A = Single dose FTC/RPV/TAF (200/25/25 mg) FDC tablet; Treatment C = Single dose E/C/F/TAF (150/150/200/10 mg) FDC tablet.
Concentration values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ for TAF is 1 ng/mL (dotted reference line indicates LLOQ). Concentration values below LLOQ are not shown.

Table 6. TAF PK parameters.

TAF PK Parameter[a]	FTC/RPV/TAF (Treatment A) (N = 95)	E/C/F/TAF (Treatment C) (N = 96)
AUC_{last} (h•ng/mL)	250.0 (43.4)	238.4 (36.5)
AUC_{inf} (h•ng/mL)	263.6 (42.0)	247.4 (36.1)
C_{max} (ng/mL)	198.0 (57.7)	191.5 (48.2)
T_{max} (h)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)
$t_{1/2}$ (h)	0.42 (0.39, 0.49)	0.41 (0.37, 0.48)
CL/F (L/h)	109.4 (35.9)	45.8 (36.2)
Vz/F (L)	72.0 (45.0)	28.7 (43.6)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).
For AUC_{inf}, $t_{1/2}$, CL/F, and Vz/F: n = 82 for Treatment A and n = 85 for Treatment C.

Table 7. Statistical comparison of TAF PK parameters.

TAF PK Parameter	N	Test GLSM	N	Reference GLSM	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	95	228.27	96	221.94	102.85	98.18, 107.75
AUC_{inf} (h•ng/mL)	82	234.87	85	226.18	103.85	98.27, 109.74
C_{max} (ng/mL)	95	177.98	96	176.60	100.78	91.63, 110.85

EVG and COBI PK parameters are shown below (Table 8).

Table 8. EVG and COBI PK parameters.

PK Parameter[a]	EVG (N = 96)	COBI (N = 96)
AUC_{last} (h•ng/mL)	21760.6 (31.8)	6817.3 (56.7)
AUC_{inf} (h•ng/mL)	26145.4 (32.8)	6937.2 (56.8)
C_{max} (ng/mL)	1823.2 (26.4)	1063.5 (36.6)
T_{max} (h)	4.00 (4.00, 5.00)	3.00 (3.00, 4.00)
$t_{1/2}$ (h)	8.71 (6.97, 10.36)	3.03 (2.80, 3.28)
CL/F (L/h)	10.5 (30.1)	46.2 (49.1)
Vz/F (L)	130.6 (26.2)	191.2 (36.9)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).
For AUC_{inf}, $t_{1/2}$, CL/F, and Vz/F: n = 92 for EVG.

Safety
All AEs were grade 1 in severity with the most common being constipation, nausea, and headache. No deaths, SAEs, or AEs leading to discontinuation were reported. No clinically relevant changes in laboratory values were reported.

DISCUSSION/REVIEWER'S COMMENTS

This study showed that exposures of FTC, RPV, and TAF were similar between the investigational combination product FTC/RPV/TAF and the approved products E/C/F/TAF and RPV.

There were no bioanalytical issues with regard to method validation or sample analysis of the analytes.

Single dose exposures of EVG and COBI in this study were similar to historical data [EVG AUC_{inf} of ~20000 ng*h/mL (EVG QBR) and COBI AUC_{inf} of 8012 ng*h/mL (COBI QBR)]. There were no outliers among individual subject PK parameters. One subject had an elevated RPV Clast value (subject 9191-1059) due to early discontinuation. All predose concentrations for all analytes were undetectable, indicating the duration of washout periods were adequate.

LABEL RECOMMENDATIONS

The basis for approval of FTC/RPV/TAF is based on demonstrating similar exposures of FTC, RPV, and TAF between E/C/F/TAF and RPV. The results of this study supports approval of FTC/RPV/TAF.

3.2 Study 366-1651 – the effect of food on FTC/RPV/TAF

A Phase 1 Study to Determine the Effect of Food on the Pharmacokinetics of Emtricitabine, Rilpivirine and Tenofovir Alafenamide (TAF) Administered as the Emtricitabine/Rilpivirine/Tenofovir Alafenamide (F/R/TAF) Fixed Dose Combination (FDC) Tablet in Healthy Volunteers	
Study Period	11/21/2014-1/02/2015
Link	(b) (4)

STUDY DESIGN

Day –28	–1	1	2-10	11	12-20	21	25-30
Period		1	In-Clinic Washout Phase	2	In-Clinic Follow-Up Phase		
Screening[a]	Check-in	Dosing, PK[b]	Washout	Dosing, PK[b]		Discharge	Follow-up telephone contact

a Screening procedures occurred within 28 days before the scheduled first dose.
b Intensive PK blood sample collection occurred following dosing on Day 1 and Day 11, through 240 hours postdose.

- Treatment A (fasted): Single-dose FTC/RPV/TAF (200/25/25 mg) FDC tablet, administered orally under fasted conditions in the morning (Cohorts 1 and 2)
- Treatment B (fed, moderate-fat): Single-dose FTC/RPV/TAF (200/25/25 mg) FDC tablet, administered orally under fed conditions (approximately 600 kcal, approximately 27% fat) in the morning (Cohort 1 only)
- Treatment C (fed, high-fat): Single-dose FTC/RPV/TAF (200/25/25 mg) FDC tablet, administered orally under fed conditions (approximately 800-1000 kcal, approximately 50% fat) in the morning (Cohort 2 only)

Cohort 1 assessed the effect of moderate-fat food (treatments A and B) and cohort 2 assessed the effect of high fat food (treatments A and C).

Population	Healthy adults
Study Rationale	Determine the effect of food on the PK of the components of the FTC/RPV/TAF FDC
Formulation	FTC/RPV/TAF 200/25/25 mg FDC tablet (Lot # EF1401B1)
Dose Selection Rationale	The doses of FTC and RPV are approved. The dose of TAF in FTC/RPV/TAF was determined to provide similar exposures to TAF administered as approved drug E/C/F/TAF in study 366-1159.
Interfering Substances Excluded	Any prescription, over-the-counter, and herbal medications excluding vitamins, acetaminophen and/or

	ibuprofen, hormonal contraceptives, and topical hydrocortisone.
Sampling Times	Day 1 and 11: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours postdose.
Bioanalytical methods	• FTC, RPV, TAF were measured using LC/MS/MS • Full method validation assessments were conducted for each analyte • All samples for each analyte were reported to have been measured within the respective duration of stability

RESULTS

Protocol deviations

240 hour post-dose PK samples in cohort 1 were collected late. These samples were collected later in the intended day for all but one subject (who returned the next day). One subject tested positive for cannibis and remained in the study.

Study population

All 60 randomized subjects completed the study. Subject demographics are detailed below (Table 9).

Concomitant medications

Non-study medications included birth control (n=5 subjects), vitamins (n=1), and acetaminophen (n=1).

Table 9. Demographics.

Characteristic	Cohort 1 Overall (N = 30)	Cohort 2 Overall (N = 30)	Overall (N = 60)
Age (years)			
N	30	30	60
Mean (SD)	36 (7.2)	34 (7.2)	35 (7.3)
Median	38	34	36
Q1, Q3	32, 42	29, 40	30, 41
Min, Max	18, 45	18, 45	18, 45
Sex (n, %)			
Male	16 (53.3%)	20 (66.7%)	36 (60.0%)
Female	14 (46.7%)	10 (33.3%)	24 (40.0%)
Race (n, %)			
White	26 (86.7%)	16 (53.3%)	42 (70.0%)
Black	4 (13.3%)	13 (43.3%)	17 (28.3%)
Other	0	1 (3.3%)	1 (1.7%)
Ethnicity (n, %)			
Hispanic or Latino	30 (100.0%)	17 (56.7%)	47 (78.3%)
Not Hispanic or Latino	0	13 (43.3%)	13 (21.7%)
Body Mass Index (kg/m^2)			
N	30	30	60
Mean (SD)	25.6 (2.36)	25.3 (2.67)	25.5 (2.50)
Median	26.2	25.4	26.0
Q1, Q3	25.1, 27.0	23.0, 27.3	23.3, 27.3
Min, Max	20.8, 29.6	20.0, 30.2[a]	20.0, 30.2[a]
Estimated Glomerular Filtration Rate by Cockcroft-Gault Formula (mL/min)			
N	30	30	60
Mean (SD)	116.7 (15.70)	113.5 (23.31)	115.1 (19.77)
Median	115.3	109.7	113.1
Q1, Q3	108.8, 127.1	95.6, 132.5	99.5, 128.3
Min, Max	86.7, 150.6	78.2, 170.7	78.2, 170.7

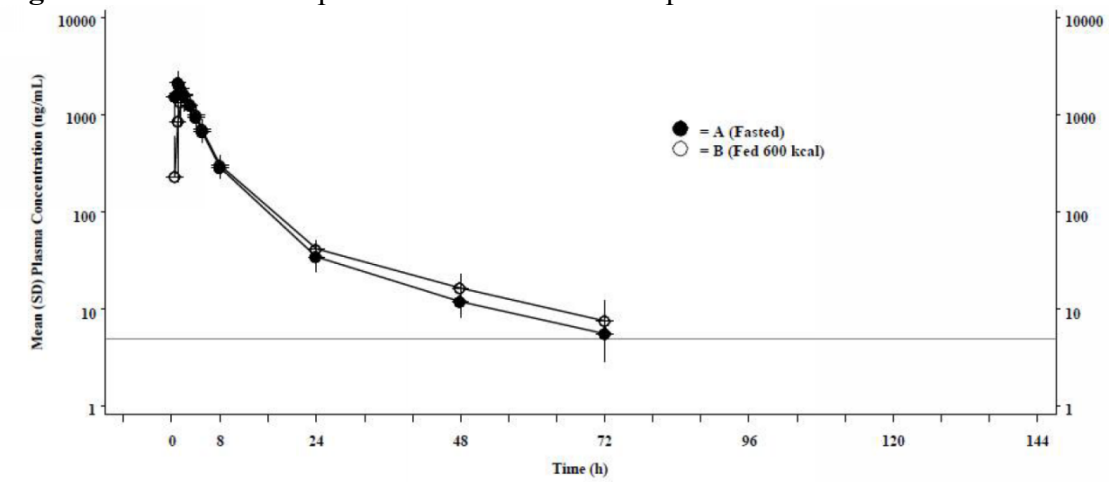
a One subject (Subject 9191-2024) met the inclusion criteria with a BMI at screening of ≤ 30 kg/m^2, but she had a Baseline (Day –1) BMI of 30.2 kg/m^2.

Pharmacokinetics

FTC, RPV, and TAF plasma concentration-time profiles, PK parameters, and statistical comparisons of PK parameters between treatments are shown below.

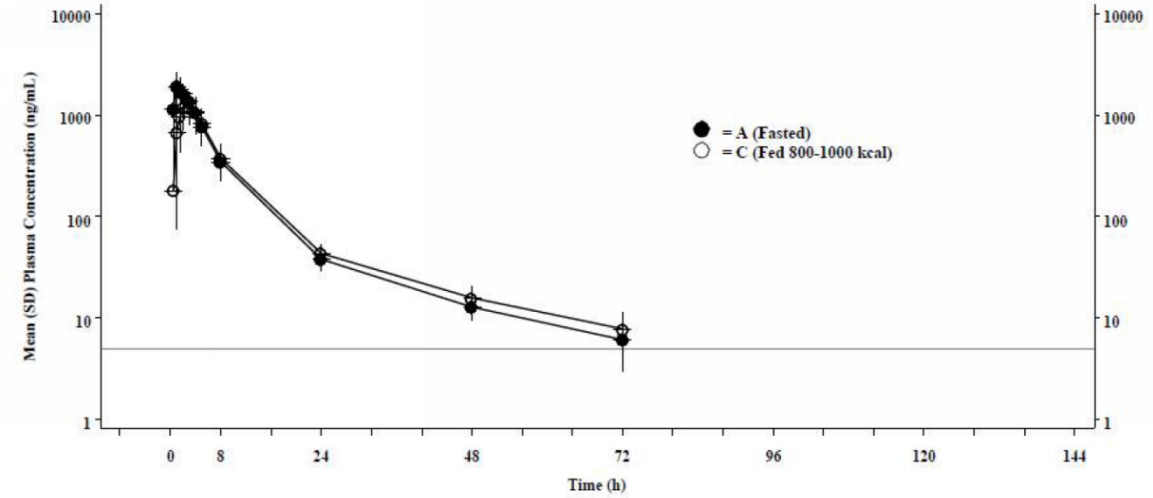
FTC

Figure 6. Cohort 1 FTC plasma concentration-time profiles.



Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)
BLQ plasma concentrations were treated as 0 at predose and half the LLOQ for postdose time points.
LLOQ for FTC is 5 ng/mL.
Reference line indicates LLOQ. Concentration values ≤ LLOQ are not presented on the figure.
FTC plasma concentrations were analyzed at time points from 0 (predose) to 144 hours postdose.

Figure 7. Cohort 2 FTC plasma concentration-time profiles.



Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)
BLQ plasma concentrations were treated as 0 at predose and half the LLOQ for postdose time points.
LLOQ for FTC is 5 ng/mL.
Reference line indicates LLOQ. Concentration values ≤ LLOQ are not presented on the figure.
FTC plasma concentrations were analyzed at time points from 0 (predose) to 144 hours postdose.

Table 10. Cohort 1 FTC PK parameters.

Mean (%CV)	Treatment A FTC/RPV/TAF Fasted (N = 30)	Treatment B FTC/RPV/TAF Fed 600 kcal (N = 30)
C_{max} (ng/mL)	2276 (23.8)	1734 (25.6)
T_{max} (h)[a]	1.0 (1.0, 1.0)	2.0 (1.5, 2.0)
λ_z (1/h)	0.058 (65.4)	0.053 (67.7)
C_{last} (ng/mL)	7.2 (23.6)	8.0 (29.0)
T_{last} (h)[a]	72 (48, 72)	72 (48, 96)
$t_{1/2}$ (h)[a]	17.968 (6.842, 20.950)	18.916 (7.554, 24.964)
AUC_{inf} (h*ng/mL)	10687.7 (15.2)	9750.2 (17.1)
AUC_{last} (h*ng/mL)	10498.2 (15.6)	9530.0 (17.1)
$\%AUC_{exp}$ (%)	1.83 (98.0)	2.25 (72.6)
V_z/F (L)	520.6 (90.3)	586.5 (71.4)
CL/F (L/h)	19.1 (15.7)	21.1 (17.4)

a Median (Q1, Q3)
Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)

Table 11. Cohort 2 FTC PK parameters.

Mean (%CV)	Treatment A FTC/RPV/TAF Fasted (N = 30)	Treatment C FTC/RPV/TAF Fed 800–1000 kcal (N = 30)
C_{max} (ng/mL)	2107 (27.7)	1551 (23.2)
T_{max} (h) [a]	1.0 (1.0, 1.5)	2.0 (2.0, 3.0)
λ_z (1/h)	0.054 (70.3)	0.040 (57.9)
C_{last} (ng/mL)	7.6 (30.5)	6.8 (31.9)
T_{last} (h)[a]	72 (48, 72)	72 (72, 96)
$t_{1/2}$ (h)[a]	18.183 (6.971, 24.965)	18.109 (16.231, 28.498)
AUC_{inf} (h*ng/mL)	11214.0 (16.9)	9827.0 (18.3)
AUC_{last} (h*ng/mL)	11008.2 (16.8)	9605.9 (18.0)
$\%AUC_{exp}$ (%)	1.80 (54.8)	2.19 (57.6)
V_z/F (L)	518.8 (61.1)	666.6 (51.9)
CL/F (L/h)	18.4 (18.2)	21.0 (17.3)

a Median (Q1, Q3)
Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)

Table 12. Cohort 1 FTC statistical comparison of PK parameters between treatments.

PK Parameter	GLSMs by Treatment: Treatment B: FTC/RPV/TAF Fed 600 kcal (N = 30)	GLSMs by Treatment: Treatment A: FTC/RPV/TAF Fasted (N = 30)	GLSM Ratio Test/Reference (%)	90% CI
Analyte: FTC				
AUC_{inf} (h*ng/mL)	9612.37	10567.69	90.96	(88.53,93.45)
AUC_{last} (h*ng/mL)	9394.59	10372.74	90.57	(88.28,92.92)
C_{max} (ng/mL)	1679.23	2210.70	75.96	(70.10,82.31)

Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)

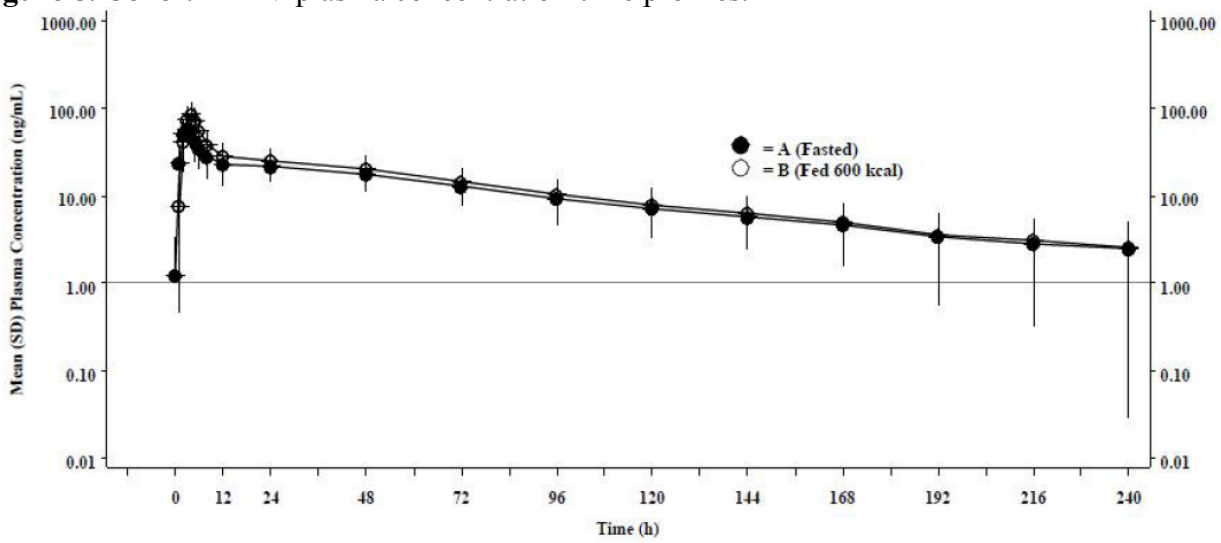
Table 13. Cohort 2 FTC statistical comparison of PK parameters between treatments.

PK Parameter	GLSMs by Treatment: Treatment C: FTC/RPV/TAF Fed 800–1000 kcal (N = 30)	GLSMs by Treatment: Treatment A: FTC/RPV/TAF Fasted (N = 30)	GLSM Ratio Test/Reference (%)	90% CI
Analyte: FTC				
AUC_{inf} (h*ng/mL)	9676.52	11053.04	87.55	(84.76,90.42)
AUC_{last} (h*ng/mL)	9463.84	10853.35	87.20	(84.48,90.00)
C_{max} (ng/mL)	1512.55	2030.81	74.48	(69.50,79.82)

Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)

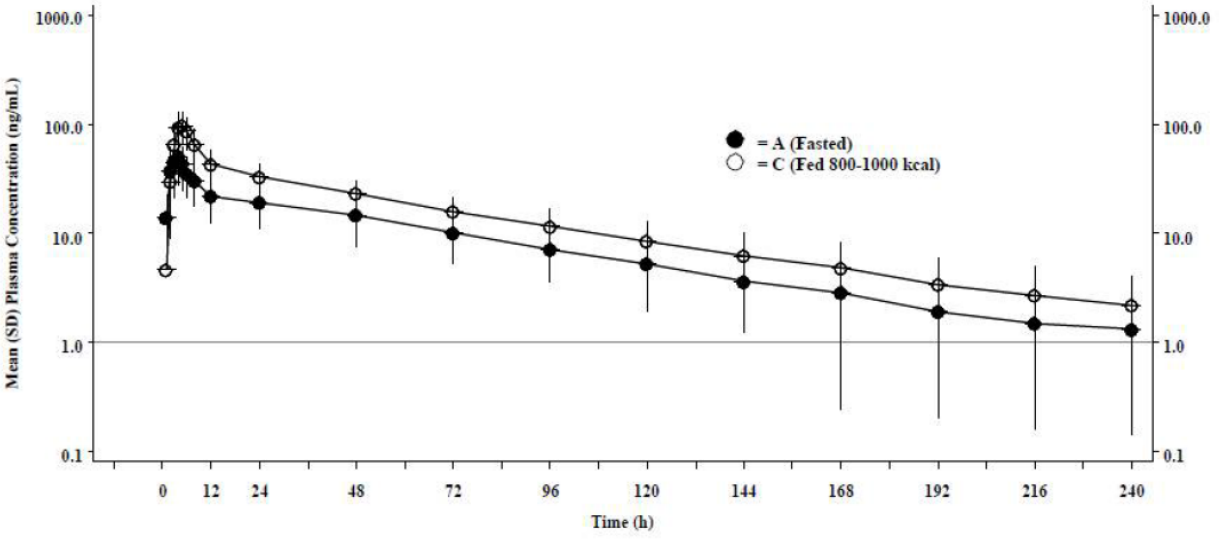
RPV

Figure 8. Cohort 1 RPV plasma concentration-time profiles.



Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)
BLQ plasma concentrations were treated as 0 at predose and half the LLOQ for postdose time points.
LLOQ for RPV is 1 ng/mL.
Reference line indicates LLOQ. Concentration values ≤ LLOQ are not presented on the figure.
RPV plasma concentrations were analyzed at time points from 0 (predose) to 240 hours postdose.

Figure 9. Cohort 2 RPV plasma concentration-time profiles.



Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)
BLQ plasma concentrations were treated as 0 at predose and half the LLOQ for postdose time points.
LLOQ for RPV is 1 ng/mL.
Reference line indicates LLOQ. Concentration values ≤ LLOQ are not presented on the figure.
RPV plasma concentrations were analyzed at time points from 0 (predose) to 240 hours postdose.

Table 14. Cohort 1 RPV PK parameters.

Mean (%CV)	Treatment A FTC/RPV/TAF Fasted (N = 30)	Treatment B FTC/RPV/TAF Fed 600 kcal (N = 30)
C_{max} (ng/mL)	65.5 (35.8)	91.5 (36.9)
T_{max} (h) [a]	3 (3, 4)	4 (4, 4)
λ_z (1/h)	0.013 (58.5)	0.013 (58.7)
C_{last} (ng/mL)	2.7 (82.9)	2.8 (63.2)
T_{last} (h)[a]	239.93 (192.00, 240.30)	239.93 (216.00, 240.32)
$t_{1/2}$ (h)[a]	59.937 (40.346, 86.305)	57.110 (45.842, 80.145)
AUC_{inf} (h*ng/mL)	2891.4 (55.0)	3175.6 (40.1)
AUC_{last} (h*ng/mL)	2451.0 (37.5)	2851.9 (37.6)
$\%AUC_{exp}$ (%)	10.73 (99.2)	8.82 (79.6)
V_z/F (L)	967.2 (48.2)	778.9 (37.4)
CL/F (L/h)	10.6 (40.8)	9.4 (48.7)

a Median (Q1, Q3)
Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)

Table 15. Cohort 2 RPV PK parameters.

Mean (%CV)	Treatment A FTC/RPV/TAF Fasted (N = 30)	Treatment C FTC/RPV/TAF Fed 800–1000 kcal (N = 30)
C_{max} (ng/mL)	55.8 (43.3)	108.1 (27.5)
T_{max} (h) [a]	4 (3, 4)	4 (4, 5)
λ_z (1/h)	0.016 (36.2)	0.016 (39.3)
C_{last} (ng/mL)	1.8 (52.0)	2.5 (62.3)
T_{last} (h)[a]	216.00 (168.00, 240.00)	239.93 (192.00, 240.00)
$t_{1/2}$ (h)[a]	46.279 (32.801, 65.130)	48.449 (34.387, 67.992)
AUC_{inf} (h*ng/mL)	2158.0 (42.8)	3579.2 (32.4)
AUC_{last} (h*ng/mL)	2014.4 (41.5)	3352.2 (30.6)
$\%AUC_{exp}$ (%)	6.44 (59.4)	5.68 (76.4)
V_z/F (L)	902.0 (49.2)	535.8 (35.0)
CL/F (L/h)	13.8 (48.8)	7.8 (37.5)

a Median (Q1, Q3)
Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)

Table 16. Cohort 1 RPV statistical comparison of PK parameters between treatments.

PK Parameter	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	Treatment B: FTC/RPV/TAF Fed 600 kcal (N = 30)	Treatment A: FTC/RPV/TAF Fasted (N = 30)		
Analyte: RPV				
AUC_{inf} (h*ng/mL)	2922.88	2592.73	112.73	(103.35,122.97)
AUC_{last} (h*ng/mL)	2656.93	2294.47	115.80	(107.42,124.83)
C_{max} (ng/mL)	85.34	61.32	139.17	(124.04,156.14)

Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)

Table 17. Cohort 2 RPV statistical comparison of PK parameters between treatments.

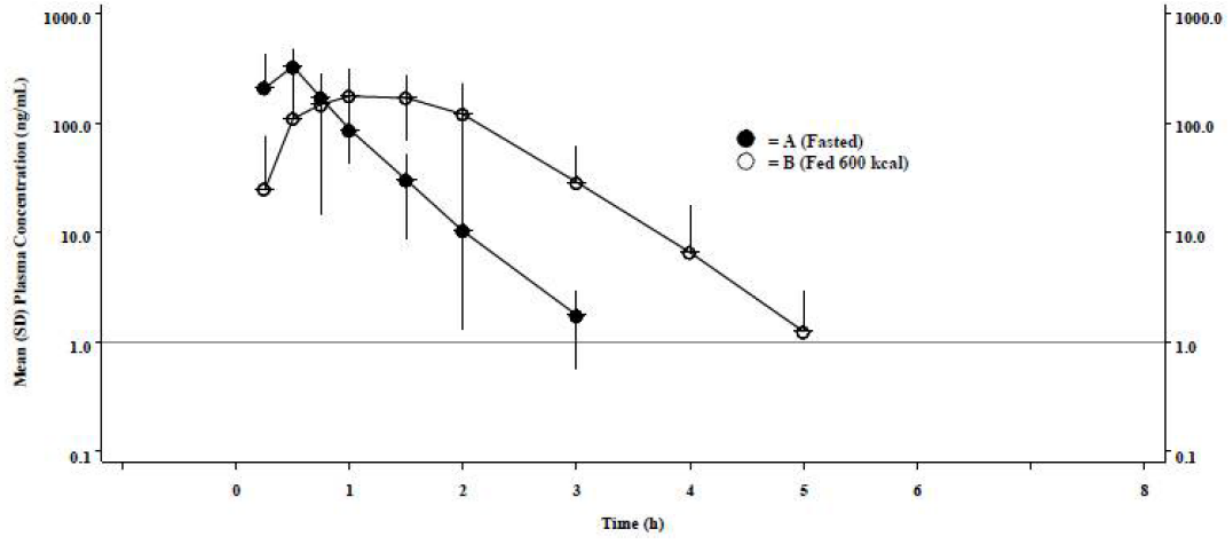
PK Parameter	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	Treatment C: FTC/RPV/TAF Fed 800–1000 kcal (N = 30)	Treatment A: FTC/RPV/TAF Fasted (N = 30)		
Analyte: RPV				
AUC_{inf} (h*ng/mL)	3390.37	1966.69[a]	172.39	(149.29,199.06)
AUC_{last} (h*ng/mL)	3194.47	1843.98[a]	173.24	(149.10,201.28)
C_{max} (ng/mL)	103.68	50.17	206.67	(179.08,238.51)

a N = 29.

Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)

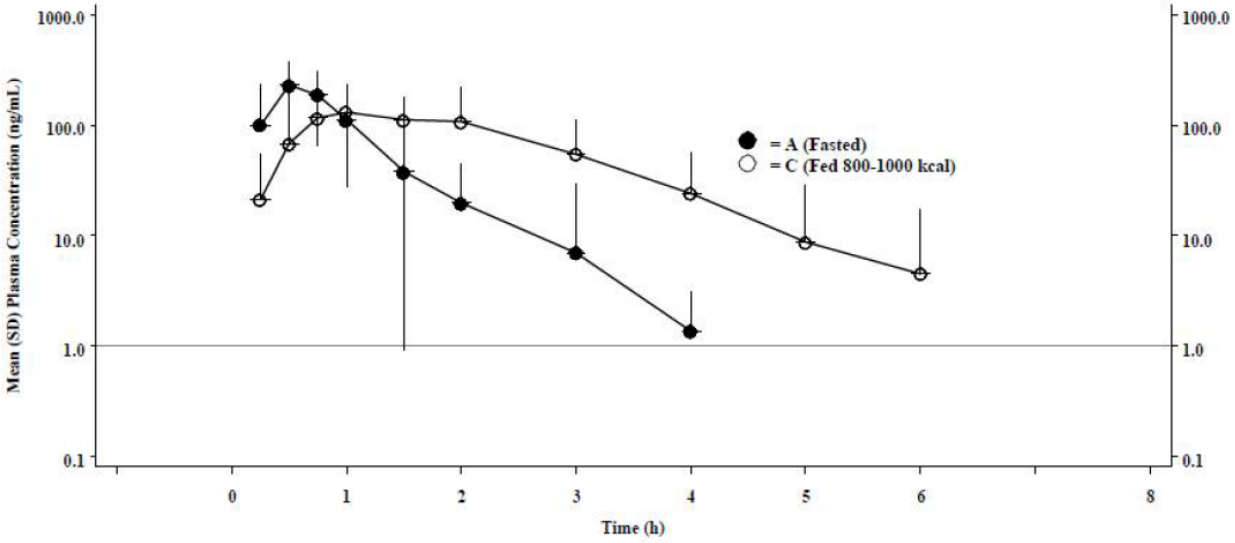
TAF

Figure 10. Cohort 1 TAF plasma concentration-time profiles.



Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)
BLQ plasma concentrations were treated as 0 at predose and half the LLOQ for postdose time points.
LLOQ for TAF is 1 ng/mL.
Reference line indicates LLOQ. Concentration values ≤ LLOQ are not presented on the figure.
TAF plasma concentrations were analyzed at time points from 0 (predose) to 8 hours postdose.

Figure 11. Cohort 2 TAF plasma concentration-time profiles.



Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)
BLQ plasma concentrations were treated as 0 at predose and half the LLOQ for postdose time points.
LLOQ for TAF is 1 ng/mL.
Reference line indicates LLOQ. Concentration values ≤ LLOQ are not presented on the figure.
TAF plasma concentrations were analyzed at time points from 0 (predose) to 8 hours postdose.

Table 18. Cohort 1 TAF PK parameters.

Mean (%CV)	Treatment A FTC/RPV/TAF Fasted (N = 30)	Treatment B FTC/RPV/TAF Fed 600 kcal (N = 30)
C_{max} (ng/mL)	386 (45.6)	306 (45.7)
T_{max} (h) [a]	0.5 (0.5, 0.5)	1.3 (0.8, 2.0)
λ_z (1/h)	1.980 (26.4)	1.809 (19.5)
C_{last} (ng/mL)	2.6 (71.2)	2.2 (60.6)
T_{last} (h)[a]	3 (3, 3)	4 (4, 5)
$t_{1/2}$ (h)[a]	0.384 (0.300, 0.432)	0.384 (0.344, 0.424)
AUC_{inf} (h*ng/mL)	228.7 (33.5)	338.8 (29.8)
AUC_{last} (h*ng/mL)	223.8 (34.9)	325.1 (33.4)
$\%AUC_{exp}$ (%)	0.58 (63.6)	0.35 (50.3)
V_z/F (L)	62.3 (28.1)	45.2 (35.2)
CL/F (L/h)	120.3 (30.9)	80.5 (33.4)

a Median (Q1, Q3)
Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)

Table 19. Cohort 2 TAF PK parameters.

Mean (%CV)	Treatment A FTC/RPV/TAF Fasted (N = 30)	Treatment C FTC/RPV/TAF Fed 800–1000 kcal (N = 30)
C_{max} (ng/mL)	316 (45.4)	230 (58.1)
T_{max} (h) [a]	0.5 (0.5, 0.8)	1.5 (1.0, 2.0)
λ_z (1/h)	1.854 (27.6)	1.320 (25.6)
C_{last} (ng/mL)	2.3 (51.1)	2.8 (61.4)
T_{last} (h)[a]	3 (3, 4)	5 (4, 6)
$t_{1/2}$ (h)[a]	0.414 (0.299, 0.447)	0.527 (0.455, 0.614)
AUC_{inf} (h*ng/mL)	201.8 (40.9)	329.3 (41.5)
AUC_{last} (h*ng/mL)	201.1 (40.4)	311.7 (42.4)
$\%AUC_{exp}$ (%)	0.77 (65.9)	0.69 (67.9)
V_z/F (L)	80.5 (40.9)	69.0 (38.7)
CL/F (L/h)	142.0 (36.9)	89.0 (42.6)

a Median (Q1, Q3)
Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)

Table 20. Cohort 1 TAF statistical comparison of PK parameters between treatments.

PK Parameter	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	Treatment B: FTC/RPV/TAF Fed 600 kcal (N = 30)	Treatment A: FTC/RPV/TAF Fasted (N = 30)		
Analyte: TAF				
AUC_{last} (h*ng/mL)	306.88	211.91	144.82	(133.13,157.54)
C_{max} (ng/mL)	270.34	348.88	77.49	(65.54,91.62)

Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment B = FTC/RPV/TAF FDC under fed conditions (moderate-fat food)

Table 21. Cohort 2 TAF statistical comparison of PK parameters between treatments.

PK Parameter	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	Treatment C: FTC/RPV/TAF Fed 800–1000 kcal (N = 30)	Treatment A: FTC/RPV/TAF Fasted (N = 30)		
Analyte: TAF				
AUC_{last} (h*ng/mL)	288.00	187.67	153.46	(139.10,169.31)
C_{max} (ng/mL)	197.40	285.57	69.12	(56.61,84.41)

Treatment A = FTC/RPV/TAF FDC tablet under fasted conditions; Treatment C = FTC/RPV/TAF FDC tablet under fed conditions (high-fat food)

The effect of food on the PK of the components of FTC/RPV/TAF is summarized below (Table 22).

Table 22. Summary of the effect of food on the PK of the components of FTC/RPV/TAF.

Analyte	Geometric mean AUC ratio	
	Moderate-fat meal relative to fasted (%), (90% CI)	High-fat meal relative to fasted (%), (90% CI)
FTC	91 (89, 93)	88 (85, 90)
RPV	113 (103, 123)	172 (149, 199)
TAF	145 (133, 158)	153 (139, 169)

Source: prepared by reviewer.

Safety

All reported AEs were of grade 1 severity. One AE of nausea, vomiting, and dizziness that resolved without treatment on the day of dosing was considered related to study drug by the investigator. There were no reported deaths, SAEs, or AEs leading to discontinuation during the study. There were no reported AEs for laboratory abnormalities.

DISCUSSION/REVIEWER'S COMMENTS

There were no bioanalytical issues regarding method validation or sample analysis of FTC, RPV, or TAF. A protocol deviation whereby the 240 hour post-dose samples were collected late did not impact the PK results because actual collection time values were used in the PK analysis. As no subjects ingested non-study medications expected to interact with study drugs, there was no impact of concomitant medications on the study.

The proposed FTC/RPV/TAF label says to take FTC/RPV/TAF (b) (4). As relative BA study 366-1159 was conducted in the fed state and similar exposures of the components of FTC/RPV/TAF were demonstrated when compared to approved products E/C/F/TAF and RPV, we agree with this recommendation. However, the recommendation to take FTC/RPV/TAF (b) (4) versus with a meal is a potential concern for RPV as single agent RPV is labeled to be taken with a meal. The pivotal RPV phase 3 trials administered RPV with a meal. According to the RPV label, its exposure in the fasted state is decreased ~40% compared to a normal meal or high-fat meal; this is the same degree of exposure reduction for RPV from FTC/RPV/TAF for the fasted state relative to a high fat meal. Therefore, we recommend that FTC/RPV/TAF should be administered with a meal.

LABEL RECOMMENDATIONS

We recommend that FTC/RPV/TAF should be taken with a meal. The proposed labeling says FTC/RPV/TAF should (b) (4).

3.3 Study TMC278-TiDP6-C154 – drug interaction study between RPV and omeprazole

A Phase I, open-label, randomized, 4-way crossover trial to evaluate the pharmacokinetics of TMC278 25 mg and 50 mg in the presence of omeprazole 20 mg q.d. in healthy subjects	
Study Period	1/20/2010-5/10/2010
Link	(b) (4)

STUDY DESIGN

Phase I, open-label, randomized, 4-way crossover trial.

	Session I	at least 14 days washout*	**Session II**	at least 14 days washout*	**Session III**	at least 14 days washout*	**Session IV**
Group 1 (n = 4)	Treatment A	→	Treatment D	→	Treatment B	→	Treatment C
Group 2 (n = 4)	Treatment B	→	Treatment A	→	Treatment C	→	Treatment D
Group 3 (n = 4)	Treatment C	→	Treatment B	→	Treatment D	→	Treatment A
Group 4 (n = 4)	Treatment D	→	Treatment C	→	Treatment A	→	Treatment B

*There was a washout period of at least 14 days between consecutive intakes of TMC278 (Day 1 of each treatment was the first day of the washout period). For Treatments B, C and D, the intake of omeprazole could start as early as the 10th day of the washout period for TMC278

Treatment A: Single dose of RPV 25 mg.

Treatment B: Omeprazole 20 mg daily 1 hour before breakfast for 7 days, with a single dose of RPV 25 mg 1.5 hours after omeprazole on the sixth day.

Treatment C: Omeprazole 20 mg in the evening on an empty stomach for 6 days, with a single dose of RPV 25 mg in the morning of the sixth day 12 hours after omeprazole intake.

Treatment D: Omeprazole 20 mg daily 1 hour before breakfast for 7 days, with a single dose of

RPV 50 mg 1.5 hours after omeprazole intake on the morning of the sixth day. All RPV treatments were administered after a standardized breakfast.	
Population	Healthy subjects
Study Rationale	Determine the effect of omeprazole on the PK of RPV
Dose Selection Rationale	Approved doses of omeprazole and RPV were used
Formulation	TMC278: 25 mg tablet (batch # 9CL1F for all treatments) Omeprazole: Antra MUPS® 20 mg tablet (batch # KM8862B1 for all treatments)
Interfering Substances Excluded	Over-the-counter, prescribed, and herbal medications were not allowed with the exception of ibuprofen, acetaminophen, hormone replacement therapy in postmenapausal women, antipruritic agents for rash, antiemetics for nausea, and loperamide for diarrhea. The use of local anesthetic was allowed for insertion of the pH probe in the stomach.
PK sampling Times	RPV: predose, and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, 72, 120, and 168 hours postdose.
Pharmacodynamics	A pH probe was inserted into the stomach via the nares. On day 1 of each treatment session (on the days of RPV intake), gastric pH was monitored over a 24-hour period, starting 2 hours before RPV intake.
Bioanalytical methods	RPV was measured using LC/MS/MS. Link to partial validation report: (b) (4)
	Link to sample analysis report: (b) (4)

RESULTS

Protocol deviations

No major protocol deviations were reported.

Study population

Seventeen subjects were randomized and treated and 15 completed the study. Two subjects withdrew consent. Subject demographics are below (Table 23).

Table 23. Demographics.

Parameter	Treatment Sequence				All Subjects
	A-D-B-C N = 3	B-A-C-D N = 4	C-B-D-A N = 5	D-C-A-B N = 5	N = 17
Age, years					
Median (range)	49.0 (43-55)	43.0 (25-46)	45.0 (37-55)	55.0 (21-55)	46.0 (21-55)
Height, cm					
Median (range)	172.0 (165-179)	180.0 (165-194)	182.0 (158-187)	180.0 (166-182)	180.0 (158-194)
Weight, kg					
Median (range)	65.0 (55-67)	84.5 (74-93)	71.0 (68-99)	68.0 (63-81)	71.0 (55-99)
BMI, kg/m^2					
Median (range)	20.30 (20.2-22.6)	25.95 (23.8-28.4)	26.50 (20.5-28.3)	21.50 (19.8-28.7)	23.80 (19.8-28.7)
Gender, n (%)					
Female Male	2 (66.6) 1 (33.3)	1 (25.0) 3 (75.0)	1 (20.0) 4 (80.0)	2 (40.0) 3 (60.0)	6 (35.3) 11 (64.7)
Race/Ethnicity, n (%)					
White/Not Hispanic or Latino	3 (100.0)	4 (100.0)	5 (100.0)	5 (100.0)	17 (100.0)
Type of Smoker, n (%)					
Light Non-smoker, n (%)	3 (100.0) 0	2 (50.0) 2 (50.0)	4 (80.0) 1 (20.0)	3 (60.0) 2 (40.0)	12 (70.6) 5 (29.4)

Concomitant medications

Seven subjects took non-study medications during the trial, including acetaminophen (n=3), ibuprofen (n=2), clindamycin (n=1), and betahistine (n=1).

Pharmacokinetics

RPV concentration-time profiles, PK parameters, and statistical analysis of PK parameters are shown below (Figure 12, Table 24, Table 25). Subject 154-0034 had a positive RPV predose concentration that was >5% of Cmax in treatments C and D and was excluded from the PK analysis.

Figure 12. RPV mean plasma concentration-time profiles by treatment.

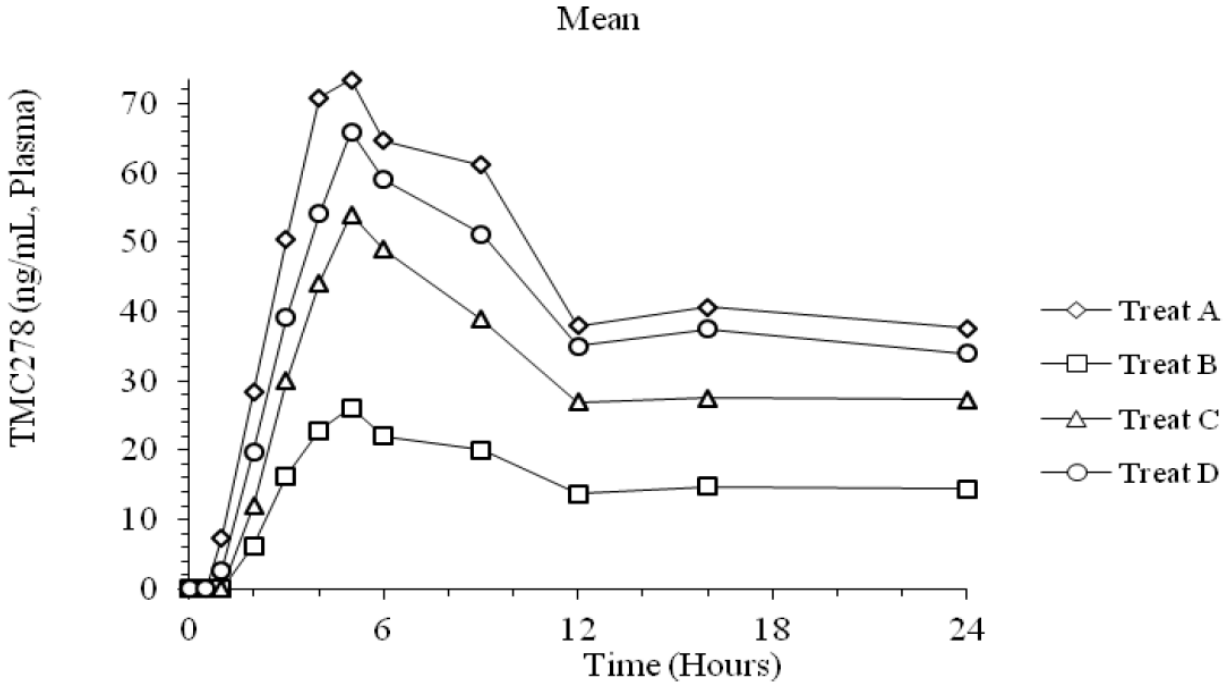


Table 24. RPV PK parameters by treatment.

Pharmacokinetics of TMC278, mean ± SD; t_{max}, median (range)	Single dose TMC278 25 mg alone (Treatment A)	Single dose TMC278 25 mg 1.5 hours after omeprazole 20 mg q.d. at steady-state (Treatment B)	Single dose TMC278 25 mg 12 hours after omeprazole 20 mg q.d. at steady-state (Treatment C)	Single dose TMC278 50 mg 1.5 hours after omeprazole 20 mg q.d. at steady-state (Treatment D)
n	15	15	14[a]	15
C_{max}, ng/mL	87.2 ± 25.3	27.5 ± 13.2	62.5 ± 33.8	70.6 ± 42.7
t_{max}, h	5.00 (3.00-9.00)	5.00 (4.00-5.00)	5.00 (3.00-6.00)	5.00 (4.00-6.00)
AUC_{last}, ng.h/mL	3016 ± 1362	1124 ± 560	2010 ± 1033	2628 ± 1361
AUC_{∞}, ng.h/mL	3620 ± 2626	1320 ± 709	2306 ± 1297	2863 ± 1439
$t_{1/2term}$, h	48.5 ± 29.8	46.9 ± 24.8	50.6 ± 36.3	41.5 ± 16.8

[a] Subject 154-0034 had a positive TMC278 predose concentration, so the plasma concentrations and derived pharmacokinetic parameters were excluded.

Table 25. Statistical analysis of RPV PK parameters.

Parameter	LSmeans		LSmeans ratio, %	90% CI,%[b]
	Reference (Treatment A)	Test (Treatment B, C or D)		
N=15	**Treatment B versus A**			
C_{max}, ng/mL	85.49	25.77	30.15	23.65 – 38.43
AUC_{last}, ng.h/mL	2814.73	997.34	35.43	28.47 – 44.09
AUC_{∞}, ng.h/mL	3133.08	1155.64	36.89	29.63 – 45.92
N=15[a]	**Treatment C versus A**			
C_{max}, ng/mL	85.49	56.06	65.58	51.14 – 84.11
AUC_{last}, ng.h/mL	2814.73	1917.49	68.12	54.43 – 85.26
AUC_{∞}, ng.h/mL	3133.08	2180.02	69.58	55.56 – 87.15
N=15	**Treatment D versus A**			
C_{max}, ng/mL	85.49	63.20	73.94	57.78 – 94.61
AUC_{last}, ng.h/mL	2814.73	2481.01	88.14	70.55 – 110.13
AUC_{∞}, ng.h/mL	3133.08	2756.81	87.99	70.36 – 110.04

[a] n=15 for reference and n=14 for test
[b] 90% CI

Pharmacodynamics

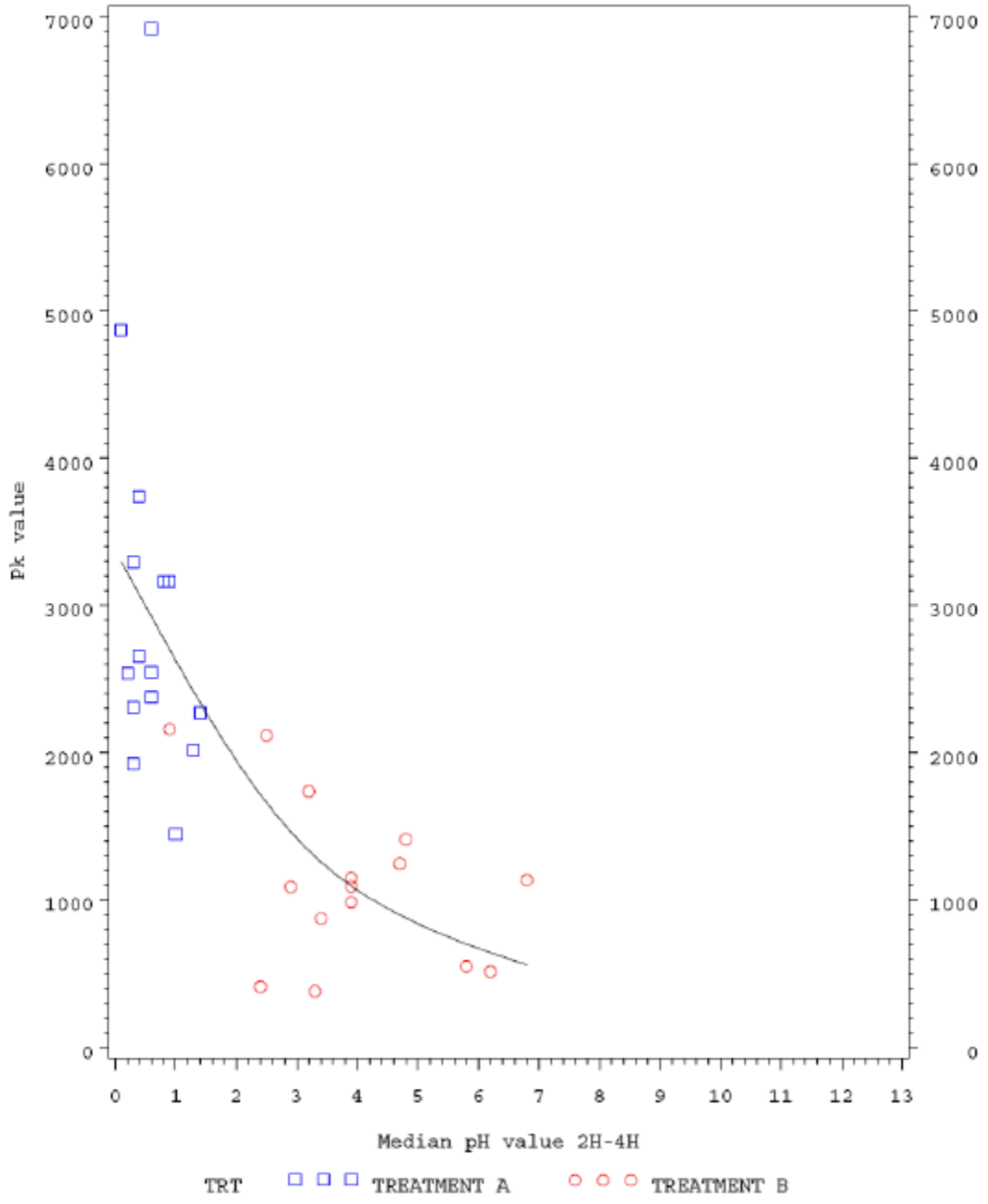
The percentage of time over the assessment period that intragastric pH values were >3, >4, >5, and >6 by treatment are shown below (Table 26). RPV AUC was found to decrease with increasing gastric pH (Figure 13).

Table 26. Percent Time pH > 3, > 4, > 5 and > 6 Over Whole Assessment Period.

	Treatment			
	A	B	C	D
Actual median pH value	1.10	3.90	3.10	4.20
Percent time[a] pH value				
> 3	31.41	63.68	50.32	63.70
> 4	25.81	47.11	40.44	51.70
> 5	22.67	26.94	31.81	35.07
> 6	20.50	16.81	23.71	19.25

[a] Percent time = time any of the pH values were above the given threshold, with the denominator being the true total assessment time: the sum of all 4-second measurements over the whole assessment.

Figure 13. RPV AUC as a function of gastric pH.



Safety

The most common AEs were headache, nasopharyngitis, and fatigue. There were no deaths, SAEs, or AEs leading to discontinuation during the trial. No AEs related to laboratory values, vital signs, or ECG parameters were reported.

DISCUSSION/REVIEWER'S COMMENTS

Bioanalysis of RPV had the following deficiencies: 1) only a partial method validation report was provided; and 2) interference between RPV and omeprazole was not evaluated. This study does not impact the labeling, but the numerical results from this study are listing in the FTC/RPV/TAF label section 12. Therefore the full method validation report will be requested and discussed in a subsequent memo to this review.

The washout period in regards to the PK of RPV was adequate in that we confirmed in our analysis of the plasma concentrations that all but one subject had predose concentrations less than 5% of Cmax. Acid inhibition due to omeprazole is at 50% of the maximum after 24 hours, thus the RPV doses given on day six of omeprazole dosing meant that the effect of the interaction was likely assessed during conditions of maximum omeprazole-mediated acid inhibition. As proton pump inhibitors have a prolonged effect, maximum acid inhibition was likely present in treatments B and D where RPV was given 1.5 hours after omeprazole. The offset of acid inhibition is 3-5 days, thus the washout period of 14 days was sufficient. Coadministration with omeprazole resulted in decreased RPV exposures for all subjects except one (subject #39, test/reference AUC ratio of 107% for treatment B, 246% for treatment C, and 175% for treatment D).

Based on a previous RPV-omeprazole drug interaction study utilizing a supratherapeutic dose of RPV 150 mg, omeprazole was already contraindicated in patients prescribed RPV (see NDA 202022 Clinical Pharmacology review, dated 9/2/2010). In this study, therapeutic doses of RPV were used except for treatment D. Relative to administration without omeprazole, RPV PK when coadministered with omeprazole resulted in a mean AUC decrease of 63% in treatment B, 30% in treatment C, and 12% in treatment D. In treatments B and C, both the mean ratios and 90% CIs were outside the standard no effect 80-125% boundaries, while in treatment D the mean AUC ratio was within the no effect boundary while the 90% CIs were not. As lower virologic response was associated with lower RPV exposure in the RPV pivotal trials (NDA 202022 Clinical Pharmacology review dated 9/2/2010), we agree with the sponsor's proposal to contraindicate RPV with omeprazole.

LABEL RECOMMENDATIONS

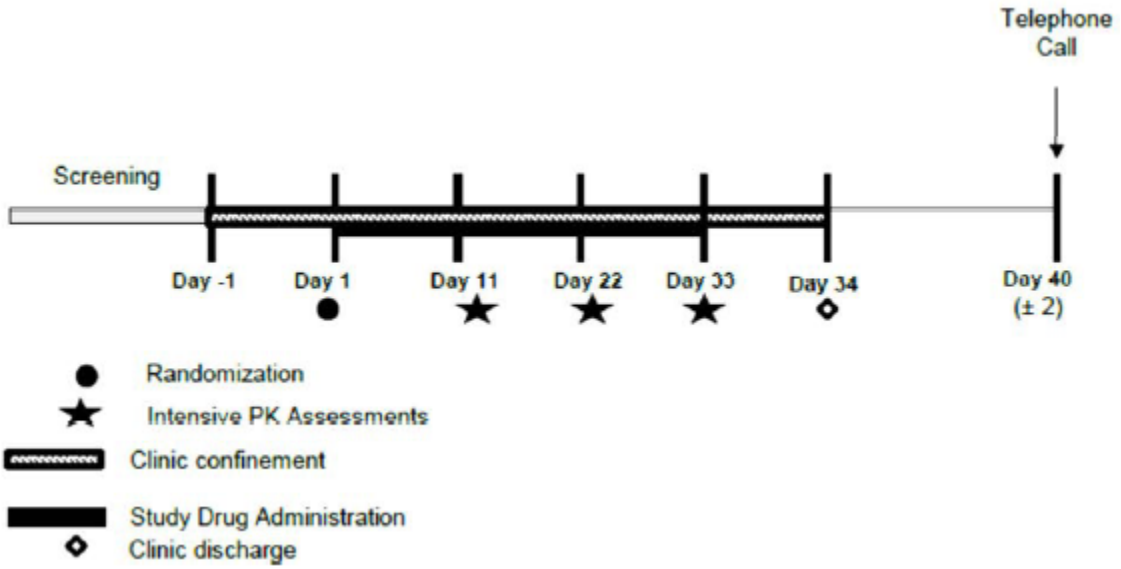
We agree with the sponsor's proposal to contraindicate the use of omeprazole with RPV.

3.4 Study 366-1689 – drug interaction study between FTC/RPV/TAF and ledipasvir/sofosbuvir

A Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between Emtricitabine/Rilpivirine/Tenofovir Alafenamide Fumarate (FTC/RPV/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablets	
Study Period	1/28/2015-3/22/2015
Link	(b) (4)

STUDY DESIGN

Randomized, open label, single-center, multiple-dose, 3-way, 6-sequence, cross-over study.



Subjects were randomized to one of the following six treatment sequences (ABC, ACB, BCA, BAC, CBA, or CAB):

Treatment Sequence	Days 1-11	Days 12-22	Days 23-33
1	A	B	C
2	A	C	B
3	B	C	A
4	B	A	C
5	C	B	A
6	C	A	B

All subjects received the following three treatments:

<table>
<tr><td colspan="2">

- **LDV/SOF:** LDV/SOF (1 × 90/400 mg tablet once daily) administered orally under fed conditions in the morning (Treatment A)
- **FTC/RPV/TAF:** FTC/RPV/TAF (1 × 200/25/25 mg tablet once daily) administered orally under fed conditions in the morning (Treatment B)
- **LDV/SOF+ FTC/RPV/TAF:** LDV/SOF (1 × 90/400 mg tablet once daily) plus FTC/RPV/TAF (1 × 200/25/25 mg tablet once daily) coadministered under fed conditions in the morning (Treatment C)

</td></tr>
<tr><td>Population</td><td>Healthy volunteers</td></tr>
<tr><td>Study Rationale</td><td>To determine the effect of LDV/SOF on the PK of FTC/RPV/TAF and vice versa</td></tr>
<tr><td>Dose Selection Rationale</td><td>The approved dose of LDV/SOF was used in this study.
The dose of FTC/RPV/TAF used in this study is the dose compared to E/C/F/TAF in a pivotal relative BA trial.</td></tr>
<tr><td>Formulation</td><td>LDV/SOF: 90/400 mg tablets (lot # DK1208B1R)
FTC/RPV/TAF: 200/25/25 mg tablets (lot # EF1401B1)</td></tr>
<tr><td>Interfering Substances Excluded</td><td>Prescription, over-the-counter, and herbal medicines were excluded with the exception of vitamins, acetaminophen, ibuprofen, hormonal contraceptives, and short-term topical hydrocortisone.</td></tr>
<tr><td>Sampling Times</td><td>Days 11, 22, and 33: predose (≤ 5 min), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 8, 10, 12, 18, and 24 hours post-dose (the 24-hour sample was collected pre-dose on Days 12 and 23)

A single blood sample for Trough PK was drawn pre-dose on the morning of Days 8, 9, 10, 19, 20, 21, 30, 31, and 32</td></tr>
<tr><td>Bioanalytical methods</td><td>According to the sponsor, plasma concentrations of FTC, RPV, TAF, TFV, SOF, GS-566500 (metabolite of SOF), GS-331007 (metabolite of SOF), and LDV were determined using fully validated LC/MS/MS methods and samples were analyzed within the timeframe supported by frozen stability storage data.

Bioanalytical methods used in this study.
<table>
<tr><th>Analyte</th><th>Method #</th></tr>
<tr><td>TAF</td><td>60-1115</td></tr>
<tr><td>TFV</td><td>60-1435</td></tr>
<tr><td>FTC</td><td>42-1410</td></tr>
<tr><td>RPV</td><td>42-1408</td></tr>
<tr><td>SOF, GS-566500, and GS-331007</td><td>60-1323</td></tr>
<tr><td>LDV</td><td>60-1433</td></tr>
</table>
</td></tr>
</table>

RESULTS

Protocol deviations

No "important" protocol deviations were reported.

Study population

42 subjects were randomized and 41 completed the study; one subject discontinued the study due to an AE.

The mean age was 34 years with a range of 18 to 45 years. Overall, there were more males than females (30 males [71.4%] and 12 females [28.6%]). The majority of subjects were white (61.9%) and Hispanic or Latino (52.4%). The mean BMI at baseline was 27.3 kg/m^2 with a range of 22.8 to 29.9 kg/m^2. The mean CL_{cr} at baseline was 122.3 mL/min with a range of 82.9 to 178.6 mL/min.

Concomitant medications

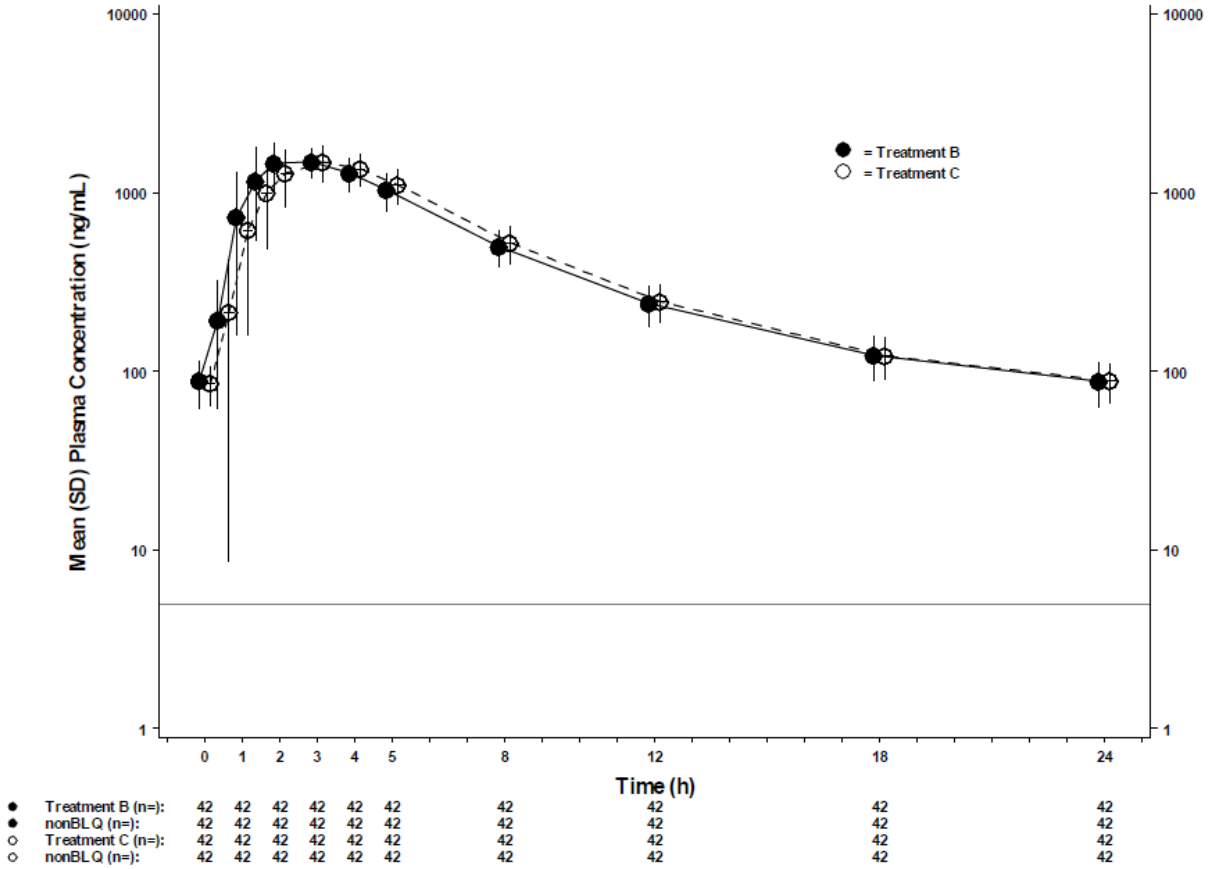
Nine subjects reported use of non-study medications during the study; the most common ones were acetaminophen (n=4) and ibuprofen (n=3).

Pharmacokinetics

Plasma concentration-time profiles, PK parameters, and statistical analyses of PK parameters between treatment arms are shown below for FTC, RPV, TAF, TFV, SOF, GS-566500, GS-331007, and LDV. Geometric mean ratios and 90% CIs of PK parameters for FTC, RPV, SOF, GS-566500, GS-331007, and LDV were within the no effect boundaries of 80-125%; these values were not within the no effect boundaries for TAF and TFV.

FTC

Figure 14. Mean plasma concentration-time profiles of FTC.



Treatment B = FTC/RPV/TAF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 5.00 ng/mL for analyte FTC.

Table 27. PK parameters of FTC.

FTC PK Parameter	Mean (%CV)	
	FTC/RPV/TAF (Treatment B) (N = 42)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{tau} (h*ng/mL)	10,764.1 (14.3)	10,805.1 (15.3)
C_{max} (ng/mL)	1707.6 (20.2)	1650.3 (17.6)
C_{tau} (ng/mL)	87.9 (28.2)	88.7 (25.1)
T_{max} (h)[a]	2.50 (1.50, 3.00)	3.00 (2.00, 3.00)
T_{last} (h)[a]	23.93 (23.93, 23.93)	23.93 (23.93, 23.93)
$t_{1/2}$ (h)[a]	6.47 (4.78, 7.71)	5.10 (4.72, 6.93)
CL/F (L/h)	18.9 (13.2)	18.9 (13.5)

a Median (Q1, Q3)

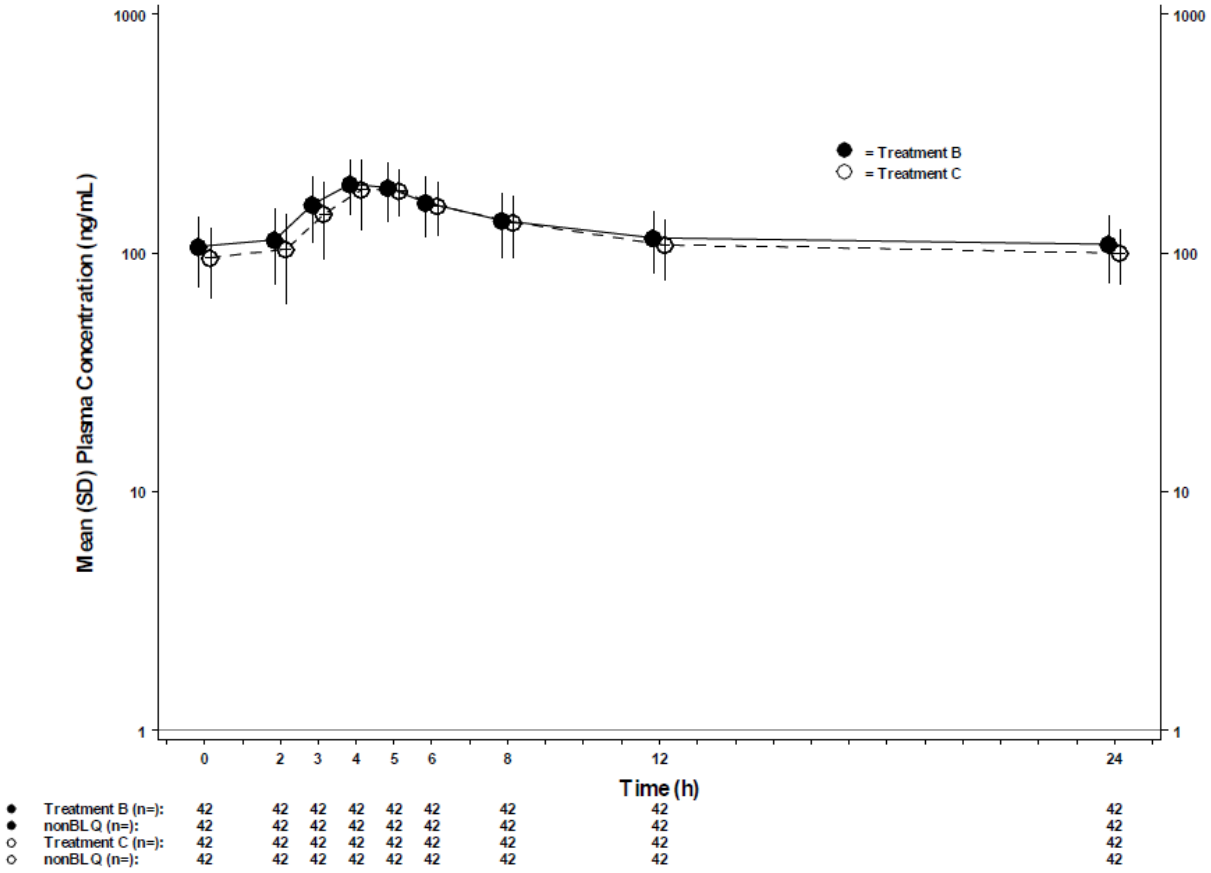
Table 28. Statistical comparison of PK parameters of FTC.

FTC PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment B
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	FTC/RPV/TAF (Treatment B) (N = 42)	
AUC_{tau} (h*ng/mL)	10,694.80	10,663.72	100.29 (98.43,102.19)
C_{max} (ng/mL)	1624.12	1673.95	97.02 (92.72,101.53)
C_{tau} (ng/mL)	86.35	85.00	101.59 (98.47,104.81)

GLSM = geometric least-squares mean

RPV

Figure 15. Mean plasma concentration-time profiles of RPV.



Treatment B = FTC/RPV/TAF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 1.00 ng/mL for analyte RPV.

Table 29. PK parameters of RPV.

RPV PK Parameter	Mean (%CV)	
	FTC/RPV/TAF (Treatment B) (N = 42)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{tau} (h*ng/mL)	3040.1 (27.3)	2857.6 (25.6)
C_{max} (ng/mL)	203.3 (25.4)	197.1 (28.3)
C_{tau} (ng/mL)	109.1 (31.6)	100.0 (26.0)
T_{max} (h)[a]	5.00 (4.00, 5.00)	4.00 (4.00, 5.00)
T_{last} (h)[a]	23.93 (23.93, 23.93)	23.93 (23.93, 23.93)
$t_{1/2}$ (h)[a]	32.80 (26.05, 53.02)	30.41 (21.55, 42.50)
CL/F (L/h)	8.9 (33.0)	9.3 (28.8)

a Median (Q1, Q3)

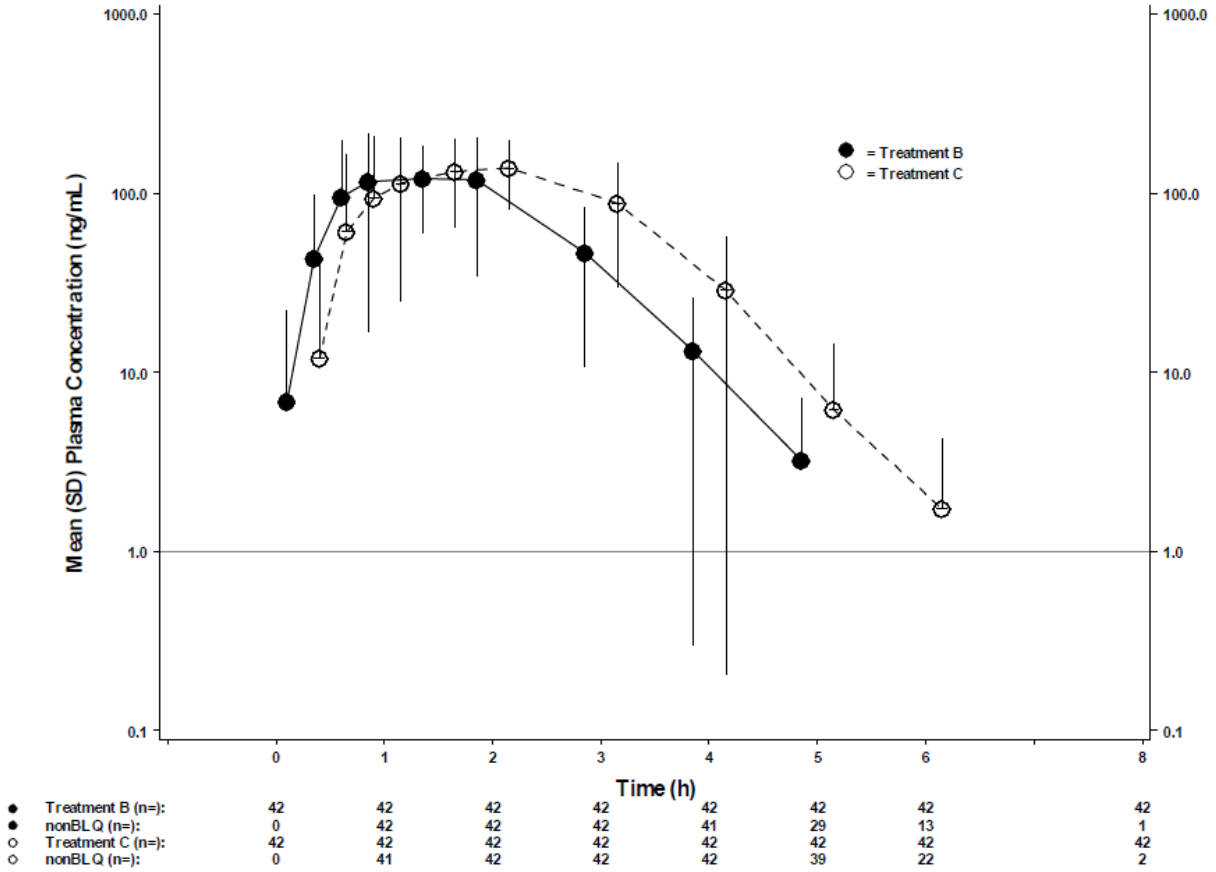
Table 30. Statistical comparison of PK parameters of RPV.

RPV PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment B
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	FTC/RPV/TAF (Treatment B) (N = 42)	
AUC_{tau} (h*ng/mL)	2769.17	2927.63	94.59 (91.20,98.10)
C_{max} (ng/mL)	189.91	196.49	96.65 (91.73,101.84)
C_{tau} (ng/mL)	96.60	103.51	93.33 (89.38,97.45)

GLSM = geometric least-squares mean

TAF

Figure 16. Mean plasma concentration-time profiles of TAF.



Treatment B = FTC/RPV/TAF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 1.00 ng/mL for analyte TAF.

Table 31. PK parameters of TAF.

TAF PK Parameter	Mean (%CV)	
	FTC/RPV/TAF (Treatment B) (N = 42)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{last} (h*ng/mL)	277.2 (37.5)	362.3 (34.4)
C_{max} (ng/mL)	200.0 (43.5)	204.5 (45.7)
T_{max} (h)[a]	1.50 (1.00, 2.00)	1.75 (1.00, 2.00)
T_{last} (h)[a]	5.00 (4.00, 6.00)	6.00 (5.00, 6.00)
$t_{1/2}$ (h)[a]	0.45 (0.40, 0.57)	0.46 (0.42, 0.54)
CL/F (L/h)	102.3 (37.1)	76.0 (34.1)

a Median (Q1, Q3)

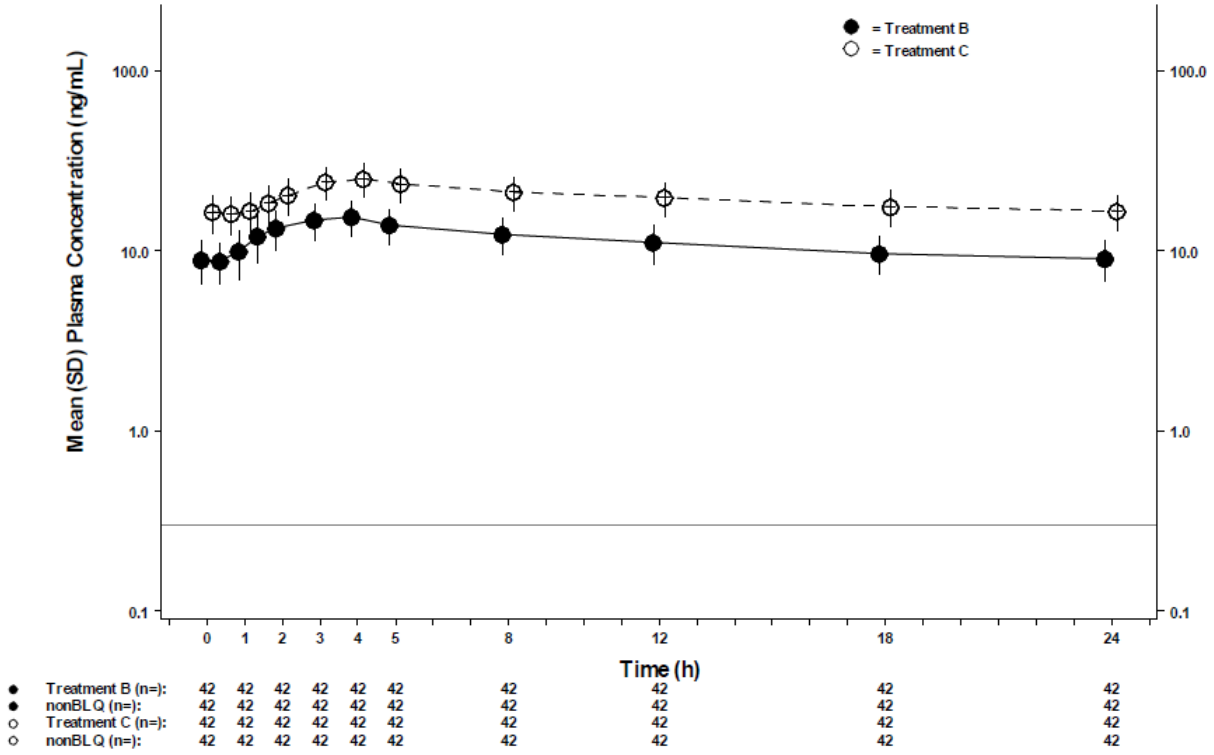
Table 32. Statistical comparison of PK parameters of TAF.

TAF PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment B
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	FTC/RPV/TAF (Treatment B) (N = 42)	
AUC_{last} (h*ng/mL)	343.04	259.12	132.39 (124.99,140.22)
C_{max} (ng/mL)	186.90	181.24	103.12 (93.58,113.63)

GLSM = geometric least-squares mean

TFV

Figure 17. Mean plasma concentration-time profiles of TFV.



Treatment B = FTC/RPV/TAF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 0.300 ng/mL for analyte TFV.

Table 33. PK parameters of TFV.

TFV PK Parameter	Mean (%CV)	
	FTC/RPV/TAF (Treatment B) (N = 42)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{tau} (h*ng/mL)	268.4 (22.6)	467.2 (21.0)
C_{max} (ng/mL)	15.8 (21.7)	25.4 (20.0)
C_{tau} (ng/mL)	9.0 (24.8)	16.7 (22.0)
T_{max} (h)[a]	4.00 (3.00, 4.00)	4.00 (3.00, 4.00)
T_{last} (h)[a]	23.93 (23.93, 23.93)	23.93 (23.93, 23.93)
$t_{1/2}$ (h)[a]	32.00 (28.40, 37.96)	44.47 (33.99, 51.88)
CL/F (L/h)	59.0 (21.5)	33.6 (19.7)

a Median (Q1, Q3)

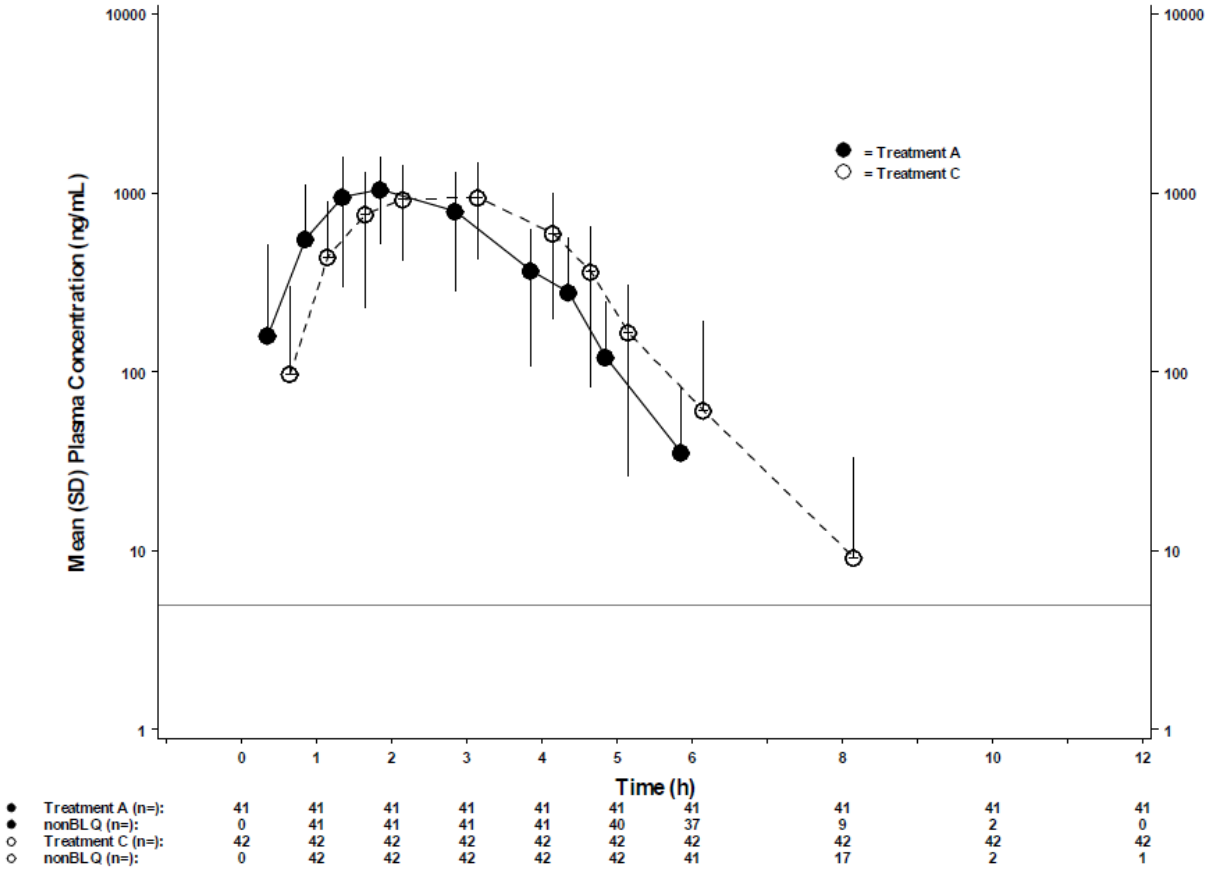
Table 34. Statistical comparison of PK parameters of TFV.

TFV PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment B
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	FTC/RPV/TAF (Treatment B) (N = 42)	
AUC_{tau} (h*ng/mL)	457.77	262.01	174.72 (168.78,180.86)
C_{max} (ng/mL)	24.88	15.40	161.50 (155.60,167.62)
C_{tau} (ng/mL)	16.20[a]	8.77	184.86 (177.57,192.46)

GLSM = geometric least-squares mean
a N = 41

SOF

Figure 18. Mean plasma concentration-time profiles of SOF.



Treatment A = LDV/SOF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 5.00 ng/mL for analyte SOF.

Table 35. PK parameters of SOF.

SOF PK Parameter	Mean (%CV)	
	LDV/SOF (Treatment A) (N = 41)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{tau} (h*ng/mL)	2909.4 (32.8)	3068.9 (30.5)
C_{max} (ng/mL)	1469.5 (35.4)	1390.6 (32.3)
T_{max} (h)[a]	2.00 (1.50, 3.00)	2.00 (2.00, 3.00)
T_{last} (h)[a]	6.00 (6.00, 6.12)	6.00 (6.00, 8.00)
$t_{1/2}$ (h)[a]	0.54 (0.43, 0.61)	0.54 (0.47, 0.62)
CL/F (L/h)	152.0 (31.6)	142.7 (31.2)

a Median (Q1, Q3)

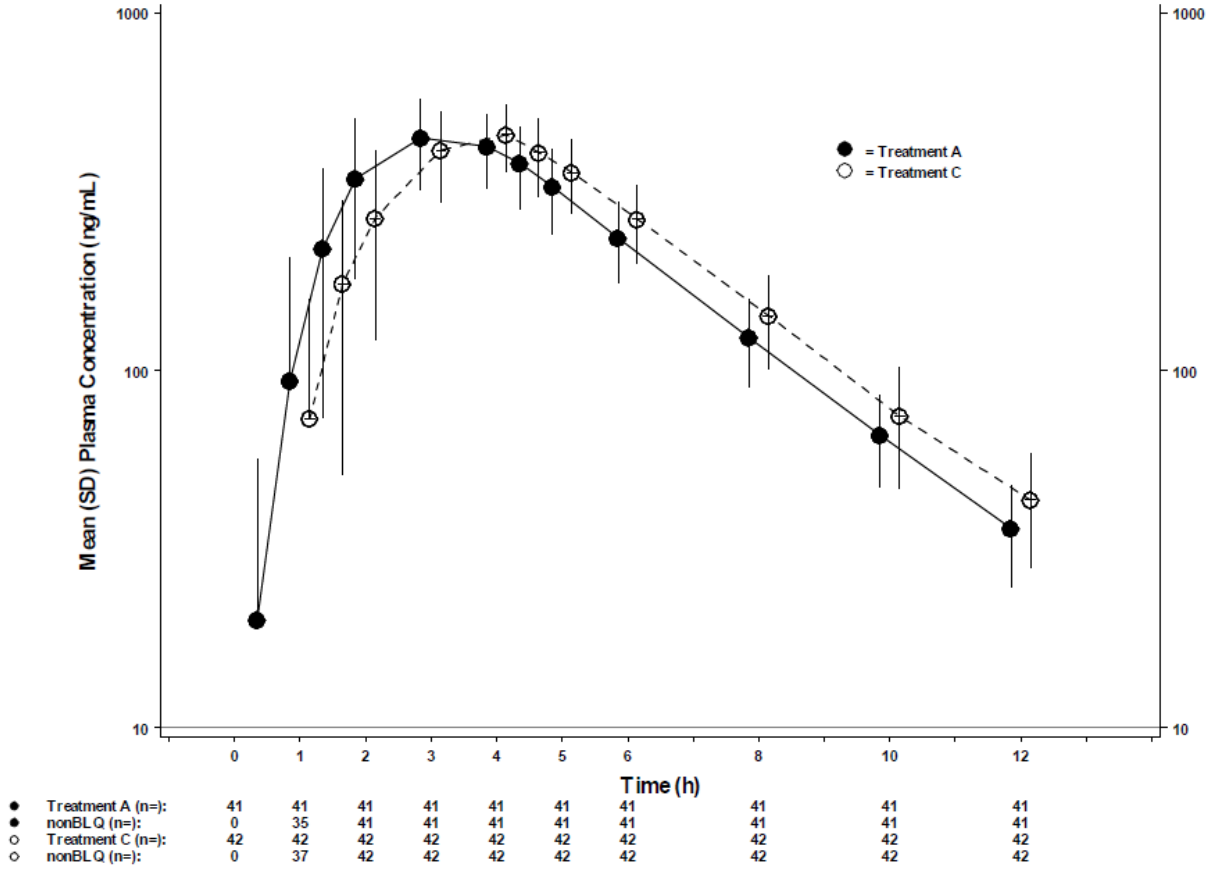
Table 36. Statistical comparison of PK parameters of SOF.

SOF PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment A
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	LDV/SOF (Treatment A) (N = 41)	
AUC_{tau} (h*ng/mL)	2934.09	2802.64	104.69 (100.51,109.04)
C_{max} (ng/mL)	1316.73	1371.73	95.99 (88.80,103.76)

GLSM = geometric least-squares mean

GS-566500

Figure 19. Mean plasma concentration-time profiles of GS-566500.



Treatment A = LDV/SOF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 10.0 ng/mL for analyte GS-566500.

Table 37. PK parameters of GS-566500.

GS-566500 PK Parameter	Mean (%CV)	
	LDV/SOF (Treatment A) (N = 41)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{tau} (h*ng/mL)	2504.0 (16.4)	2575.4 (16.2)
C_{max} (ng/mL)	510.2 (20.1)	502.2 (18.2)
T_{max} (h)[a]	3.00 (2.00, 4.00)	4.00 (3.00, 4.00)
T_{last} (h)[a]	12.00 (12.00, 12.00)	12.00 (12.00, 18.00)
$t_{1/2}$ (h)[a]	2.22 (2.04, 2.46)	2.40 (2.13, 2.87)

a Median (Q1, Q3)

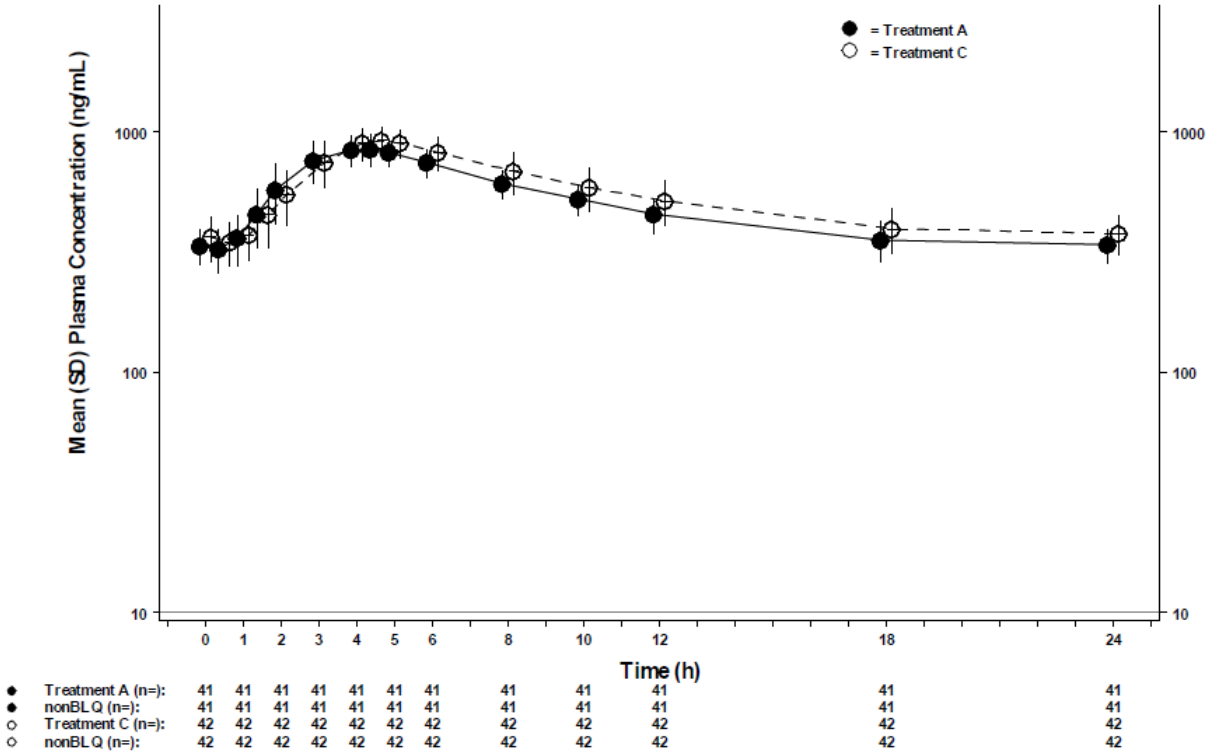
Table 38. Statistical comparison of PK parameters of GS-566500.

GS-566500 PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment A
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	LDV/SOF (Treatment A) (N = 41)	
AUC_{tau} (h*ng/mL)	2542.56	2491.55	102.05 (99.34,104.83)
C_{max} (ng/mL)	493.40	498.24	99.03 (95.24,102.97)

GLSM = geometric least-squares mean

GS-331007

Figure 20. Mean plasma concentration-time profiles of GS-331007.



Treatment A = LDV/SOF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 10.0 ng/mL for analyte GS-331007.

Table 39. PK parameters of GS-331007.

GS-331007 PK Parameter	Mean (%CV)	
	LDV/SOF (Treatment A) (N = 41)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{tau} (h*ng/mL)	11,766.4 (12.8)	12,883.3 (16.1)
C_{max} (ng/mL)	884.4 (13.7)	960.4 (14.8)
C_{tau} (ng/mL)	339.8 (16.4)	378.1 (18.9)
T_{max} (h)[a]	4.50 (4.00, 4.50)	4.50 (4.00, 5.00)
T_{last} (h)[a]	23.93 (23.93, 23.93)	23.93 (23.93, 23.93)
$t_{1/2}$ (h)[a]	16.69 (13.77, 21.85)	16.51 (14.50, 21.80)

a Median (Q1, Q3)

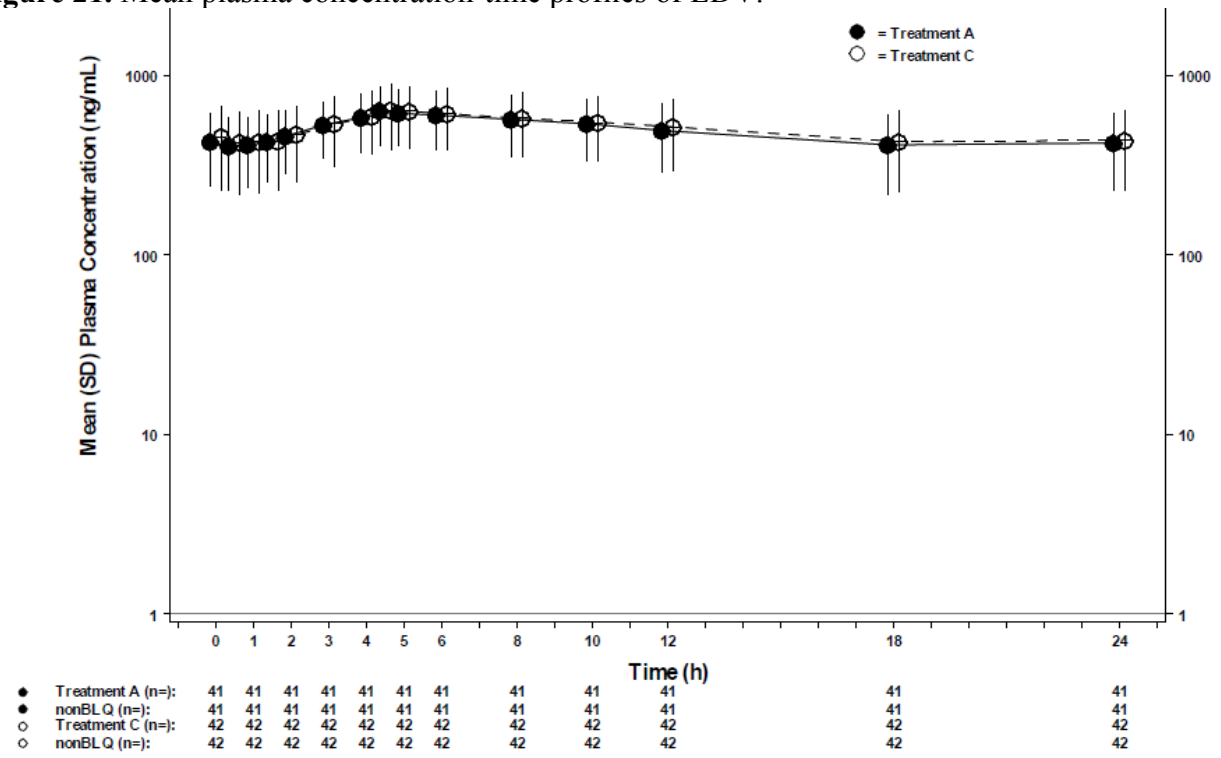
Table 40. Statistical comparison of PK parameters of GS-331007.

GS-331007 PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment A
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	LDV/SOF (Treatment A) (N = 41)	
AUC_{tau} (h*ng/mL)	12727.94	11787.09	107.98 (106.20,109.79)
C_{max} (ng/mL)	950.49	879.39	108.09 (105.05,111.20)
C_{tau} (ng/mL)	371.42	337.90	109.92 (107.46,112.44)

GLSM = geometric least-squares mean

LDV

Figure 21. Mean plasma concentration-time profiles of LDV.



Treatment A = LDV/SOF; Treatment C = LDV/SOF+FTC/RPV/TAF
Reference line indicates LLOQ. Summarized postdose concentration values that were ≤ LLOQ were not displayed in the plot.
Values below the LLOQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ = 1.00 ng/mL for analyte LDV.

Table 41. PK parameters of LDV.

LDV PK Parameter	Mean (%CV)	
	LDV/SOF (Treatment A) (N = 41)	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)
AUC_{tau} (h*ng/mL)	11,590.4 (40.3)	11,944.8 (42.7)
C_{max} (ng/mL)	647.4 (35.8)	658.4 (37.7)
C_{tau} (ng/mL)	419.7 (45.9)	434.3 (47.4)
T_{max} (h)[a]	4.50 (4.50, 5.00)	4.50 (4.50, 5.00)
T_{last} (h)[a]	23.93 (23.93, 23.93)	23.93 (23.93, 23.93)
$t_{1/2}$ (h)[a]	32.58 (22.07, 40.56)	31.25 (24.20, 37.45)
CL/F (L/h)	9.4 (56.1)	9.0 (48.5)

a Median (Q1, Q3)

Table 42. Statistical comparison of PK parameters of LDV.

LDV PK Parameter	GLSM		%GLSM Ratio (90% CI) Treatment C vs Treatment A
	LDV/SOF+FTC/RPV/TAF (Treatment C) (N = 42)	LDV/SOF (Treatment A) (N = 41)	
AUC_{tau} (h*ng/mL)	10,957.13	10,791.66	101.53 (97.36, 105.88)
C_{max} (ng/mL)	615.23	611.43	100.62 (96.76, 104.63)
C_{tau} (ng/mL)	390.55	381.39	102.40 (98.02, 106.99)

GLSM = geometric least-squares mean

Geometric mean AUC ratios and 90% CIs for each analyte (test/reference) are summarized below (Table 43).

Table 43. Summary of geometric mean AUC ratios and 90% CIs for each analyte (test/reference).

Analyte	Geometric mean ratio (%), (90% CI)
FTC	100 (98, 102)
RPV	95 (91, 98)
TAF	132 (125, 140)
TFV	174 (169, 181)
SOF	105 (101, 109)
GS-566500	102 (99, 105)
GS-331007	108 (106, 110)
LDV	102 (97, 106)

Source: prepared by reviewer.

Safety

The most common AEs were constipation and headachel; all AEs reported were grade 1-2 in severity. There were no deaths or SAEs during the study. One subject discontinued the study due to an AEs. On day 12 the subject had a grade 2 AE of colitis. The subject continued study drug through day 28 and discontinued on that day due to the ongoing AE of colitis. The subject received treatment for colitis and the event resolved 10 weeks after onset. The AE was considered related to study drug. No reported laboratory abnormalities resulted in an AE. No notable changes in vital signs were reported to have occurred during the study.

DISCUSSION/REVIEWER'S COMMENTS

The bioanalytical methods used in this study were validated and were acceptable according to the criteria in the 2013 FDA Bioanalytical Guidance. None of the non-study medications used by a subset of subjects were perpetrators of drug interactions. No outliers were observed among individual subject PK parameters for any of the analytes.

The AUC of TAF and TFV were increased when coadministered with LDV/SOF; other analytes were unaffected. The mean 32% TAF AUC increase is not clinically significant as no exposure-safety relationships for TAF have been identified. The mean 74% TFV AUC increase is not clinically significant because TFV AUC from TAF is 90% lower compared to TFV from TDF. For example, mean TFV AUC from TDF administered as E/C/F/TDF was ~3300 ng*h/mL (see NDA 207561 Clinical Pharmacology Summary) compared to a mean TFV AUC from TAF in this study of 262 ng*h/mL in the reference arm and 458 ng*h/mL in the test arm.

LABEL RECOMMENDATIONS

We agree with the proposed labeling statement that there is no clinically significant interaction of FTC/RPV/TAF with LDV/SOF.

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
12/01/2015

ISLAM R YOUNIS
12/01/2015