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RESEARCH**

*APPLICATION NUMBER:*

**208464Orig1s000**

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

# CLINICAL PHARMACOLOGY REVIEW

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<b>NDA/SDN</b>	208464/1
<b>Submission Type</b>	Non-NME NDA
<b>Applicant Name</b>	Gilead
<b>Submission Dates</b>	1/11/2016
<b>Generic Name</b>	Tenofovir alafenamide (TAF)
<b>Dosage Form (Strength)</b>	Tablet (25 mg)
<b>Indication</b>	Treatment of hepatitis B viral (HBV) infection
<b>Review Team</b>	Mario Sampson, PharmD, Amal Ayyoub, PhD, Jeffrey Florian, PhD, Islam Younis, PhD

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## 2 Executive summary

Tenofovir alafenamide (TAF) is a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir (TFV), and is approved as a component of several combination products for the treatment of HIV. TAF is primarily eliminated through conversion to the metabolite tenofovir (TFV), while TFV is primarily renally eliminated. TFV is associated with bone and renal adverse events. TAF clinical pharmacology properties have been previously described (NDA 207561 Clinical Pharmacology review dated 7/10/2015).

Two phase 3 clinical studies in HBV-infected subjects form the basis of approval of this application. Study GS-US-320-0108 (study 108) was in HBe antigen-negative subjects and study GS-US-320-0110 (study 110) was in HBe antigen-positive subjects. Subjects were randomized (2:1) to TAF 25 mg daily with food or tenofovir disoproxil fumarate (TDF) once daily with food. The primary efficacy endpoint was the fraction of subjects with HBV DNA concentration <29 IU/mL at week 48. Efficacy rates were 93-94% in both arms of study 108 and 64-67% in both arms of study 110.

Nine clinical pharmacology studies were reviewed in this application, including antiviral activity (n=1), in vitro drug interactions (n=1), in vivo drug interactions (n=2), intrinsic factors (n=2; race and hepatic impairment), extrinsic factors (n=1; food effect), and modeling and simulation (n=2).

### 2.1 Summary of clinical pharmacology findings

#### 2.1.1 *Adequacy of the TAF population PK model*

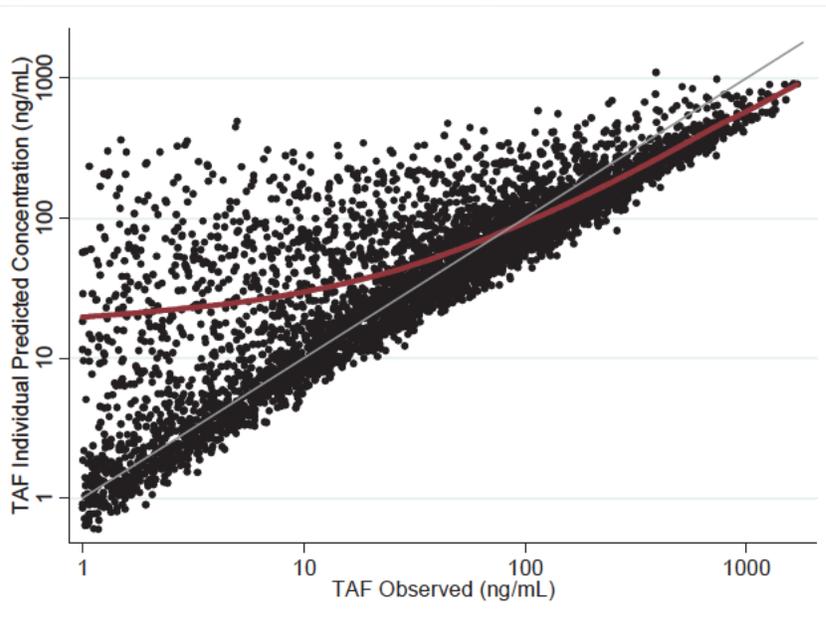
Twelve TAF studies were included in the popPK dataset, including studies in healthy volunteers (n=6), HBV-infected subjects (n=3), HIV-infected subjects (n=2), and renal impairment (n=1). The TAF dose range in the dataset was 8-240 mg. TAF concentrations were detectable between 0.0167 h to 8 hours post-dose. Within this time after dose range, 33% of TAF samples were below the limit of quantification (BLOQ). The median (range) percent of BLOQ samples in the detectable range (within 0.0167 h to 8 hours post-dose) by study was 31.5% (14, 48). The applicant attempted to incorporate BLOQ samples into the model (i.e. M3 method). However, the final model did not apply such a method. The inability to account for the large fraction of BLOQ samples at timepoints when detectable samples were expected is a significant model flaw.

Another flaw in the TAF popPK model was significant bias in goodness-of-fit plots whereby TAF concentrations were overpredicted at low observed concentrations and underpredicted at high observed TAF concentrations (Figure 1).

Due to the large fraction of BLOQ samples and inability to incorporate them into the model, in addition to poor goodness-of-fit, we considered the model to be inadequate for accurately describing TAF exposures. As such, no exposure response analyses could be conducted based on TAF exposures.

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**Figure 1.** TAF final model - individual predicted versus observed concentrations.

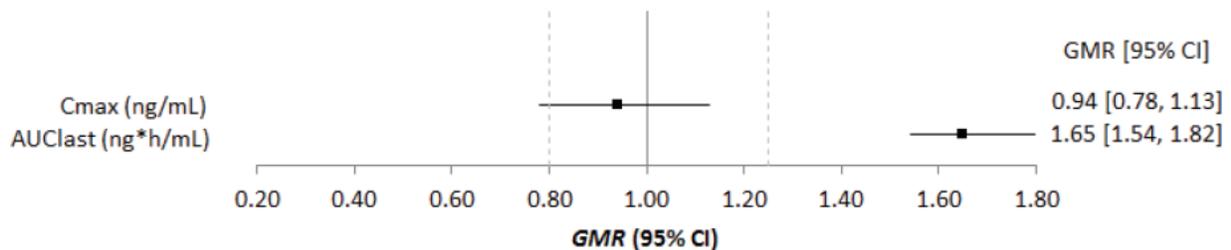


Source: plotted by reviewer.

## 2.1.2 Dosing with regard to food intake

In phase 3 studies, subjects were instructed to take TAF with food. In a single-dose, crossover study evaluating TAF PK under fasted versus fed (high-fat meal) conditions (n=40), TAF exposures were ~40% lower in the fasted state relative to fed (Figure 2). The applicant proposed (b) (4). The observation of similar week 4 antiviral activity for TAF 8 mg and 25 mg in study 320-0101 suggests exposures up to 3-fold lower (TAF PK is dose proportional) than exposures associated with 25 mg may be efficacious. However, it is unclear if lower exposures would also be efficacious upon long term use. Because efficacy has not been established and exposure-response relationships at lower exposures expected upon fasted administration have not been characterized, we recommend that TAF should be administered with food.

**Figure 2.** TAF exposures changes in food effect study 320-1382.



Source: prepared by reviewer. GMR = geometric mean ratio (fed/fasted); CI = confidence interval.

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### 2.1.3 Dosing in patients with severe renal impairment

TAF (combined with other agents in GENVOYA<sup>®</sup>) is approved for use in patients with CrCL  $\geq 30$  mL/min. In subjects with severe renal impairment versus normal renal function, TAF and TFV exposures were ~2- and ~6-fold higher, respectively (NDA 207561 Clinical Pharmacology review dated 7/10/2015). The applicant proposes no dose adjustment in patients with renal impairment.

The phase 3 studies in HBV-infected subjects predominantly enrolled subjects with normal renal function (creatinine clearance [CrCL] of  $\geq 90$  mL/min) or mild renal impairment (CrCL of 60- $<90$  mL/min); five subjects with moderate renal impairment were enrolled. As there are minimal safety concerns related to TAF exposure, we do not consider a 2-fold elevation in TAF exposures to be clinically relevant. The ~6-fold increase in TFV exposures in subjects with severe renal impairment is not clinically relevant because these exposures would still be below those associated with administration of the approved drug TDF to patients with normal renal function (TAF results in TFV exposures 90% lower than TFV exposures associated with TDF). Our assessment of the safety of elevated TAF and TFV exposures assumes no alteration of exposure-safety relationships in subjects with renal impairment.

### 2.1.4 Dosing in patients with end stage renal disease on dialysis

[REDACTED] (b) (4)  
Ongoing study GS-US-292-1825 is an efficacy, safety, and PK study of TAF in combination with other agents for treatment of HIV in subjects with end stage renal disease (ESRD) on dialysis. The applicant simulated TFV exposures in subjects on dialysis following the administration of TAF [REDACTED] (b) (4). The limitation of the TFV exposure prediction is that TFV concentrations rebounded by 50% after dialysis in a study of TDF in dialysis patients. Nevertheless, the key limitation is the lack of predicted TAF exposures in dialysis patients. [REDACTED] (b) (4)

[REDACTED] Dosing recommendations for patients with ESRD on dialysis can be re-evaluated upon submission and review of the ongoing study of TAF in subjects on dialysis.

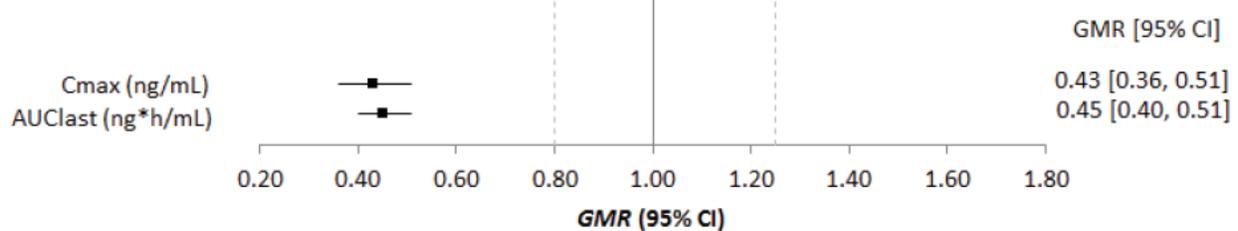
### 2.1.5 Dosing when coadministered with carbamazepine

Carbamazepine (CBZ) is a CYP3A4 and Pgp inducer; TAF is a substrate of Pgp. When coadministered with CBZ, TAF (administered as emtricitabine [FTC, F]/TAF) AUC was reduced 55% (Figure 3). In two of three subjects that used Pgp inducers in the phase 3 studies, virologic rebound occurred after coadministration of the Pgp inducer (1 week in one case, 10 weeks in the other case, Table 1). Due to the small number of subjects on Pgp inducers in the phase three

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studies (all HBeAg positive), it is unclear if the 33% response rate for these subjects is different from the overall TAF response rate of 64% in HBeAg- positive subjects.

**Figure 3.** TAF exposures changes in TAF-CBZ drug interaction study 311-1387.



Source: prepared by reviewer. TAF was administered as F/TAF. GMR = geometric mean ratio (TAF+CBZ/TAF alone); CI = confidence interval.

**Table 1.** Virologic outcome of subjects that used Pgp inducers in the phase 3 studies.

Subject ID	HBeAg status	Pgp inducer use	Virologic outcome
04844-4697	positive	CBZ from week 46-48	Discontinued after virologic rebound at week 56
06341-5297		Phenobarbital from week 9-12	Responded
06336-5050		Rifampicin from week 23; no end date	Discontinued after virologic rebound at week 24

Source: prepared by reviewer.

(b) (4)  
(b) (4)  
(b) (4) As stated above, we do not think the observation of similar week 4 anti-HBV activity for TAF 8 mg and TAF 25 mg (study GS-US-320-0101) proves that long-term exposures lower than associated with TAF 25 mg are efficacious. Because efficacy has not been established and exposure-efficacy relationships have not been characterized at exposures expected to be lower than evaluated in phase 3 studies, we recommend doubling the TAF dose to two tablets once daily with food.

We proposed that use of TAF was not recommended with oxcarbazepine, phenobarbital, or phenytoin unless the applicant could provide data to support some other recommendation. In response to our request, the applicant submitted information concerning the Pgp inductive potential for oxcarbazepine, phenobarbital, or phenytoin (NDA 208464 SDN 28). Based on drug interaction data showing greater Pgp induction versus CBZ, and a similar effect to St. John's Wort, we agree with the applicant that phenytoin is a potent Pgp inducer and we agree with the labeling proposal that phenytoin is not recommended to be coadministered with TAF. For

(b) (4)  
(b) (4) Because we are not aware of data showing the magnitude of Pgp induction by oxcarbazepine and phenobarbital versus CBZ, we proposed that coadministration of TAF with oxcarbazepine or phenobarbital is not recommended.

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## 2.1.6 Dosing in patients with hepatic impairment

A single dose PK study (TAF administered with a moderate-fat meal) was conducted in subjects with severe hepatic impairment (Child-Pugh C, n=10) and matched controls (n=10). In subjects with severe hepatic impairment relative to those with normal hepatic function, total TAF exposures were ~50% lower while unbound TAF exposures were not significantly changed (Figure 4). TFV C<sub>max</sub> and AUC were 10% and 37% lower in subjects with severe hepatic impairment, respectively. One issue with this study is that a similar food effect must be assumed in both groups in order to attribute exposure differences between the groups to hepatic function.

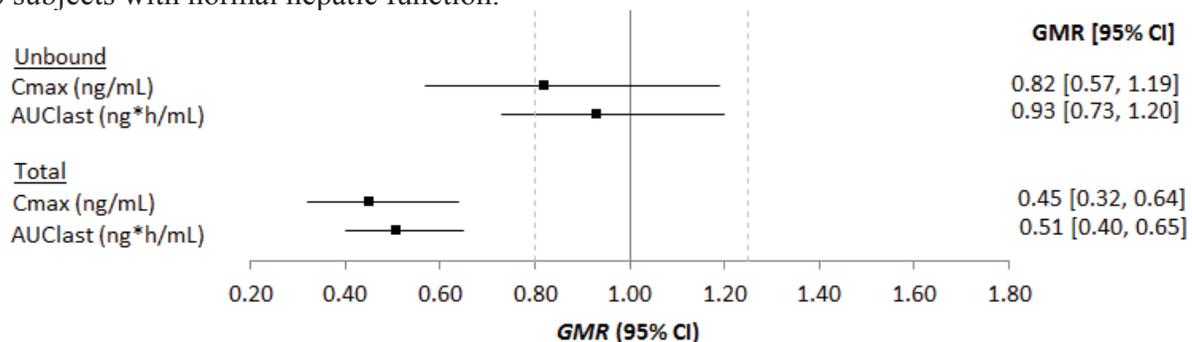
The phase 3 population was limited to subjects with compensated liver disease because most subjects were non-cirrhotic and none were decompensated. The Child-Pugh classification was not applied in the phase 3 studies. The review team thinks the phase 3 population with liver disease would be likely consistent with Child-Pugh A.



(b) (4)

In sections 2 and 8, we proposed that no dose adjustment is needed in subjects with mild hepatic impairment (Child-Pugh A), and use in patients with moderate to severe hepatic impairment is not recommended. In addition, in section 8 we proposed to add that safety and efficacy has not been established in patients with moderate to severe hepatic impairment.

**Figure 4.** Total and unbound TAF exposures in subjects with severe hepatic impairment relative to subjects with normal hepatic function.



Source: prepared by reviewer. GMR = geometric mean ratio (severe hepatic impairment/normal hepatic function); CI = confidence interval.

## 2.2 Recommendations

The Office of Clinical Pharmacology review team finds this application acceptable and recommends approval. No Postmarketing Requests or Postmarketing Commitments are warranted at this time.

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## 2.3 Labeling recommendations

Labeling negotiations are currently ongoing. Our recommendations for revisions of the applicant’s initial labeling proposal are described in section 2.1.

We agreed with the applicant’s conclusions and/or labeling recommendations for several studies as summarized in Table 2.

**Table 2.** Studies for which we agreed with the applicant’s conclusions and/or labeling recommendations.

Study	Results and conclusion	Labeling recommendation
311-1790 - Effect of F/TAF on the PK of norgestimate / ethinyl estradiol (EE)	No effect of F/TAF on the PK of norgestimate, its metabolites, or EE	EE and norgestimate are listed in the Drug Interactions section that lists drugs that have no significant interaction with TAF
320-0101 – Anti-HBV activity and PK in HBV-infected subjects	Similar antiviral activity was observed among TAF doses of 8-120 mg, and between all TAF doses and TDF 300 mg. One exception was less activity observed in the TAF 40 mg group, which was attributed to lower baseline HBV DNA levels in this group.	None
320-1228 – PK of TAF in healthy Japanese and non-Japanese subjects	No clinically relevant difference in the PK of TAF and TFV between Japanese and non-Japanese subjects	Section 12.3 states that “No clinically relevant pharmacokinetic differences due to race have been identified”
AD-120-2042 – Effect of OATP inhibitor TAF uptake into human hepatocytes	In human hepatocytes, rifampicin (OATP inhibitor) inhibited TAF uptake by 13%.	Section 12.4 states that “Tenofovir alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3”

Source: Prepared by reviewer.

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## 3 Individual study reviews

### Notes

Studies 311-1790, 320-1228, and AD-120-2042 were reviewed by AA and MS; the others were reviewed by MS.

We used FDA bioanalytical guidance to evaluate bioanalytical methods and study sample analyses; major criteria are listed in 4.1.

### 3.1 Population PK analysis of TAF and TFV

#### **TAF model**

#### Studies included in the analysis

Twelve TAF studies were included in the popPK dataset used for development of the TAF and TFV models, including studies in healthy volunteers (n=6), HBV-infected subjects (n=3), HIV-infected subjects (n=2), and renal impairment (n=1).

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**Table 3.** Summary of studies included in the TAF and TFV models.

Study number	Description	Population	Phase	Intensive sampling	Sparse sampling
120-0104	Antiviral activity	HIV	1	x	
120-0107	QT study	Healthy	1	x	
120-0108	Renal impairment	Severe renal impairment	1	x	
120-0109	Mass balance	Healthy	1	x	
120-0117	DDI between TAF and RPV	Healthy	1	x	
120-0118	DDI between TAF and ATV/r, DRV/r, LPV/r	Healthy	1	x	
292-0101	Relative BA of several TAF formulations	Healthy	1	x	
311-1089	TDF to TAF switch study	HIV	3		x
320-0101	Antiviral activity	CHB	1b	x	x
320-0108	Pivotal	CHB	3	x (substudy)	x
320-0110	Pivotal	CHB	3	x (substudy)	x
320-1228	Effect of Japanese race on PK	Healthy	1	x	

Source: Prepared by reviewer.

### Data handling

The dataset contained 12575 TAF samples from 1464 subjects. 1444 TAF samples were excluded from the analysis due to missing time of sampling or inconsistencies with the expected concentration-time profile; 721 of these excluded samples were detectable. Of the remaining 11131 samples, 5798 (52%) were undetectable. TAF concentrations were detectable between 0.0167 h to 8 h post-dose. Of the 8005 samples collected within 0.0167 h to 8 h post-dose, 2673 (33%) were undetectable. The median (range) percent of BLOQ samples in the detectable range (within 0.0167 h to 8 h post-dose) by study was 31.5% (14, 48). The analysis dataset of detectable samples consisted of 5333 samples from 1268 subjects.

### Model development

TAF and TFV were modeled separately due to substantial differences in time scale (TAF has a half-life of ~0.5 h compared to 47 h for TFV). The applicant arrived at a 2-compartment model with sequential zero and first order absorption (model 128). Covariates included food, use of ATV/r and LPV/r, HIV-infection status, and sex (see parameters on p15). ATV/r and LPV/r increased TAF exposure by 82% and 39%; other covariates altered AUC and C<sub>max</sub> by <40%.

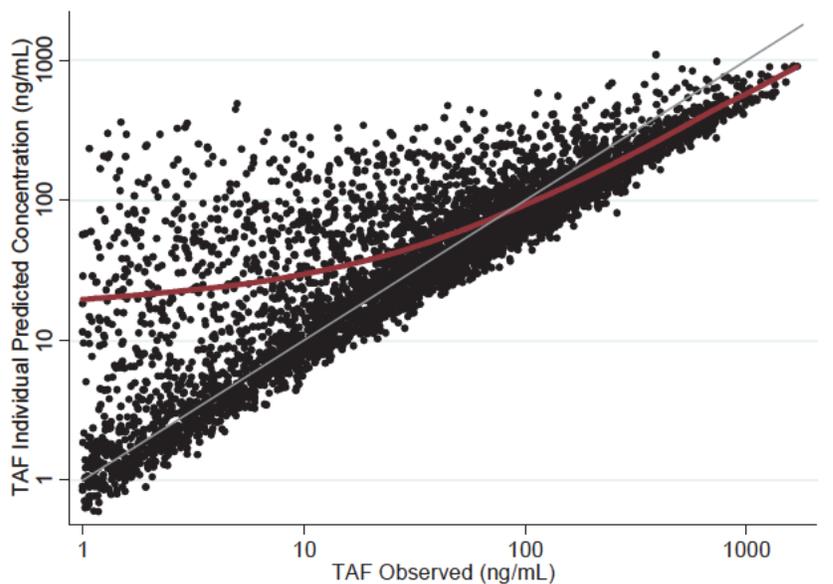
## CLINICAL PHARMACOLOGY REVIEW

The applicant attempted to incorporate BLOQ samples into the model (i.e. M3 method). However, the final model did not apply such a method.

### Model evaluation

There was substantial overprediction of low concentrations and underprediction at high observed concentrations (Figure 5). This difference between observed and predicted concentrations was not apparent on a visual predictive check (VPC, Figure 6).

**Figure 5.** TAF final model 128 - individual predicted versus observed concentrations.



Source: plotted by reviewer.

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**Figure 6.** TAF model 128 prediction-corrected visual predictive check.



## Reviewer's analysis

Very similar objective function value (OFV) and parameter estimates were obtained when we ran the applicant's model at FDA using NONMEM 7.3. Individual predicted TAF exposures in patients were considered to be unreliable due to the poor goodness of fit and the high fraction of undetectable samples within the time after dose range where detectable samples were expected. As such, no exposure-response analyses could be conducted based on individual patient TAF exposures.

## **TFV model**

### Studies included in the analysis

See studies included in the TAF model.

### Data handling

The TFV dataset contained 12511 samples from 1465 subjects. 1411 TFV samples were excluded from the analysis due to missing time of sampling or inconsistencies with the expected concentration-time profile; 22 of these excluded samples were detectable. Of the remaining

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11131 samples, 351 (3%) were undetectable. The analysis dataset of detectable samples consisted of 10749 samples from 1462 subjects.

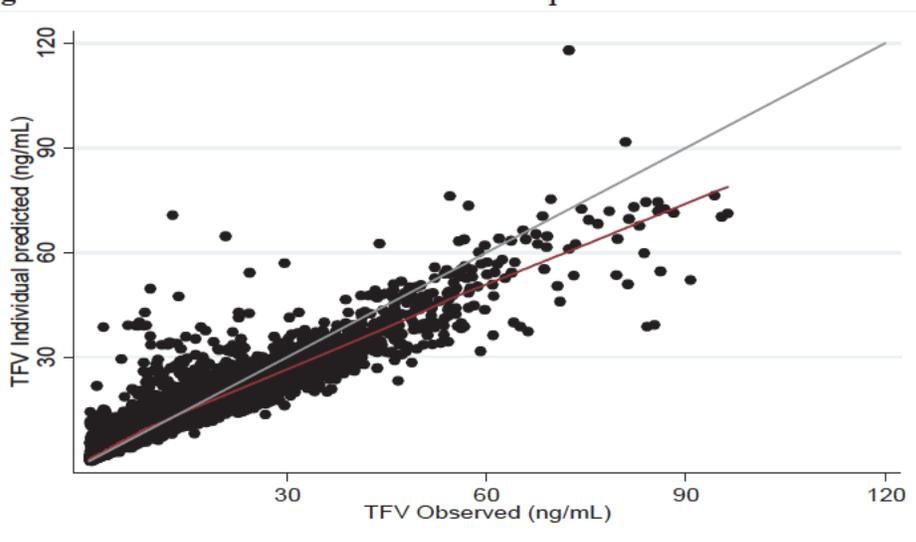
### Model development

The applicant arrived at a 2-compartment model with sequential zero and first order absorption (model 249a). Covariates included food, use of ATV/r, DRV/r, and LPV/r, baseline creatinine clearance, disease status (HBV-infected versus healthy), black race, and sex (see parameters on p15). Differences in TFV exposure due to individual covariates were within 32% relative to the reference value of the covariate.

### Model evaluation

There was reasonable agreement between observed and individual predicted concentrations, and between observed and model-simulated data on the VPC (Figure 7, Figure 8).

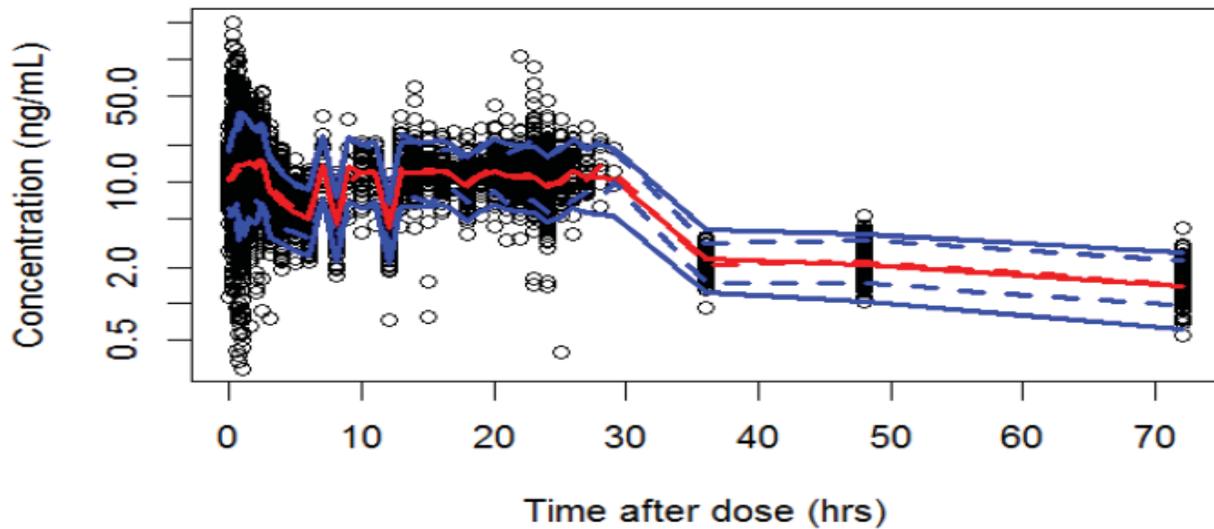
**Figure 7.** TFV final model 249a - individual predicted versus observed concentrations.



Source: Plotted by reviewer.

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**Figure 8.** TFV model 249a prediction-corrected visual predictive check.



Source: Popk report p231.

TFV prediction-corrected (pc) concentrations are plotted versus time after dose. The circles show the observed pc-concentrations. The lines show median (red), and the 5<sup>th</sup> and 95<sup>th</sup> percentiles (blue) of the simulated (bold solid lines) and observed (dash lines) pc-concentrations. The simulated values were computed from 100 simulations with dosing, sampling, and the covariate values of the analysis dataset.

## Reviewer's analysis

Nearly identical objective function value (OFV) and parameter estimates were obtained when we ran the applicant's model at FDA using NONMEM 7.3.

## Exposure-response

TFV exposures were not evaluated for an association with efficacy. TFV exposures were not associated with rates of common adverse events (diarrhea, nausea, vomiting, GI/abdominal pain) or events of special interest (bone mineral density, creatinine clearance, total cholesterol) (see Clinical Pharmacology summary p118).

## **Discussion/reviewer's comments**

The bioanalytical method validation and sample analysis reports for determination of TAF and TFV concentrations for all studies included in the models were reviewed and were acceptable.

## TAF model

We found the TAF model to be inadequate for use in exposure-response analyses or to evaluate the effects of intrinsic/extrinsic factors on exposure. The reasons are the large fraction of undetectable samples within the time after dose range where detectable concentrations were observed and the inability to incorporate them into the model, in addition to poor goodness-of-fit.

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## TFV model

The TFV model was acceptable. This model was of less utility compared to TAF. For exposure-efficacy, TFV concentrations are less relevant compared to TAF concentrations. This is because TFV concentrations from administration of TAF are ~10% of TFV concentrations after administration of TDF while efficacy of TAF and TDF are similar. Similarly for TFV exposure-safety, we did not expect novel findings because the safety profile of TDF (results in much higher TFV exposures compared to TAF) is well known.

## **Labeling recommendations**

In the “Specific Populations” subsection within section 12.3, we proposed the labeling statement “No clinically relevant pharmacokinetic differences due to adult age, race, or gender have been identified”. (b) (4)

(b) (4) Labeling  
negotiations are ongoing.

## **References**

PopPK report: <\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pop-pk-taf-hbv\report-body.pdf>

Clinical Pharmacology summary: <\\cdsesub1\evsprod\nda208464\0000\m2\27-clin-sum\summary-clin-pharm.pdf>

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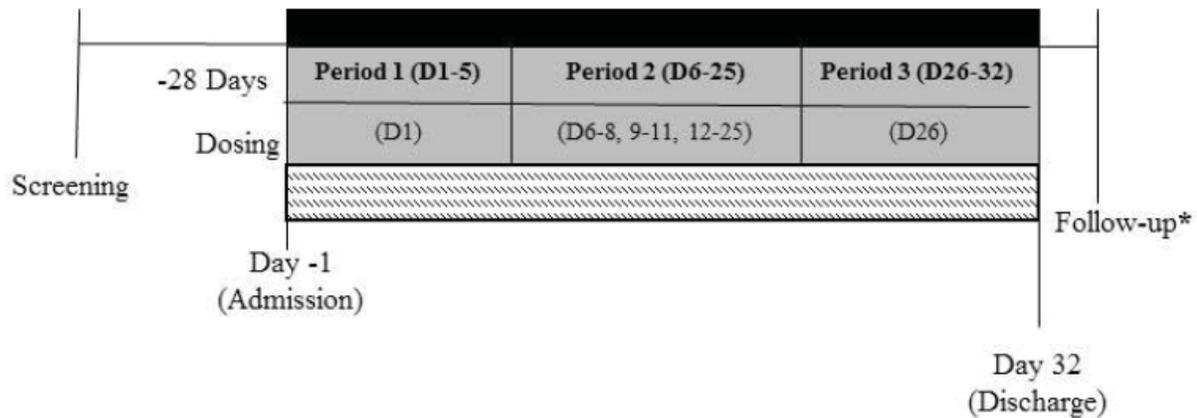
## 3.2 311-1387 – Effect of carbamazepine on the PK of TAF

<b>A Phase 1, Open-Label, Adaptive, Two-Part, Three Period, Fixed Sequence Study to Evaluate the Effect of Carbamazepine on the PK of TAF and GS-9883 in Healthy Adult Subjects</b>	
Study Period	6/23/2015 – 10/5/2015
Link	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-1387\report-body.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-1387\report-body.pdf</a>

### STUDY DESIGN

Phase 1, open-label, adaptive, 2-part, 3-period, fixed-sequence, single-center study in healthy subjects.

#### GS-US-311-1387: Study Schema (Parts A and B)



- Clinic Confinement
- Study Drug Administration Days
- PK Sampling
- \* 7 days (+/- 2 days) after last dose, phone call

Period 1		Period 2			Period 3	
Day 1	Days 2–5	Days 6–8	Days 9–11	Days 12–25	Day 26	Days 27–32
F/TAF FDC 200/25 mg	–	CBZ 100 mg BID <sup>a</sup>	CBZ 200 mg BID <sup>a</sup>	CBZ 300 mg BID <sup>a</sup>	CBZ 300 mg BID <sup>a</sup> + F/TAF FDC 200/25 mg	–

a CBZ was administered twice daily (BID) (every 12 hours).

- Note Part B is the same study design as Part A, with the difference being substitution of F/TAF for GS-9883/F/TAF. This CSR only contains data from Part A.

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	<ul style="list-style-type: none"> <li>F/TAF and CBZ were administered with a moderate-fat meal</li> </ul>
Population	Healthy adults aged 18-45 years
Study Rationale	The effect of steady-state carbamazepine (CBZ) on the PK of TAF
Dose Selection Rationale	F/TAF 200/25 mg is the approved dose. CBZ 300 mg BID is within the range of approved adult dosing (initial dosing of 200 mg BID and maximum daily dose of 1200 mg per day).
Formulation	F/TAF 200/25 mg tablet (lot # CR1408B1) CBZ 100 mg tablet (lot # 300545)
Adherence	All doses were administered at the study center under supervision of staff
Concomitant medications	All prescription, over-the-counter, and herbal medications were excluded except vitamins, acetaminophen, ibuprofen, hormonal contraceptives, and short term topical hydrocortisone.
PK sampling	<ul style="list-style-type: none"> <li>Day 1: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, 48, 72, 96, 120, and 144 hours postdose</li> <li>Day 25: 0 (predose), 1, 2, 3, 3.5, 4, 5, 6, 8, and 12 hours postdose</li> <li>Day 26: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours postdose</li> </ul> <p>Trough (predose) plasma CBZ PK samples were collected on the following days, in the morning: Days 9, 12, 20, 23, and 26.</p>
Bioanalytical methods	Analyses: TAF, TFV, CBZ, carbamazepine-10,11-epoxide (CBZE) Matrix: plasma Method: LC/MS/MS

RESULTS	
Study population	Twenty six subjects were enrolled; four discontinued during period 2 (CBZ dosing) due to AEs. Twenty two subjects completed the study. Mean age was 33 years. The population was 85% male, 58% white, 35% black, and 73% non-Hispanic. All subjects were non-obese (BMI <30 kg/m <sup>2</sup> ) and had normal renal function (CrCL >90 mL/min).
Protocol deviations	No important protocol deviations were reported.
Adherence	All doses were documented as being taken. The applicant reports that drug concentrations also confirmed drug dosing.
Concomitant medications	Use of disallowed medications included antacid/diphenhydramine/lidocaine (n=1), diphenhydramine (n=2), prune juice (n=1), and triamcinolone (n=1).
Bioanalytical methods	All methods were reported to be fully validated. Calibration ranges (ng/mL): -TAF: 1-1000 -TFV: 0.3-300 -CBZ: 20-20000 -CBZE: 5-5000

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## Pharmacokinetics

Compared to TAF alone, mean TAF AUC was 55% lower when coadministered with CBZ (Table 4, Figure 9). Almost all subjects had a reduction in TAF exposure when coadministered with CBZ (Figure 10). Two subjects had vomiting episodes (Table 5).

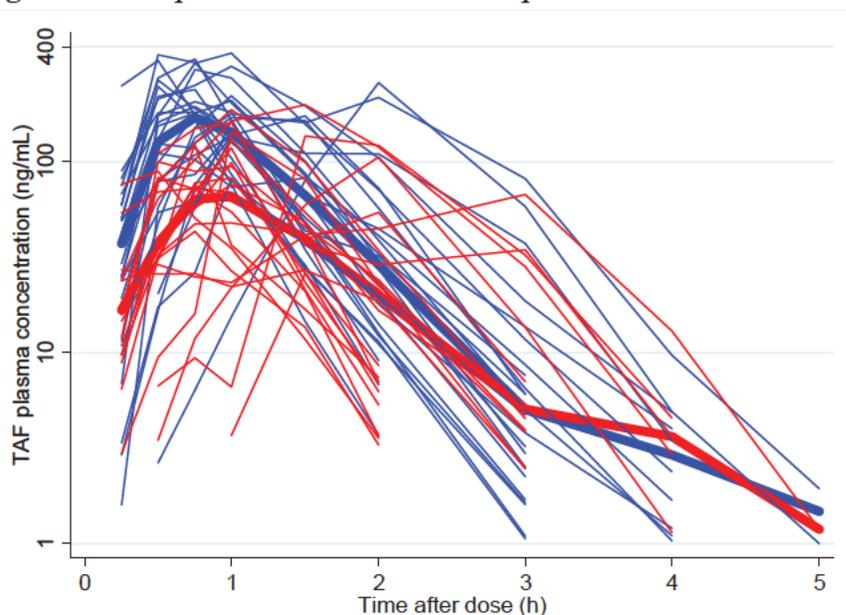
**Table 4.** Statistical analysis of TAF PK parameters.

PK Parameter	Treatment				GLSM Ratio Test/Reference (%)	90% CI (%)
	Test: CBZ 300 mg BID + F/TAF FDC (200/25 mg)		Reference: F/TAF FDC (200/25 mg)			
	n	GLSM	n	GLSM		
Analyte: TAF						
AUC <sub>last</sub> (h*ng/mL)	22	92.08	26	204.61	45.00	(39.66, 51.06)
AUC <sub>inf</sub> (h*ng/mL)	13	103.81	23	224.68	46.21	(39.68, 53.81)
C <sub>max</sub> (ng/mL)	22	87.80	26	204.59	42.92	(35.87, 51.35)

Treatment: Day 1 = F/TAF FDC, Days 6-8 = CBZ 100 mg BID, Days 9-11 = CBZ 200 mg BID, Days 12-25 = CBZ 300 mg BID, Day 26 = CBZ 300 mg BID + F/TAF FDC.

Source: CSR.

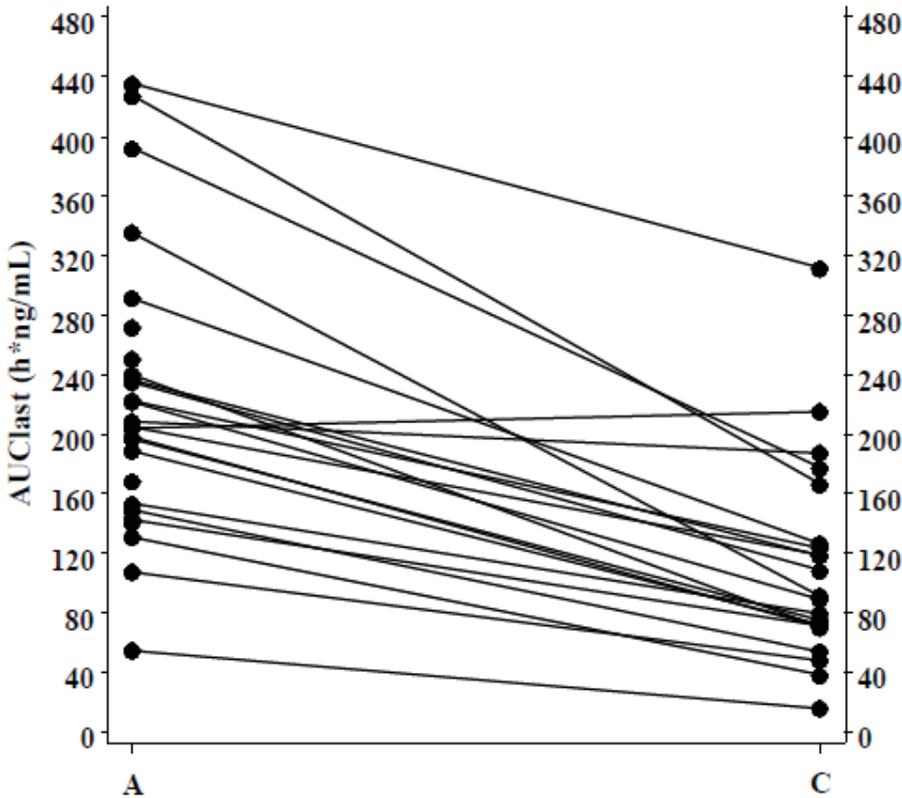
**Figure 9.** TAF plasma concentration-time profiles.



Source: Plotted by reviewer. Thin blue lines = TAF alone; thick blue line = median of TAF alone profiles; thin red lines = TAF + CBZ; thick red line = median of TAF + CBZ profiles.

# CLINICAL PHARMACOLOGY REVIEW

**Figure 10.** TAF PK parameters across treatments.



Source: CSR. A = F/TAF; C = F/TAF + CBZ.

**Table 5.** TAF PK in subjects who vomited after F/TAF dosing or CBZ+F/TAF dosing.

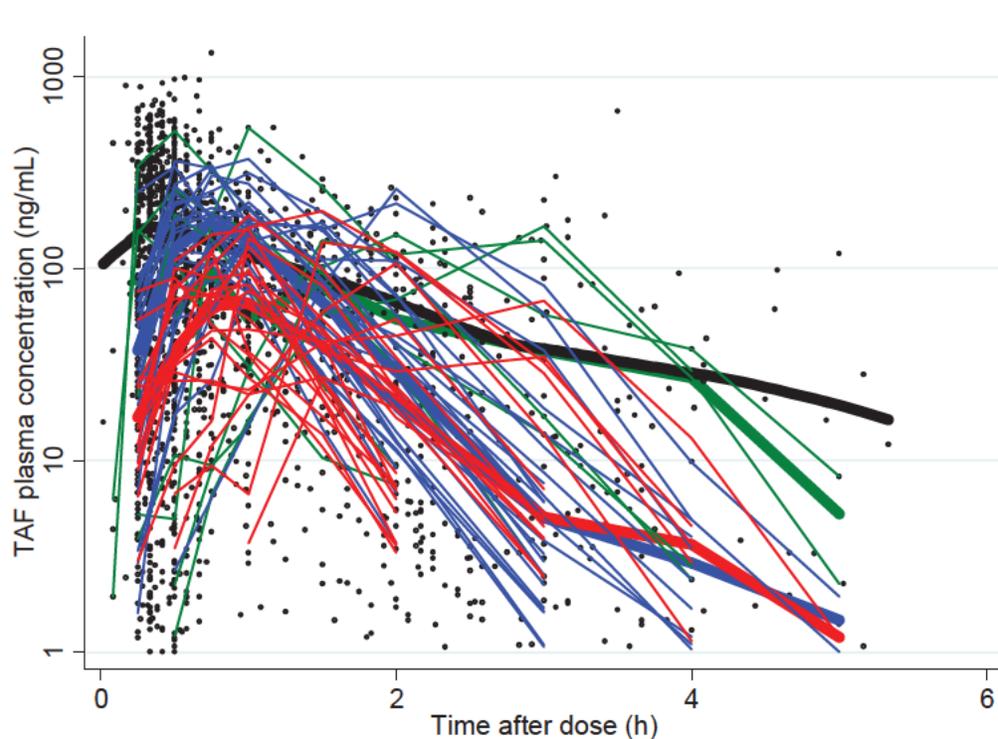
Subject	Day of vomiting	Study drug	TAF AUC (ng*h/mL)	TAF Cmax (ng/mL)
11033-1011	1	F/TAF	130.7	124
11033-1011	26	CBZ+F/TAF	38.3	43
11033-1018	1	F/TAF	240.0	339

Source: Prepared by reviewer.

Compared to intensive PK profiles and sparse samples collected in phase 3 studies, median exposures in both arms of the drug interaction study were generally lower, especially after two hours post-dose (Figure 11).

## CLINICAL PHARMACOLOGY REVIEW

**Figure 11.** TAF concentration-time profiles in the CBZ drug interaction study and in phase 3 studies.



Source: Plotted by reviewer. Black circles = sparse samples from phase 3 studies 0108 and 0110; black line = lowess of sparse samples; thin green lines = intensive PK profiles from studies 0108 and 0110; thick green line = median of intensive PK profiles from studies 0108 and 0110; thin blue lines = individual subject profiles in the F/TAF arm of the DDI study; thick blue line = median of the individual subject profiles in the F/TAF arm of the DDI study; thin red lines = individual subject profiles in the F/TAF + CBZ arm of the DDI study; thick red line = median of individual subject profiles in the F/TAF + CBZ arm of the drug interaction study.

TFV AUC and C<sub>max</sub> were decreased 25% and 30%, respectively, when coadministered with CBZ (CSR p52).

CBZ and CBZE trough concentrations were shown to have reached steady-state by day 12 and to be within the therapeutic range of CBZ (CSR p53).

### Safety

There were no deaths. Four subjects had AEs leading to discontinuation, all following CBZ. Two subjects had SAEs (life-threatening thrombocytopenia and Stevens-Johnson syndrome) that were attributed to CBZ. Vomiting was the most common AE in the F/TAF group (two subjects). The most common laboratory abnormalities were elevated LDL, elevated total cholesterol, and low sodium. Grade 3-4 laboratory abnormalities included grade 4 low platelets (after CBZ dosing) and grade 3 elevated creatinine kinase following CBZ+F/TAF dosing.

# CLINICAL PHARMACOLOGY REVIEW

## DISCUSSION/REVIEWER'S COMMENTS

When compared to median phase 3 intensive and sparse drug concentrations, TAF drug concentrations in both the F/TAF and CBZ+F/TAF groups were generally lower, especially after two hours post-dose. It should be noted that the studies differ in that the drug interaction trial was conducted in healthy volunteers versus HBV-infected subjects in the phase 3 trials. Also, F/TAF was given in the drug interaction study and TAF in the phase 3 studies. Nevertheless, even if population or formulation affects TAF PK, the magnitude of interaction determined in the drug interaction study would apply to TAF administered to HBV-infected subjects.

Two subjects vomited in this study. Although exposures in both were well below the mean, when we excluded these subjects from the analysis, mean and median AUC ratios were similar. Therefore the applicant's analysis, which included the subjects that vomited, is acceptable.

TFV AUC was decreased by 25% when given with CBZ. Doubling the TAF dose to two tablets once daily (see labeling recommendation below) would result in 50% higher TFV exposures compared to those taking TAF once daily and not on CBZ. This increase is not clinically relevant because TFV exposures from TAF are 90% lower compared to TFV exposures from TDF.

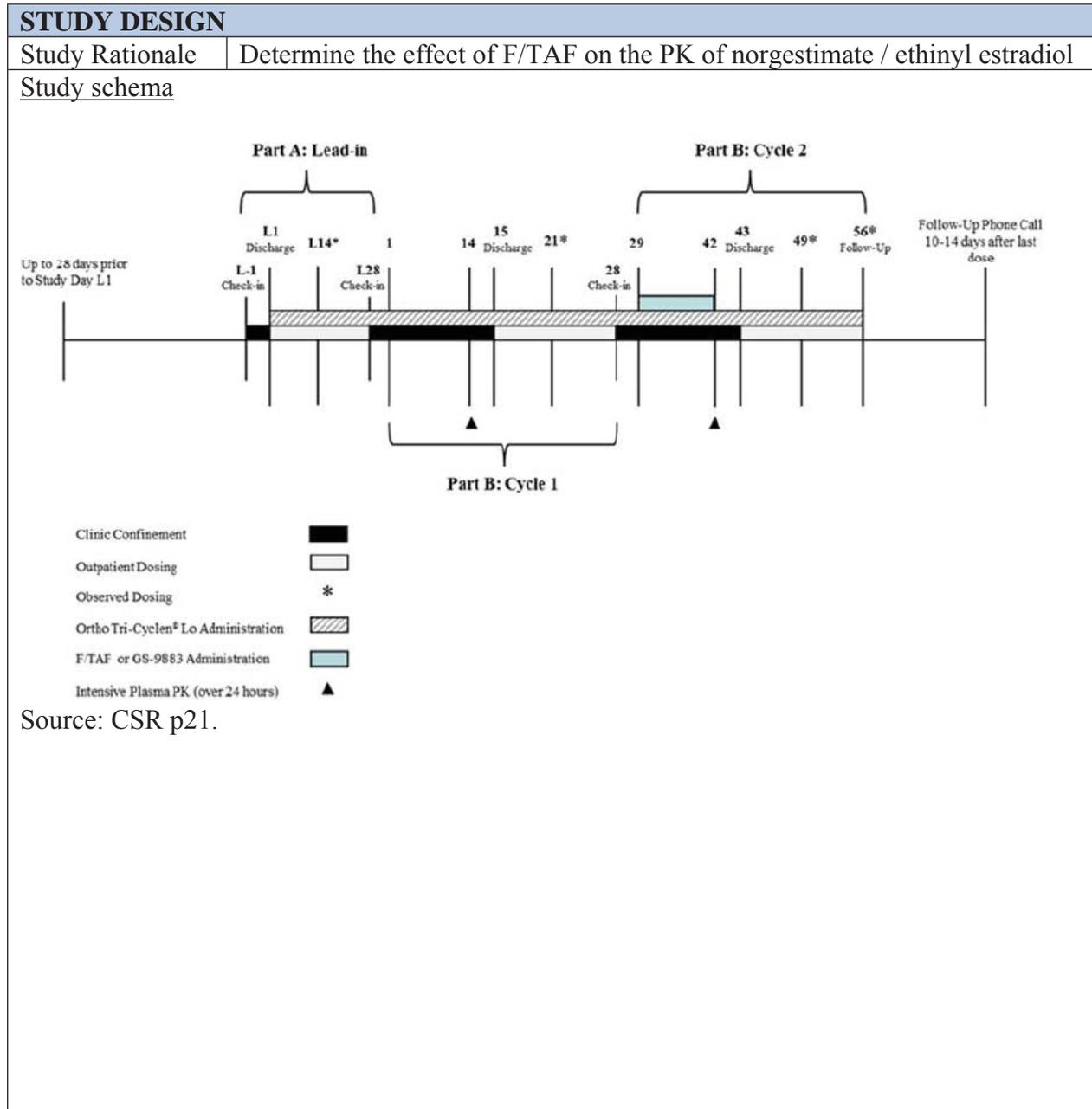
## LABEL RECOMMENDATIONS

(b) (4)  
Based on the ~55% reduction in TAF exposure when coadministered with CBZ, we proposed that the TAF dose should be doubled to two tablets once daily when when coadministered with CBZ. This was accepted by the applicant.

# CLINICAL PHARMACOLOGY REVIEW

## 3.3 311-1790 – Effect of F/TAF on the PK of norgestimate / ethinyl estradiol

A Phase 1, Randomized, Open Label, Drug Interaction Study Evaluating the Effect of Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Tablet or GS-9883 on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol	
Study #	311-1790
Study period	4/14/2015 – 9/29/2015
Link to study report	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-1790\report-body.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-1790\report-body.pdf</a>



# CLINICAL PHARMACOLOGY REVIEW

## Treatment schema

### Cohort 1

	Part A	Part B		
	Lead-in	Cycle 1	Cycle 2	
<b>Study Day</b>	<b>L1-L28</b>	<b>1-28</b>	<b>29-42</b>	<b>43-56</b>
<b>Cycle Day</b>	<b>1-28</b>	<b>1-28</b>	<b>1-14</b>	<b>15-28</b>
<b>OC <sup>a</sup></b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
<b>F/TAF 200/25 mg<sup>a</sup></b>			<b>X</b>	

<sup>a</sup> Administered once daily in the morning with food

Source: CSR p22.

\*Note that cohort 2, which evaluated the effect of GS-9883 on the PK of the oral contraceptive (OC), was not included in this review.

Population	Healthy, nonpregnant, nonlactating), premenopausal women -age 18-45 years -BMI 19-30 kg/m <sup>2</sup> -CrCL $\geq$ 90 mL/min
Objectives	Primary: the effect of F/TAF on the PK of the OC Secondary: safety, tolerability of F/TAF coadministered with the OC
Dose Selection Rationale	F/TAF contains 25 mg TAF, which is the TAF dose studied in phase 3 trials of HBV-infected subjects
Administration with regard to food	During confinement, F/TAF and OC were administered with a moderate fat breakfast. When not confined, OC (F/TAF was only taken during confinement) was to be taken with food.

### Formulation

F/TAF: 200/25 mg tablet

Norgestimate (NGM)/Ethinyl Estradiol (EE):

-supplied as Ortho Tri-Cyclen Lo

-NGM: 0, 0.180, 0.215, or 0.250 mg

-EE: 0 or 0.025 mg

Dosing scheme by menstrual cycle day:

Ortho Tri-Cyclen Lo Hormones	Menstrual Cycle Day			
	1-7	8-14	15-21	22-28
Ethinyl Estradiol (mg/daily dose)	0.025	0.025	0.025	inert, "reminder pills"
Norgestimate (mg/daily dose)	0.180	0.215	0.250	

Source: CSR p26.

## CLINICAL PHARMACOLOGY REVIEW

Interfering Substances Excluded	Subjects taking any medications within 28 days of the study were excluded (acetaminophen, ibuprofen, vitamins, and hormonal contraceptives excepted)
<p><u>PK sampling Times</u></p> <p><b><i>Cohorts 1 and 2: Part B, Cycle 1</i></b></p> <p>Serial blood samples were collected relative to OC administration as follows:</p> <ul style="list-style-type: none"> <li><b>Study Day 14:</b> predose (<math>\leq 5</math> minutes prior to dosing), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose.</li> </ul> <p><b><i>Cohort 1: Part B, Cycle 2</i></b></p> <p>Serial blood samples were collected relative to OC and F/TAF coadministration as follows:</p> <ul style="list-style-type: none"> <li><b>Study Day 42:</b> predose (<math>\leq 5</math> minutes prior to dosing), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose.</li> </ul> <p><u>Pharmacodynamic sampling times</u></p> <p>Luteining hormone (LH) and follicle stimulating hormone (FSH): predose on days 14 and 42            Progesterone: predose on days 21 and 49</p>	
Bioanalysis	Matrix: plasma Analytes: TAF, TFV, FTC, norgestrel (NG), NGM, norelgestromin (NGMN), and EE Method: LC/MS/MS
PK analysis	Noncompartmental

# CLINICAL PHARMACOLOGY REVIEW

STUDY CONDUCT								
Bioanalysis								
Reported bioanalytical method and stability information:								
Parameter	TAF	IFV	FTC	GS-9883	NG	NGM	NGMN	EE
Calibrated Range (ng/mL)	1 to 1000	0.3 to 300	5 to 3000	1 to 1000	0.02 to 20	0.05 to 50	0.02 to 10	0.0025 to 0.5
Interassay Precision Range (%CV)	1.8 to 7.3	1.1 to 5.9	2.1 to 8.1	3.9 to 5.7	1.3 to 5.6	1.8 to 3.8	2.1 to 3.6	3.8 to 7.9
Interassay Accuracy Range (%RE)	-3.7 to 6.5	-3.3 to 6.2	-1.3 to 3.7	2.4 to 7.8	-2.3 to 4.3	-10.8 to 5.8	-3.3 to 1.8	-4.1 to 1.2
Stability in Frozen Matrix (days)	520 at -70°C	464 at -20°C and -70°C	190 at -20°C and 340 at -70°C	44 at -20°C and -70°C	618 at -20°C and -70°C	618 at -20°C and -70°C	153 at -20°C and -70°C	182 at -20°C and -70°C
EE = ethinyl estradiol; FTC = emtricitabine; NG = norgestrel; NGM = norgestimate; NGMN = norelgestromin; TAF = tenofovir alafenamide; IFV = tenofovir								
Source: CSR p39.								
Protocol deviations	No important protocol deviations were reported							
Concomitant medications	The most common concomitant medications were acetaminophen and ondansetron							

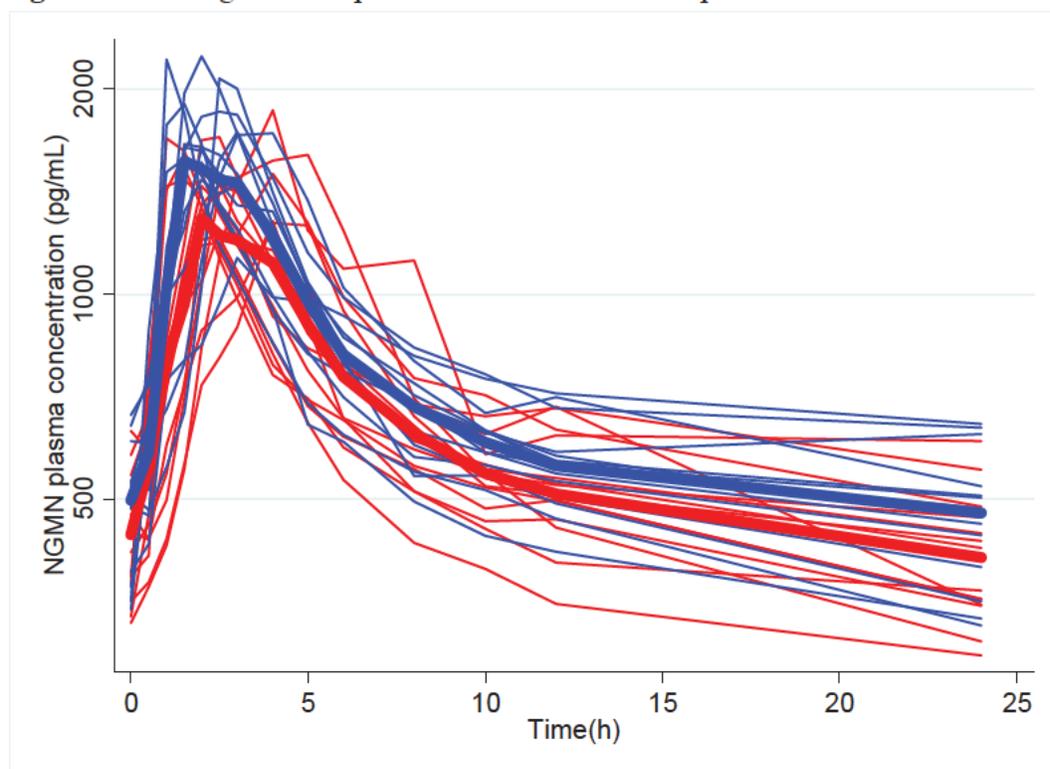
RESULTS															
Study population	<p>Sixteen subjects in cohort 1 received at least one dose of study drug. Three subjects discontinued early, due to withdrawn consent (n=1), positive test for opiates (n=1), and lost to follow up (n=1, last dose on day 43) (Table 6).</p> <p><b>Table 6.</b> Subject demographics.</p> <table border="1" style="margin-left: 20px;"> <thead> <tr> <th></th> <th>N(%) or Median (min, max)</th> </tr> </thead> <tbody> <tr> <td>Female</td> <td>16 (100%)</td> </tr> <tr> <td>Age</td> <td>41 (24, 45)</td> </tr> <tr> <td>White race</td> <td>14 (88%)</td> </tr> <tr> <td>Hispanic</td> <td>16 (100%)</td> </tr> <tr> <td>BMI (kg/m<sup>2</sup>)</td> <td>26 (23, 30)</td> </tr> <tr> <td>CrCL (mL/min)</td> <td>128 (99, 153)</td> </tr> </tbody> </table> <p>Source: prepared by reviewer.</p>		N(%) or Median (min, max)	Female	16 (100%)	Age	41 (24, 45)	White race	14 (88%)	Hispanic	16 (100%)	BMI (kg/m <sup>2</sup> )	26 (23, 30)	CrCL (mL/min)	128 (99, 153)
	N(%) or Median (min, max)														
Female	16 (100%)														
Age	41 (24, 45)														
White race	14 (88%)														
Hispanic	16 (100%)														
BMI (kg/m <sup>2</sup> )	26 (23, 30)														
CrCL (mL/min)	128 (99, 153)														
Data handling	No subjects were excluded from the analysis.														

# CLINICAL PHARMACOLOGY REVIEW

## Pharmacokinetics

The majority of NGM concentrations were below the limit of quantification and concentration-time profiles and PK parameters could not be obtained. Concentration-time profiles of NGNM, NG, EE, FTC, TAF, and TFV are shown in Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, and Figure 17). AUC ratios (OC + F/TAF over OC alone) and 90% confidence intervals for OC analytes were within 80-125% (Table 7).

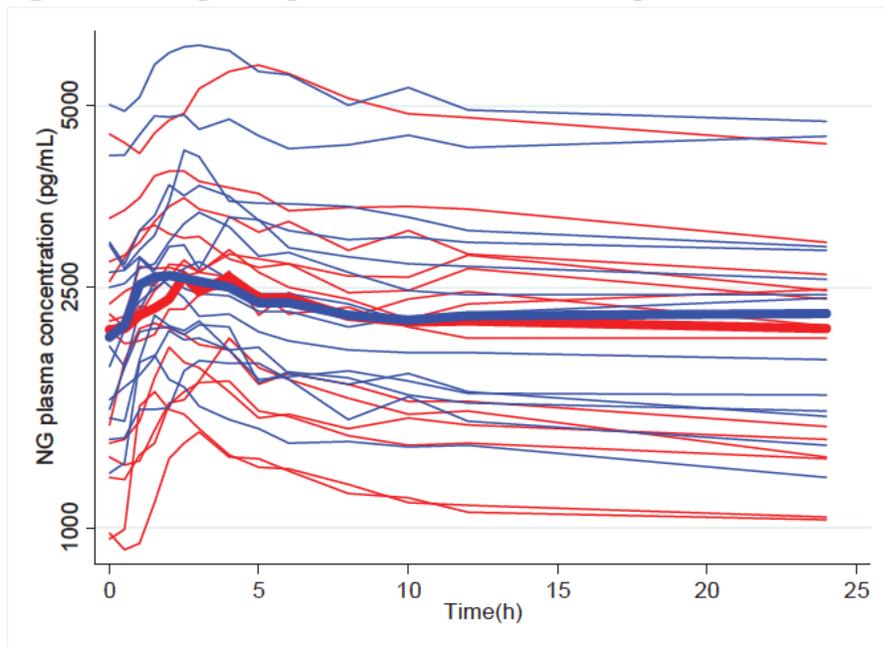
**Figure 12.** Norelgestromin plasma concentration-time profiles.



Source: Plotted by reviewer. Red = OC alone; blue = OC + F/TAF. Thin lines = individual subjects; thick lines = median of individual subject profiles.

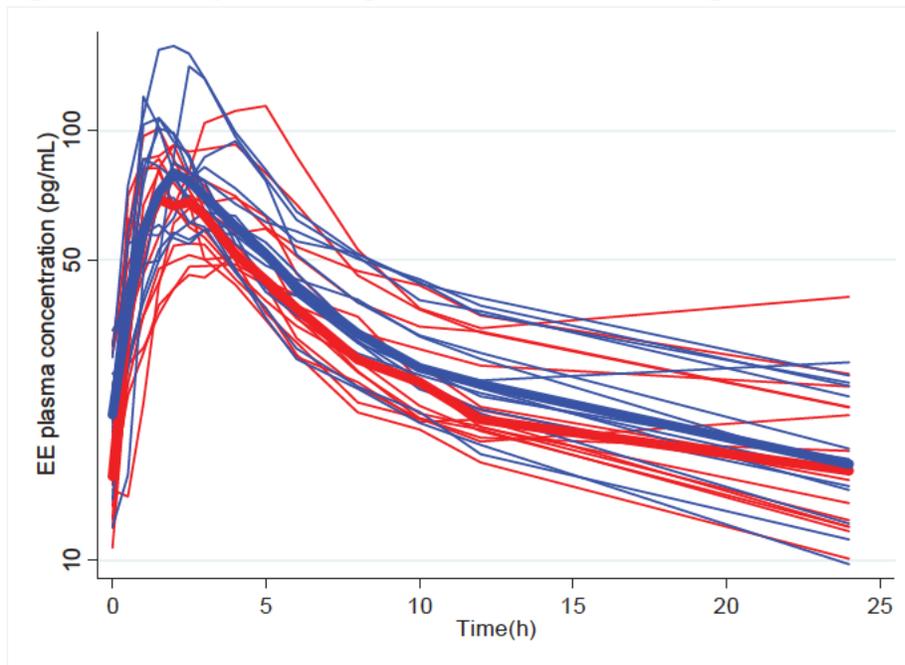
# CLINICAL PHARMACOLGY REVIEW

**Figure 13.** Norgestrel plasma concentration-time profiles.



Source: Plotted by reviewer. Red = OC alone; blue = OC + F/TAF. Thin lines = individual subjects; thick lines = median of individual subject profiles.

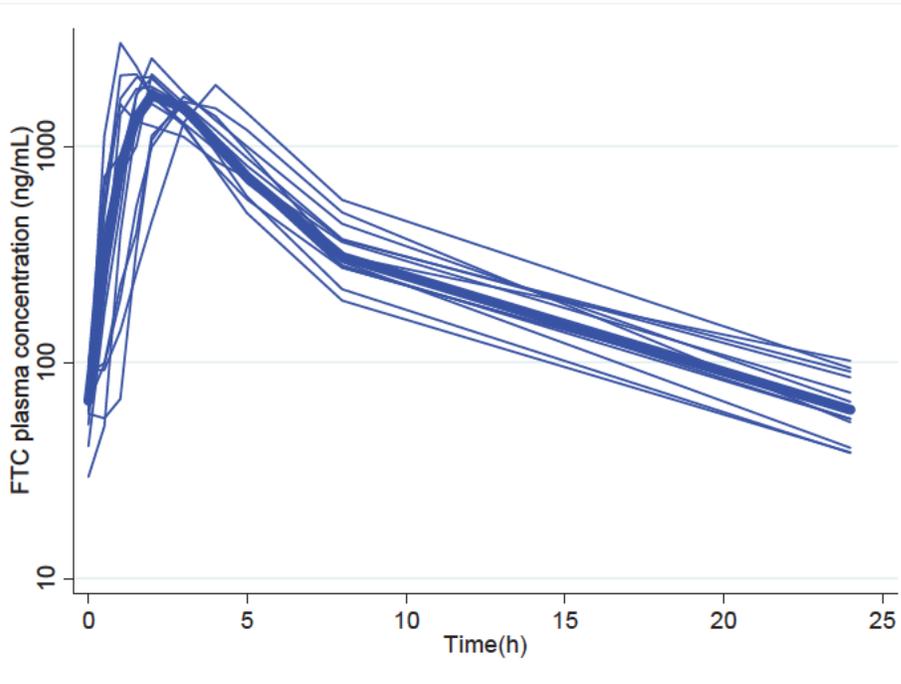
**Figure 14.** Ethinyl estradiol (EE) plasma concentration-time profiles.



Source: Plotted by reviewer. Red = OC alone; blue = OC + F/TAF. Thin lines = individual subjects; thick lines = median of individual subject profiles.

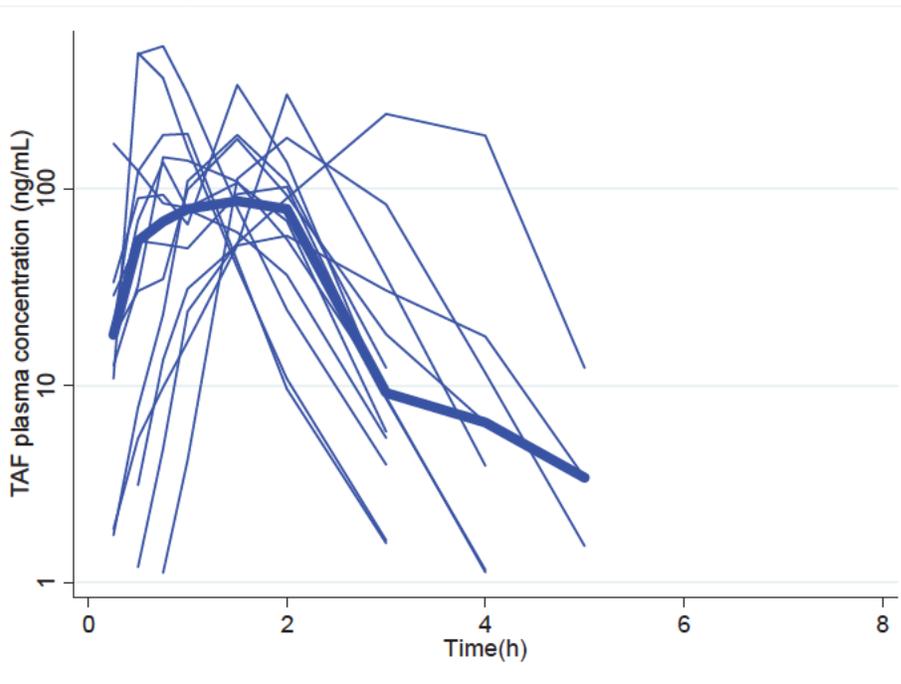
# CLINICAL PHARMACOKINETICS REVIEW

**Figure 15.** Emtricitabine plasma concentration-time profiles.



Source: Plotted by reviewer. Blue = OC + F/TAF. Thin lines = individual subjects; thick lines = median of individual subject profiles.

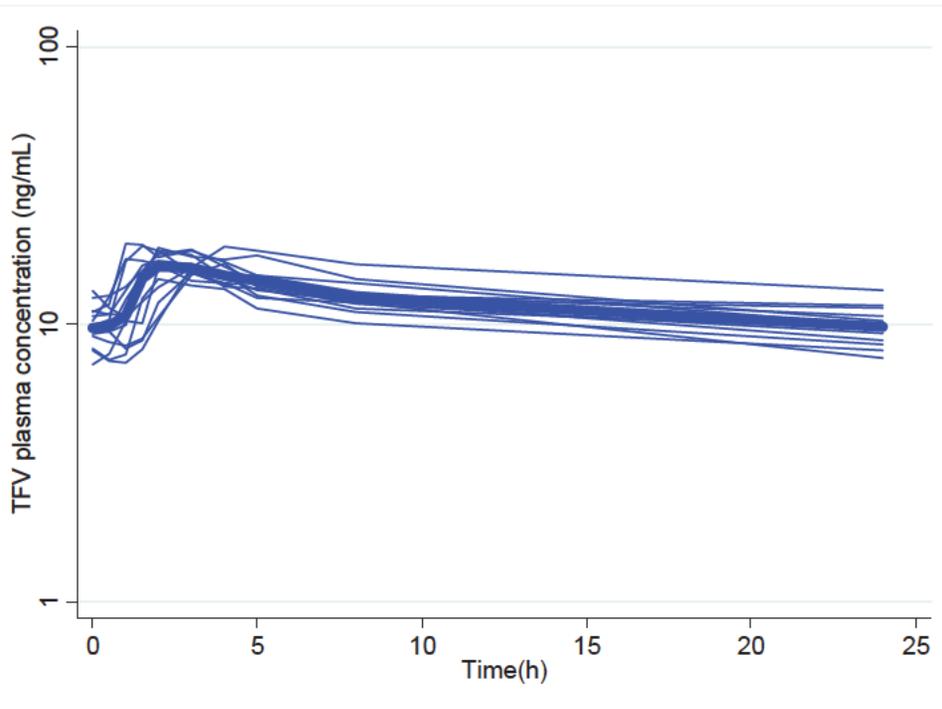
**Figure 16.** TAF plasma concentration-time profiles.



Source: Plotted by reviewer. Blue = OC + F/TAF. Thin lines = individual subjects; thick lines = median of individual subject profiles.

## CLINICAL PHARMACOLOGY REVIEW

**Figure 17.** TFV plasma concentration-time profiles.



Source: Plotted by reviewer. Blue = OC + F/TAF. Thin lines = individual subjects; thick lines = median of individual subject profiles.

**Table 7.** Statistical comparisons of OC PK parameters.

Analyte	Geometric mean AUC (OC + F/TAF)	Geometric mean AUC (OC alone)	GMR (90% CI)
NGMN	16875	15103	1.12 (1.07, 1.17)
NG	54829	50276	1.09 (1.01, 1.18)
EE	848	762	1.11 (1.07, 1.16)

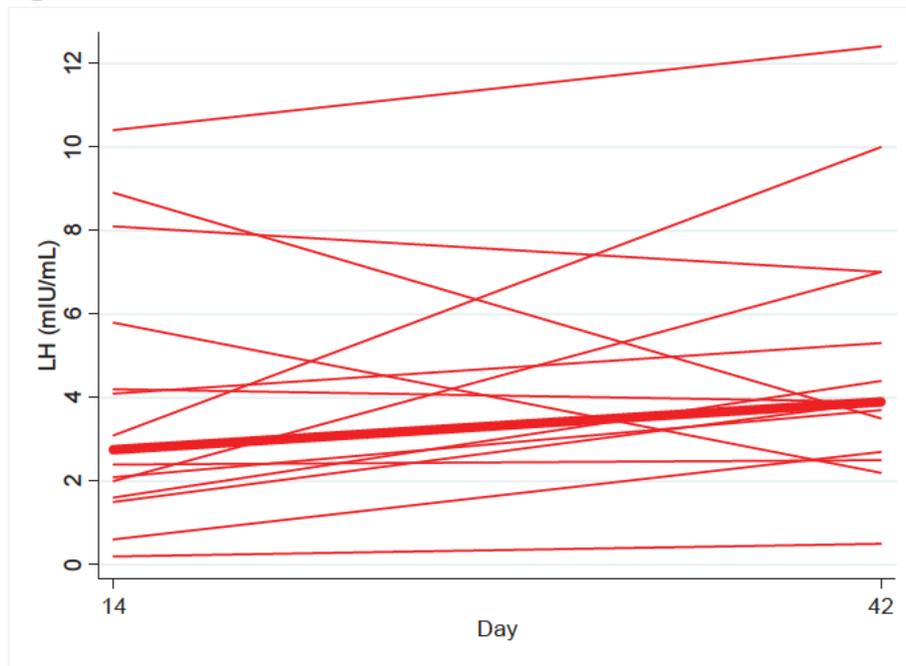
GMR = geometric mean ratio of OC + F/TAF to OC alone.

### *Pharmacodynamics*

Day 21 testosterone concentrations were detectable for four subjects. Subject 3648-1004 had high outlier LH and FSH concentrations on day 14; this subject withdrew consent and had no PK or PD assessments at day 42. Among subjects with day 14 and day 42 values, median LH concentrations were 2.75 mIU/mL on day 14 and 3.9 mIU/mL on day 42 (Figure 18). Among subjects with day 14 and day 42 values, median FSH concentrations were 1.7 mIU/mL on day 14 and 3.35 mIU/mL on day 42 (Figure 19).

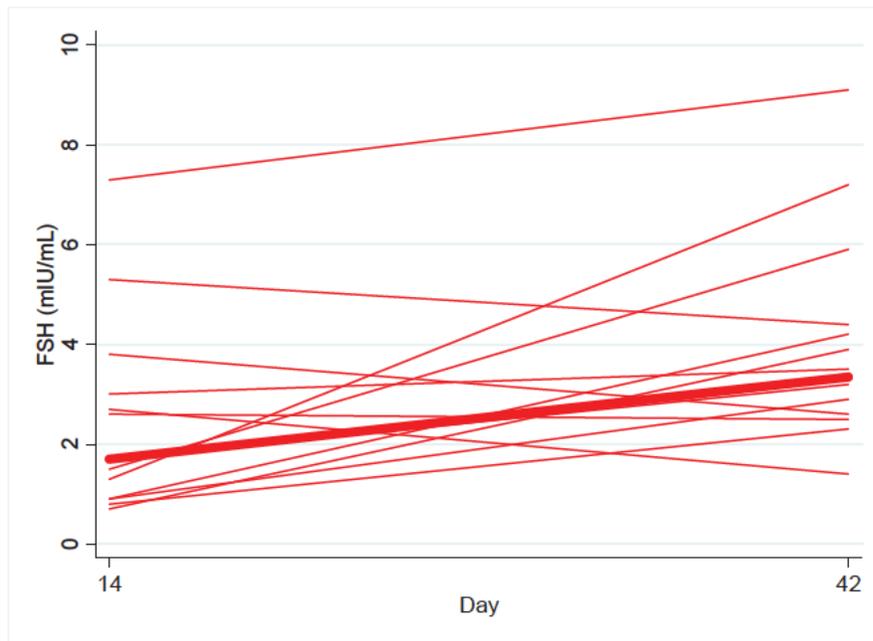
# CLINICAL PHARMACOLOGY REVIEW

**Figure 18.** LH concentrations.



Source: Plotted by reviewer. LH was measured on days 14 and 42. Thin lines = individual subjects; thick lines = median of individual subjects.

**Figure 19.** FSH concentrations.



Source: Plotted by reviewer. FSH was measured on days 14 and 42. Thin lines = individual subjects; thick lines = median of individual subjects.

## CLINICAL PHARMACOLOGY REVIEW

Safety	<p>There were no SAEs, AEs leading to discontinuation, grade 3-4 AEs, or deaths in the study. The most common AEs in cohort 1 were metrorrhagia, constipation, and headache in the OC only phase, and constipation in the F/TAF + OC phase. One subject in cohort 1 (3648-1004) had a grade 2 AE (right bundle branch block and urinary tract infection), which resolved while on treatment.</p> <p>The most common laboratory abnormalities were occult blood, hemoglobin, phosphate, sodium, and urine protein; most were grade 1. Two subjects in cohort 1 had grade 3 occult blood on urinalysis. Grade 2 laboratory abnormalities occurred in four subjects in cohort 1, all on OC only.</p>
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### REVIEWER'S COMMENTS AND CONCLUSION

Discussion / reviewer's comments	<p>Study conduct was acceptable. There were no issues with bioanalytical methods or protocol deviations. No interacting concomitant medications were reported.</p> <p>There were no clinically relevant changes in the PK of OC analytes when coadministered with F/TAF. This is the expected result because FTC and TAF are not known to cause drug interactions. It is acceptable that the PK of TAF was not assessed when coadministered with OC because OCs are not known to perpetrate drug interactions. FTC, TAF, and TFV exposures were adequate to detect an effect on the PK of the OC, as exposures (AUC) were similar to those in the F/TAF label. There were no PK outliers for any of the analytes.</p>
Labeling recommendations	<p>We agree with inclusion of EE and norgestimate in the Drug Interactions section of the label as drugs that have no significant interaction with TAF.</p>

## CLINICAL PHARMACOLOGY REVIEW

### 3.4 320-0101 – Anti-HBV activity and PK in HBV-infected subjects

<b>A Phase 1b Randomized, Open Label, Active-Controlled Study to Assess the Safety, Viral Kinetics, and Anti-HBV Activity of GS-7340 in Treatment-Naive Adults with Chronic Hepatitis B (CHB) Infection</b>	
<b>Study #</b>	320-0101
<b>Study period</b>	12/20/2011 - 4/30/2013
<b>Link to study report</b>	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\gs-us-320-0101\report-body.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\gs-us-320-0101\report-body.pdf</a>

<b>STUDY DESIGN</b>	
Study Rationale	Evaluate the antiviral activity of varying doses of TAF in relation to TDF
Population	HBV-infected adults -screening plasma HBV DNA $\geq 2 \times 10^3$ IU/mL -no diseases (other than HBV-infection) that are clinically significant or require treatment -age 18-65 -without cirrhosis -no prior anti-HBV nucleos(t)ide therapy -CrCL $\geq 70$ mL/min
Treatments	Subjects were randomized 1:1:1:1 to receive treatment with TAF 8, 25, 40, or 120 mg or TDF 300 mg orally once daily for 28 days.
Objectives	Primary: time weighted average change from baseline through Week 4 (DAVG <sub>4</sub> ) in serum HBV DNA (log <sub>10</sub> IU/mL) Secondary: Short-term antiviral activity, PK, safety Exploratory: changes in quantitative hepatitis B surface antigen (HBsAg), changes in alanine aminotransferase (ALT), kinetics of viral rebound in subjects during follow-up who chose not to continue on an oral anti-HBV therapy, effects of TAF and TDF on bone and renal biomarkers
Dose Selection Rationale	TAF: the 8 and 25 mg doses were expected to provide PBMC TFV concentrations 2-fold higher than TDF. TDF: 300 mg is the approved dose
Administration with regard to food	Fasted
Formulation	TAF: 8, 25, and 40 mg tablets TDF: 300 mg tablet
Interfering Substances Excluded	Drugs with antiretroviral activity other than study drug, nephrotoxic agents, probenecid, herbals, agents that reduce renal function or compete for active tubular secretion, chemotherapy, immunosuppressants, immunomodulators, bisphosphonates
Sampling Times	Day 1: predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours postdose Days 2, 5, 8, 10, 15, 19, 22, and 29: predose
Bioanalysis	Matrix: plasma Analytes: TAF and TFV Method: LC/MS/MS

# CLINICAL PHARMACOLOGY REVIEW

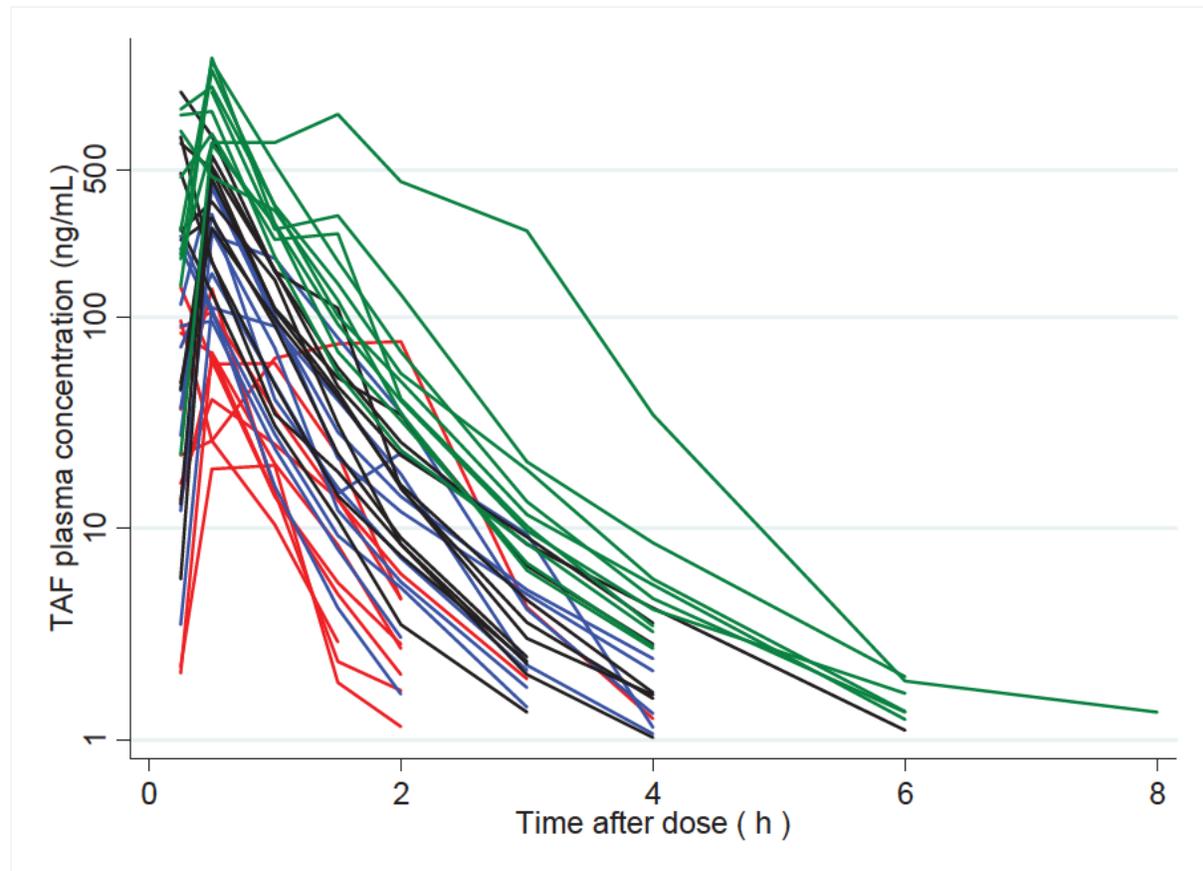
PK analysis	Noncompartmental
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STUDY CONDUCT	
Bioanalysis	Calibration ranges -TAF: 1-1000 ng/mL -TFV: 5-3000 ng/mL
Protocol deviations	60 important protocol deviations were reported in 27 subjects. The most common types of deviations were missing safety or virology lab samples (n=15), dosing-related (n=10), and visit out of window (n=7). Six deviations were missed PK samples.
Concomitant medications	Two subjects took antidiabetic medications during the study.

RESULTS																																					
Study population	<p>Fifty-one subjects were treated and 50 completed the study; one subject in the TAF 120 mg arm was lost to follow up (last recorded day of treatment was day 22). Selected demographics are summarized in Table 8.</p> <p><b>Table 8.</b> Selected demographic characteristics.</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>TAF 8 mg</th> <th>TAF 25 mg</th> <th>TAF 40 mg</th> <th>TAF 120 mg</th> <th>TDF 300 mg</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>10</td> <td>10</td> <td>11</td> <td>10</td> <td>10</td> </tr> <tr> <td>Age</td> <td>34</td> <td>34</td> <td>40</td> <td>42</td> <td>34</td> </tr> <tr> <td>Male</td> <td>40%</td> <td>80%</td> <td>73%</td> <td>80%</td> <td>60%</td> </tr> <tr> <td>Asian race</td> <td>40%</td> <td>70%</td> <td>73%</td> <td>50%</td> <td>50%</td> </tr> <tr> <td>BMI (mg/kg<sup>2</sup>)</td> <td>27</td> <td>26</td> <td>24</td> <td>25</td> <td>26</td> </tr> </tbody> </table> <p>Source: CSR p65. Age and BMI values are medians.</p>		TAF 8 mg	TAF 25 mg	TAF 40 mg	TAF 120 mg	TDF 300 mg	N	10	10	11	10	10	Age	34	34	40	42	34	Male	40%	80%	73%	80%	60%	Asian race	40%	70%	73%	50%	50%	BMI (mg/kg <sup>2</sup> )	27	26	24	25	26
	TAF 8 mg	TAF 25 mg	TAF 40 mg	TAF 120 mg	TDF 300 mg																																
N	10	10	11	10	10																																
Age	34	34	40	42	34																																
Male	40%	80%	73%	80%	60%																																
Asian race	40%	70%	73%	50%	50%																																
BMI (mg/kg <sup>2</sup> )	27	26	24	25	26																																
Data handling	No subjects were excluded from the PK analysis																																				
<p><u>Pharmacokinetics</u></p> <p>TAF AUC and C<sub>max</sub> were reported to be proportional across the dose range (CSR p90). Mean day 29 TFV trough concentrations from administration of TAF 25 mg and TDF 300 mg were 9.2 ng/mL and 55.7 ng/mL, respectively. TAF concentration-time profiles are shown in Figure 20.</p>																																					

## CLINICAL PHARMACOLOGY REVIEW

**Figure 20.** TAF plasma concentration time profiles by dose group.



Source: Plotted by reviewer. Red = TAF 8 mg; blue = TAF 25 mg; black = TAF 40 mg; green = TAF 120 mg.

### Antiviral activity

Similar week 4 antiviral activity was observed for TAF and TDF study arms with the exception of TAF 40 mg, where lower activity was attributed to lower baseline HBV DNA concentrations (Table 9).

## CLINICAL PHARMACOLOGY REVIEW

**Table 9.** Baseline and week 4 change from baseline HBV DNA concentrations (log<sub>10</sub> IU/mL).

	TAF (8 mg) (n = 10)	TAF (25 mg) (n = 10)	TAF (40 mg) (n = 11)	TAF (120 mg) (n = 10)	TDF (300 mg) (n = 10)
<b>Baseline HBV levels</b>					
n	10	10	11	10	10
Mean (SD)	6.48 (1.975)	6.17 (1.893)	5.47 (2.026)	6.50 (2.488)	5.52 (1.781)
Median	6.26	6.35	5.37	5.98	4.78
Q1, Q3	5.01, 8.50	4.10, 7.68	3.42, 7.78	4.34, 8.83	4.11, 6.86
Min, Max	3.73, 8.98	3.56, 8.93	3.27, 8.57	3.71, 9.74	3.97, 8.85
<b>DAVG<sub>4</sub></b>					
n	10	10	11	10	10
Mean (SD)	-2.14 (0.424)	-2.05 (0.418)	-1.75 (0.425)	-2.20 (0.349)	-2.14 (0.356)
Median	-2.18	-2.05	-1.69	-2.15	-2.31
Q1, Q3	-2.37, -1.87	-2.29, -1.99	-2.23, -1.43	-2.33, -2.06	-2.40, -1.71
Min, Max	-2.77, -1.32	-2.70, -1.11	-2.42, -1.12	-2.83, -1.66	-2.55, -1.59
SD = standard deviation; Q1 = first quartile; Q3 = third quartile					
Note: Baseline is defined as the last available measurement prior to the first dose of the study drug					
Source: CSR p72. DAVG <sub>4</sub> = time-weighted average change from baseline through week 4.					
Safety	<p>There were no SAEs, AEs leading to discontinuation, or deaths in the study. The most common AEs were GI disorders (nausea and constipation), fatigue, headache, dizziness, and cough. No grade 3-4 AEs were reported.</p> <p>Most laboratory abnormalities were grades 1-2. Grade 3 laboratory abnormalities (n=1 for each) included ALT increase in the TAF 120 mg arm, creatine kinase increase in the TAF 40 mg arm, serum amylase increase in the TAF 120 mg arm, glycosuria in the TAF 40 mg arm, and hematuria in the TAF 40 mg arm. There were no grade 4 laboratory abnormalities.</p>				

## CLINICAL PHARMACOLOGY REVIEW

REVIEWER'S COMMENTS AND CONCLUSION	
Discussion / reviewer's comments	<p>Regarding study conduct, bioanalytical methods were acceptable. There were numerous protocol deviations, though no outliers were observed on day 1 intensive PK and all subjects had at least a 1 log drop in HBV DNA, indicating likely adequate compliance.</p> <p>Two subjects took concomitant antidiabetic medication. Diabetes was listed as an exclusion criteria. It is unclear why this was not noted as a protocol deviation. Both subjects were listed as having been on antidiabetic medication from the start of the study.</p> <p>Demographics were comparable between study arms with the exception of one morbidly obese woman (one of the subjects with diabetes) with a BMI of 46. It is unusual to see enrollment of a morbidly obese subject in a study in healthy volunteers. However, this study had no exclusion criteria related to BMI.</p> <p>An omission from the protocol was that Pgp inducers and inhibitors were not on the list of prohibited medication as they could have significantly affected TAF PK/PD. However, no strong Pgp inducers/inhibitors were observed on the list of concomitant medications.</p> <p>In conclusion, similar antiviral activity was observed among TAF doses of 8-120 mg, and between all TAF doses and TDF 300 mg. One exception was less activity observed in the TAF 40 mg group, which was attributed to lower baseline HBV DNA levels in this group. TAF 25 mg was selected for study in phases 2-3.</p>
Labeling recommendations	<p>This study is not referenced in the label.</p>

# CLINICAL PHARMACOLOGY REVIEW

## 3.5 320-1228 – PK of TAF in healthy Japanese and non-Japanese subjects

<b>A Phase 1 Single Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Tenofovir Alafenamide in Healthy Japanese and Non-Japanese Subjects</b>	
<b>Study #</b>	320-1228
<b>Study period</b>	10/14/2013 – 11/12/2013
<b>Link to study report</b>	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-320-1228\report-body.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-320-1228\report-body.pdf</a>

<b>STUDY DESIGN</b>	
Study Rationale	The effect of Japanese race (relative to non-Japanese) on the PK of TAF
Study schema	
<p style="text-align: center;"> <span style="margin-right: 100px;">-28 Days</span> <span style="margin-right: 100px;">Day -1</span> <span style="margin-right: 100px;">Day 1</span> <span style="margin-right: 100px;">Day 5</span> </p> <p style="text-align: center;"> <span style="margin-right: 100px;">Screening</span> <span style="margin-right: 100px;">Single Dose</span> <span style="margin-right: 100px;">Discharge</span> <span style="margin-right: 100px;">Follow-up*</span> </p> <p style="text-align: center;"> <span style="border: 1px solid black; display: inline-block; width: 20px; height: 10px; background-color: #cccccc; margin-right: 5px;"></span> Clinic Confinement              * 7-10 days post dose           </p>	
Source: CSR p19.	
Study description	Open label, single dose, parallel group, PK study -the study was conducted at one site by a CRO (b) (4)
Population	20 healthy Japanese and non-Japanese subjects -age 18-45 -BMI of 18-30 kg/m <sup>2</sup> -Japanese subjects had to have been born in Japan, not lived outside Japan >10 years, and have a similar lifestyle (including diet) since leaving Japan -Non-Japanese subjects were not of Japanese or Asian descent
Treatments	Single dose of TAF 25 mg on day 1

## CLINICAL PHARMACOLOGY REVIEW

Objectives	Primary: PK Secondary: Safety
Dose Selection Rationale	TAF 25 mg was studied in phase 3 trials
Administration with regard to food	Study drug was administered within 5 minutes of completion of a standardized Japanese breakfast
Formulation	TAF 25 mg tablet
Interfering Substances Excluded	Any medications except vitamins, acetaminophen, ibuprofen, or hormonal contraceptives
PK sampling Times	<u>Plasma</u> Day 1: predose ( $\leq 5$ minutes) and at the following postdose time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, and 72 hours  <u>Urine</u> Day 1: postdose 0-6, 6-12, 12-24, 24-48, and 48-72, and 72-96 hours
Bioanalysis	Matrices: Plasma and urine Analytes: TAF and TFV Method: LC/MS/MS
PK analysis	Noncompartmental

### STUDY CONDUCT

Bioanalysis	Linear ranges reported for plasma methods: -TAF: 1-1000 ng/mL -TFV 0.3-300 ng/mL  Methods for analysis of urine samples were not submitted.
Protocol deviations	None reported
Concomitant medications	There was no reported use of prescription medicines. Six subjects used prune juice for constipation.

### RESULTS

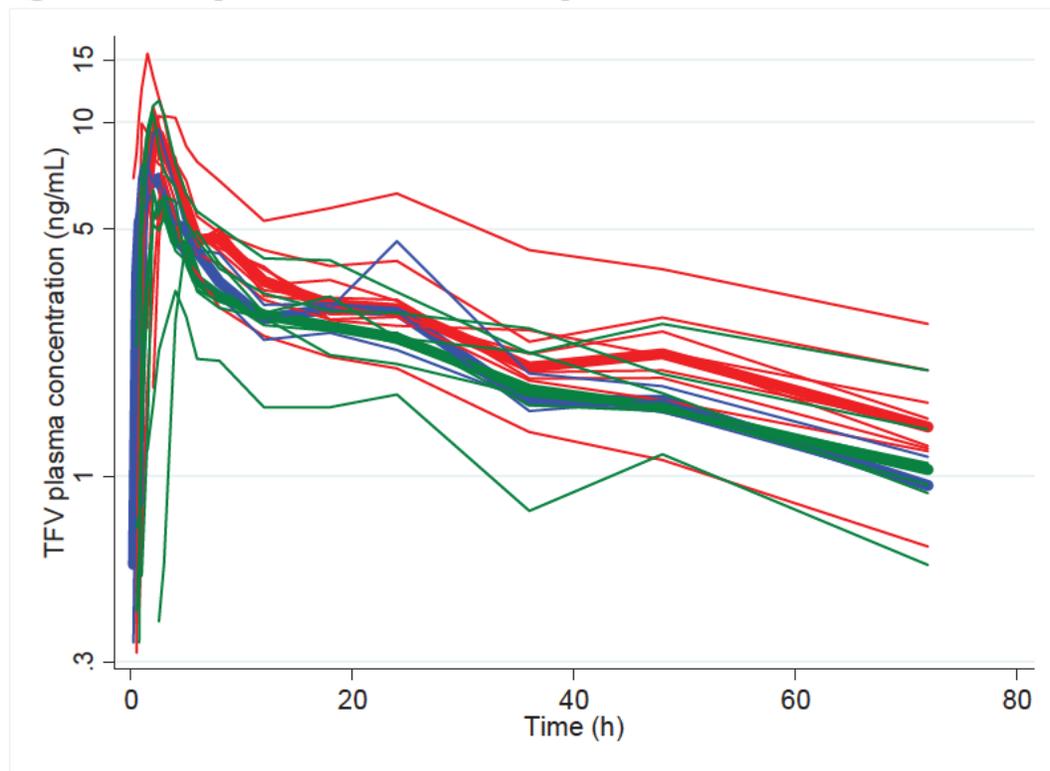
Study population	20 subjects were enrolled and all completed the study (Table 10).
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## CLINICAL PHARMACOLOGY REVIEW

	<b>Table 10.</b> Subject demographics.	
	Japanese (n=10)	Non-Japanese (n=10)
Female	7 (70%)	6 (60%)
Age	42 (27, 45)	30 (23, 38)
Race	Asian: 10 (100%)	White: 7 (70%) Black: 3 (30%)
Hispanic	0 (0%)	4 (40%)
BMI (kg/m <sup>2</sup> )	21.5 (18, 28)	25 (20, 28)
CrCL (mL/min)	99 (94, 117)	127 (110, 164)
	Source: Prepared by reviewer from CSR p45. Values are n (%) or median (min, max).	
Data handling	No subjects were excluded from the PK analysis.	
<b>Pharmacokinetics</b>		
<p>Urine samples were not analyzed. TAF and TFV AUC was ~30% higher in Japanese versus non-Japanese subjects (Figure 21, Figure 22, Table 11); TAF and TFV C<sub>max</sub> values were 32% and 45% higher, respectively.</p>		
<p><b>Figure 21.</b> TAF plasma concentration-time profiles.</p>		
<p>Source: Prepared by reviewer from PC dataset. Red = Asian; blue = black race; green = white race. Thin lines = individual subjects; thick lines = median of individual subjects. Note the thick green line is drawn only up to 4 hours. Five samples were detectable beyond 4 hours post-dose; these were not included in the figure.</p>		

# CLINICAL PHARMACOLOGY REVIEW

**Figure 22.** TFV plasma concentration-time profiles.



Source: Prepared by reviewer from PC dataset. Red = Asian; blue = black race; green = white race. Thin lines = individual subjects; thick lines = median of individual subjects.

**Table 11.** Statistical comparison of TAF and TFV PK parameters.

Analyte	Geometric mean AUC (Japanese)	Geometric mean AUC (Non-Japanese)	GMR (90% CI)
TAF	190	151	1.26 (0.82, 1.92)
TFV	200	156	1.28 (1.04, 1.58)

Source: Prepared by reviewer from CSR p52-54. GMR = geometric mean ratio of Japanese to non-Japanese. AUC = AUC<sub>last</sub> (ng\*h/mL).

Safety	<p>No deaths, SAEs, or AEs leading to discontinuation occurred during the study. The most common AEs were constipation (n=2 subjects) and headache (n=2 subjects). All AEs were grade 1 except one instance of grade 2 vomiting. Of note, one AE was QT prolongation on day 2.</p> <p>Six subjects had laboratory abnormalities. All were grade 1. The most common were blood in urine (n=3) and amylase (n=2).</p>
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## CLINICAL PHARMACOLOGY REVIEW

REVIEWER'S COMMENTS AND CONCLUSION	
Discussion / reviewer's comments	<p>Study design was acceptable. One missing piece of information was the calorie and fat content of the standard Japanese breakfast that was administered prior to dosing.</p> <p>Regarding study conduct, there were no issues with bioanalysis or protocol deviations. However, there was an issue with concomitant medications. Six subjects reported use of prune juice for constipation. Prune juice was started on day 2-4 after dosing, with a typical duration of one day. This was coded as an herbal/traditional medicine; these medicines were not allowed according to the protocol. A search of Pubmed resulted in no studies of prune juice in relation to drug interactions.</p> <p>Demographic characteristics were not matched between groups. Age was higher in the Japanese group. CrCL and BMI were higher in non-Japanese. Had CrCL and BMI been matched between groups, there would have been a better assessment of the influence of race on PK. Nevertheless, the 30% higher TAF exposures in the Japanese are not clinically relevant as no exposure-related AEs have been associated with TAF. Also, though TFV exposures were 30-40% higher in the Japanese, this is not clinically relevant because these exposures are well below those associated with the approved drug TDF.</p> <p>There was one outlier TAF concentration-time profile from subject 8686-2007 (non-Japanese group). Removal of this subject from the analysis lowered the TAF geometric mean AUC in the non-Japanese group from 151 ng*h/mL to 149 ng*h/mL. Thus including this subject in the analysis had no effect on the results.</p>
Labeling recommendations	We agree with the labeling statement in section 12.3 that "No clinically relevant pharmacokinetic differences due to race have been identified".

# CLINICAL PHARMACOLOGY REVIEW

## 3.6 320-1382 – Effect of food on the PK of TAF

A Phase 1, Randomized, Open-Label Study to Determine the Effect of Food on the Pharmacokinetics of Tenofovir Alafenamide (TAF) in Healthy Volunteers	
Study Period	3/23/2015 – 4/24/2015
Link	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-320-1382\report-body.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-320-1382\report-body.pdf</a>

STUDY DESIGN	
Phase 1, randomized, open-label, single-center, single-dose, 2-treatment, 2-period, crossover study	
<p>The diagram illustrates a crossover study design. It begins with a 'Screening' phase. This is followed by 'Period 1', where subjects receive either 'Treatment A' or 'Treatment B'. After a 'Washout Period', subjects enter 'Period 2', where they receive the opposite treatment from Period 1. The study concludes with a 'Follow-up phone call'.</p>	
<ul style="list-style-type: none"> <li>• <b>Treatment A:</b> a single dose of TAF 25 mg (1 × 25-mg tablet) administered orally under fasted conditions</li> <li>• <b>Treatment B:</b> a single dose of TAF 25 mg (1 × 25-mg tablet) administered orally under fed conditions (standardized high-fat meal)</li> <li>• Treatments were administered on days 1 and 8. There was a six day washout interval between periods.</li> </ul>	
Population	Healthy adults
Study Rationale	Effect of food on the PK of TAF
Dose Selection Rationale	TAF 25 mg, the dose evaluated in phase 3 studies, was used
Formulation	TAF 25 mg tablet
Adherence	Mouth checks and plasma drug concentrations were used to assess adherence
Concomitant medications	All prescription, over-the-counter, and herbal medications were excluded except vitamins, acetaminophen, ibuprofen, hormonal contraceptives, and short term topical hydrocortisone.
PK sampling	Days 1 and 8: 0 (predose ≤ 5 min), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours postdose.
Bioanalytical methods	TAF plasma concentrations were measured using LC/MS/MS

RESULTS	
Protocol deviations	No important protocol deviations were reported
Study population	Forty subjects were enrolled and 39 completed the study; one subject withdrew consent. The mean age was 34 years. The study population was 65% male, 53% white, 40% black, and 60% Hispanic.

## CLINICAL PHARMACOLOGY REVIEW

Adherence	All subjects were reported to have taken both doses. PK profiles were observed for all subjects in both periods with the exception of one subject who withdrew consent prior to day 8.
Concomitant medications	There was no reported use of excluded medications
Bioanalytical methods	Methods were reported to have been fully validated. The TAF LLOQ was reported to be 1 ng/mL.

### Pharmacokinetics

Relative to the fed state, mean TAF AUCs were 40% lower in the fasted state (Table 12, Figure 23, Figure 24). Lower AUC values in the fasted state were observed in the majority of subjects (Figure 25).

**Table 12.** TAF plasma PK parameters.

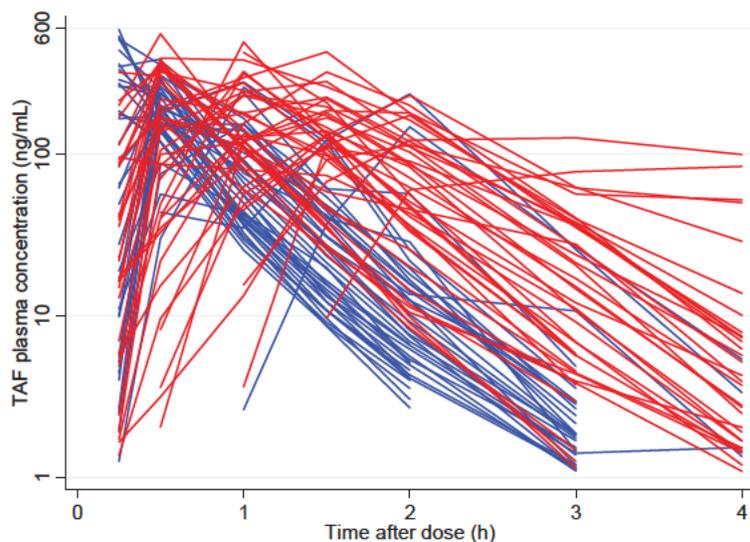
TAF PK Parameter <sup>a</sup>	Treatment A, TAF 25 mg Fasted (N = 39) <sup>b</sup>	Treatment B, TAF 25 mg Fed (N = 40)
AUC <sub>inf</sub> (ng•h/mL)	171.5 (33.6)	288.9 (39.2)
AUC <sub>last</sub> (ng•h/mL)	170.1 (34.0)	282.7 (40.0)
C <sub>max</sub> (ng/mL)	266.3 (46.9)	252.6 (46.4)
t <sub>1/2</sub> (h)	0.35 (0.30, 0.42)	0.45 (0.40, 0.59)
T <sub>max</sub> (h)	0.50 (0.25, 0.50)	1.00 (0.50, 1.50)

a Data are mean (%CV), except t<sub>1/2</sub> and T<sub>max</sub> that are reported as median (Q1, Q3).

b Subject 9191-1009 (BA sequence) withdrew consent and missed the Day 8 study drug dose, therefore did not have TAF PK concentrations with Treatment A.

Source: CSR.

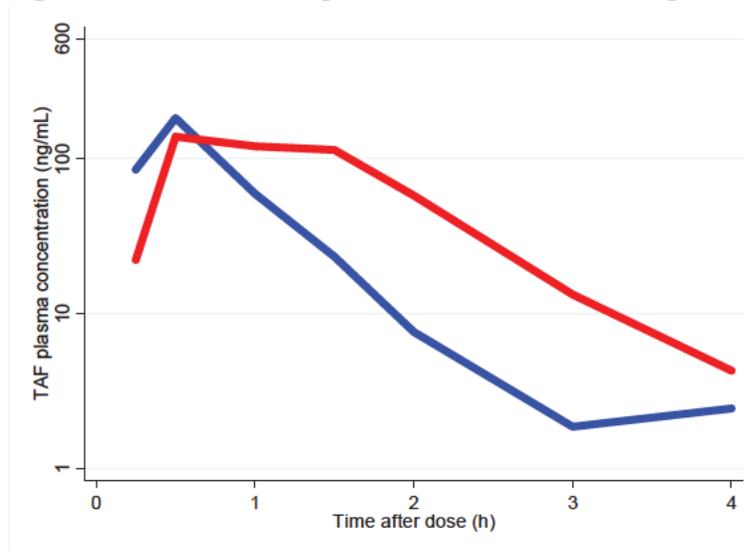
**Figure 23.** Individual subject TAF plasma concentration-time profiles.



Source: Plotted by reviewer. Red = fed; blue = fasted.

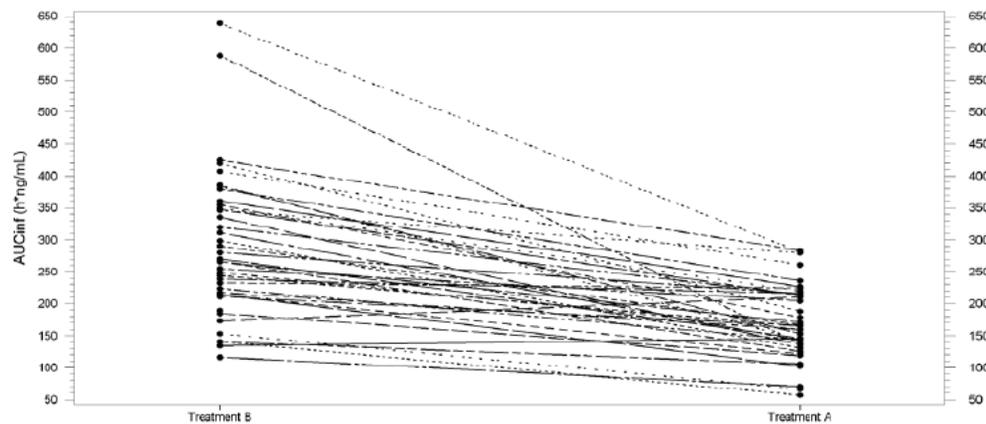
# CLINICAL PHARMACOLOGY REVIEW

**Figure 24.** Median TAF plasma concentration-time profiles.



Source: Plotted by reviewer. Red = fed; blue = fasted.

**Figure 25.** Individual subject TAF AUC values between treatments.

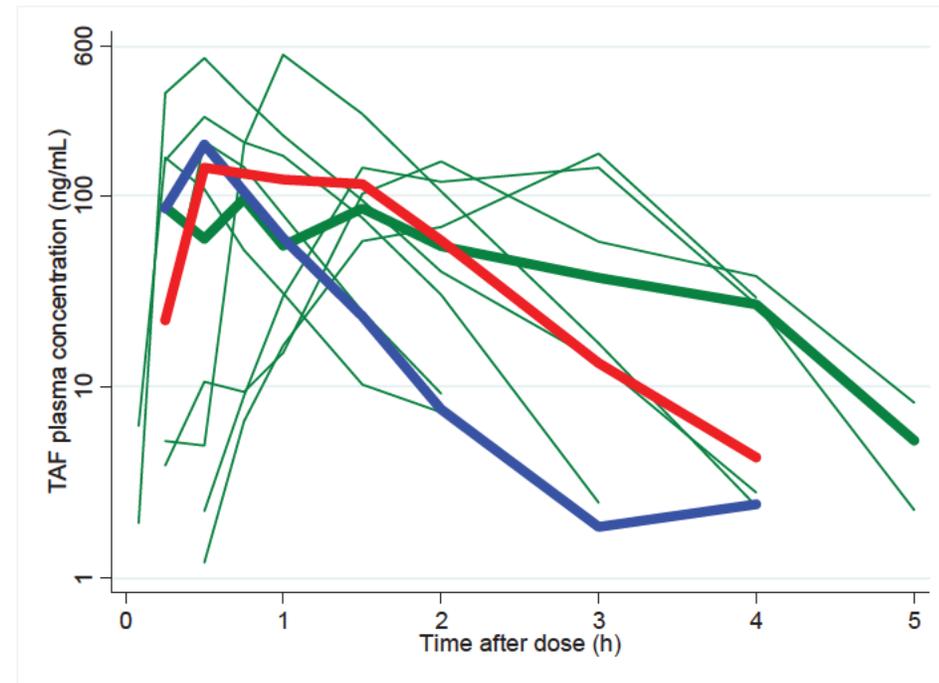


Source: CSR. Treatment A = fasted; B = fed.

Compared to HBV-infected subjects (studies 0108 and 0110) in the phase 3 trials where subjects were instructed to take TAF with food, TAF intensive PK profiles appeared to be similar to the fed arm of the food effect study and appeared to result in increased TAF exposures compared to the fasted arm of the food effect study (Figure 26).

## CLINICAL PHARMACOLOGY REVIEW

**Figure 26.** TAF plasma concentrations from the food effect study compared to phase 3 studies in HBV-infected subjects (0108 and 0110).



Source: Plotted by reviewer. Red = fed; blue = fasted; green = phase 3. Thick line = median of individual subjects in group; Thin green lines = individual phase 3 subjects.

Safety	<p>No deaths, SAEs, or AEs that led to study drug discontinuation occurred.</p> <p>Adverse events occurring in <math>\geq 2</math> subjects included headache, dizziness, oropharyngeal pain, and rhinorrhea (each occurred in one subject in the fasted group and one subject in the fed group).</p> <p>One subject had day 7 urinalysis laboratory abnormalities including grade 3 occult blood and grade 2 protein; menses was confirmed on day 7. Subsequent urinalysis tests were negative.</p> <p>Other laboratory abnormalities were grade 1-2. Grade 1-2 abnormalities occurring in <math>\geq 2</math> subjects included elevated corrected calcium, LDL cholesterol, low sodium, total cholesterol, and occult blood.</p>
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## CLINICAL PHARMACOLOGY REVIEW

### DISCUSSION/REVIEWER'S ANALYSIS AND COMMENTS

There were no issues regarding protocol deviations, adherence, or concomitant medications. Bioanalytical methods were acceptable.

Regarding the TAF PK analysis, the 6 day washout interval was acceptable (TAF is not detectable beyond ~8 hours post-dose). There were no outliers.

[REDACTED] (b) (4). Because efficacy has not been established and exposure-response relationships at lower exposures expected upon fasted administration have not been characterized, we recommend that TAF should be administered with food.

### LABEL RECOMMENDATIONS

[REDACTED] (b) (4). We recommend that TAF should be administered with food. Labeling negotiations are ongoing.

## CLINICAL PHARMACOLOGY REVIEW

### 3.7 320-1615 – Study of TAF PK in subjects with normal hepatic function and severe hepatic impairment

<b>A Phase 1, Open-Label, Parallel-Group, Single Dose Study to Evaluate the Pharmacokinetics of Tenofovir Alafenamide (TAF) in Subjects with Normal Hepatic Function and Subjects with Severe Hepatic Impairment</b>	
Study Period	12/22/2014 - 4/17/2015
Link	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-320-1615\report-body.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-320-1615\report-body.pdf</a>

<b>STUDY DESIGN</b>	
Population	Subjects with severe hepatic impairment (Child Pugh score of 10-15) and matched (age, gender, BMI) subjects with normal hepatic function
Study Rationale	Effect of severe hepatic impairment on the PK of TAF and TFV
Treatments	Single dose of TAF 25 mg with a moderate-fat meal
Dose Selection Rationale	TAF 25 mg was used in phase 3 studies
Formulation	TAF 25 mg tablet
Concomitant medications	<p><u>Excluded medications</u> Any prescription, over-the-counter, and herbal medications with the exception of vitamins, acetaminophen, ibuprofen, hormonal contraceptives, and topical hydrocortisone</p> <p><u>Allowed medications in hepatic impairment group</u> Medications for comorbid disease whose dose had not been changed within 28 days of baseline and were approved by the investigator.</p> <p><u>Excluded medications in the hepatic impairment group</u></p> <ul style="list-style-type: none"> <li>• Agents that reduce renal function or compete for active tubular secretion with tenofovir</li> <li>• P-gp inhibitors and inducers</li> </ul>
PK sampling	<p>Plasma: Predose (<math>\leq 5</math> minutes), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, 36, 48, 60, 72, 96, 120, and 144 hours postdose</p> <p>Protein binding: 0.5, 1, 2, and 3 hours postdose</p> <p>Urine: 0 (predose void), 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-96, 96-120, and 120-144 hours postdose</p>
Bioanalytical methods	<p>Plasma: LC/MS/MS</p> <p>Urine: samples were not analyzed</p> <p>Protein binding: TAF protein binding was measured by ultrafiltration and TFV protein binding was measured by equilibrium dialysis</p>

# CLINICAL PHARMACOLOGY REVIEW

## RESULTS

### Protocol deviations

No important protocol deviations were reported.

### Study population

Ten subjects in each group were enrolled and completed the study (Table 13).

**Table 13.** Subject demographics.

Characteristic	Severe hepatic impairment (n=10)	Matched normal hepatic function group (n=10)
Age (years)	57 (44, 66)	55 (41, 69)
Male sex	5 (50%)	5 (50%)
Hispanic ethnicity	7 (70%)	6 (60%)
White race	10 (100%)	9 (90%)
BMI (kg/m <sup>2</sup> )	29 (23, 36)	26 (23, 33)
Creatinine clearance (mL/min)	136 (94, 181)	101 (61, 158)

Source: CSR. Values are median (min, max) or number (%).

### Concomitant medications

The most commonly used concomitant medications in the study were medications used for subjects with liver disease and included furosemide (n=10), spironolactone (n=9), and lactulose (n=6). All other medications were used by  $\leq 2$  subjects. No use of P-gp inhibitors or inducers were reported.

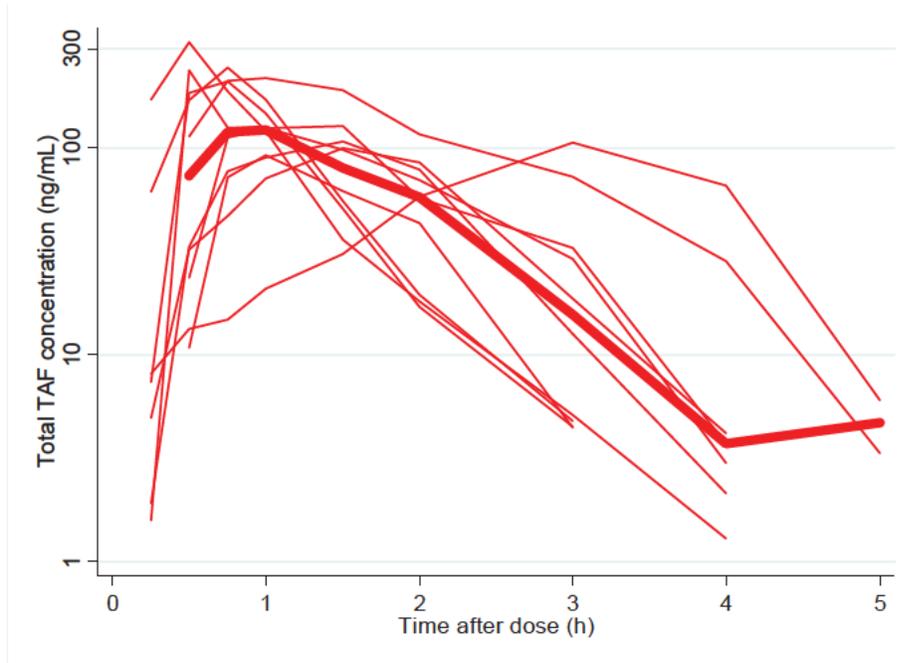
### TAF pharmacokinetics

#### *Total concentrations*

TAF concentration-time profiles in subjects with normal hepatic function were highly variable (Figure 27). However, the variability is similar to that seen in intensive PK profiles of HBV-infected subjects (Figure 28). Total TAF concentrations were ~50% lower in subjects with severe hepatic impairment compared to those with normal hepatic function: geometric mean ratios (90% confidence intervals) [severe hepatic impairment/normal] of TAF C<sub>max</sub> and AUC<sub>last</sub> were 0.45 (0.32, 0.64) and 0.51 (0.40, 0.65), respectively.

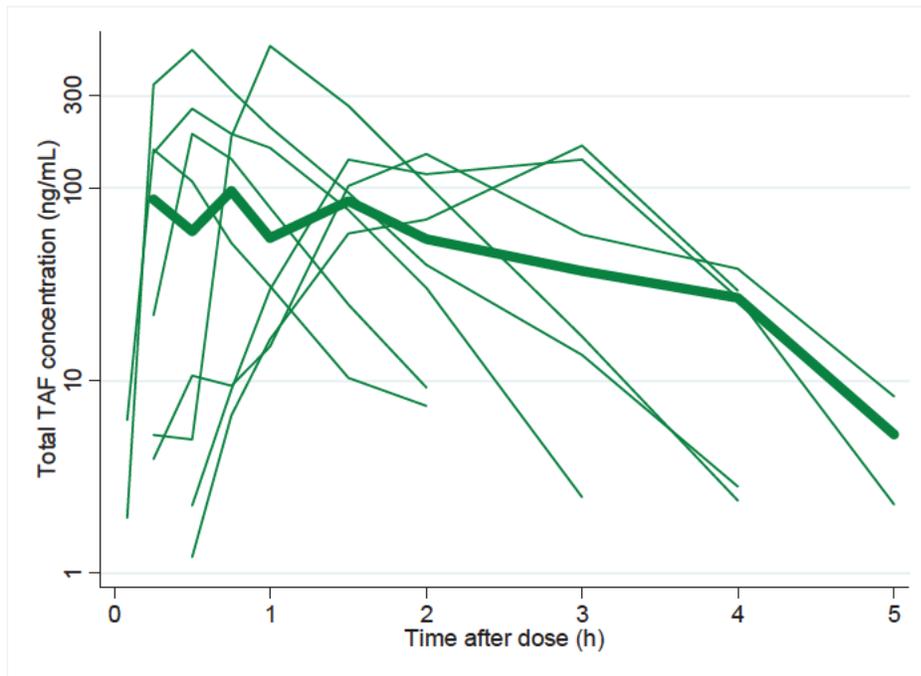
# CLINICAL PHARMACOLOGY REVIEW

**Figure 27.** Total TAF concentration-time profiles in subjects with normal hepatic function.



Source: Prepared by reviewer. Thick line = median.

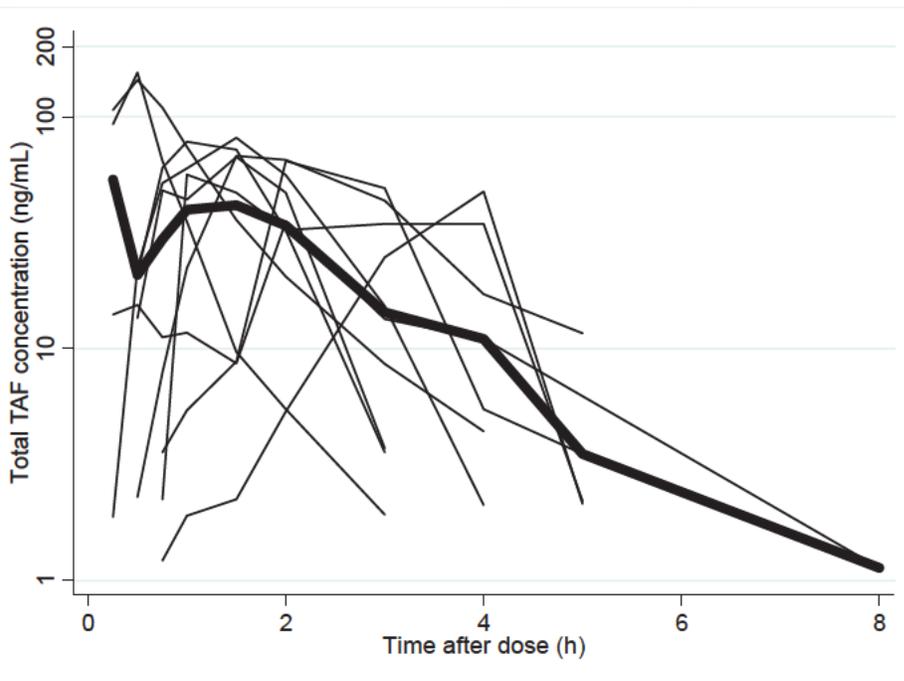
**Figure 28.** Total TAF concentration-time profiles in HBV-infected subjects in studies 0108 and 0110.



Source: Prepared by reviewer. Thick line = median.

## CLINICAL PHARMACOLOGY REVIEW

**Figure 29.** Total TAF concentration-time profiles in subjects with severe hepatic impairment.



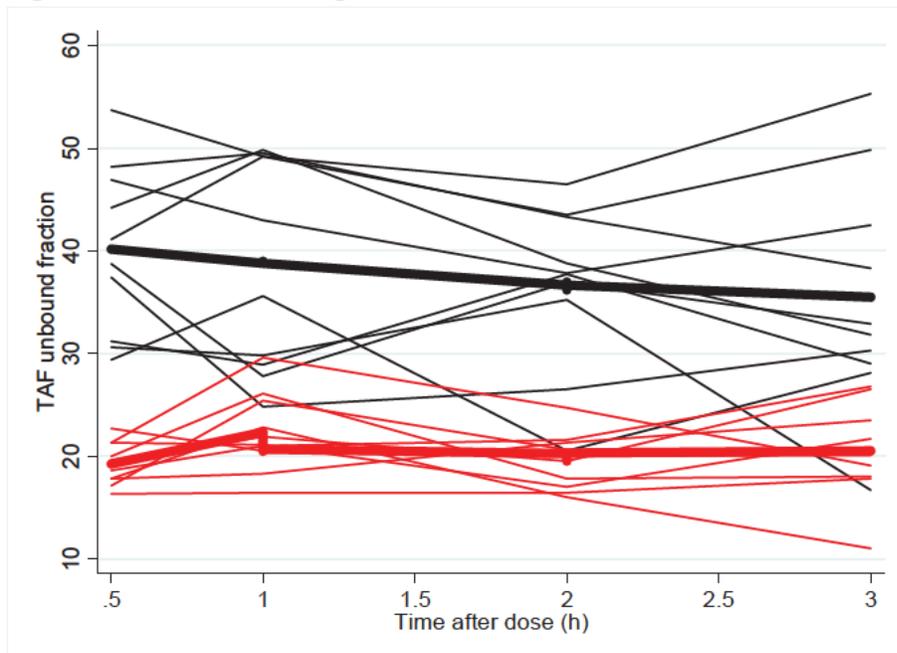
Source: Prepared by reviewer. Thick line = median.

### *Unbound concentrations*

TAF unbound concentrations and unbound PK parameters were derived by multiplying the total concentration or PK parameter value by the subjects' mean fraction unbound. Median TAF fraction unbound values in subjects with severe hepatic impairment at 0.5, 1, 2, and 3 hours post-dose were 39.9, 39.3, 37.7, and 32.3 percent, respectively. Median TAF fraction unbound values in subjects with normal hepatic function at 0.5, 1, 2, and 3 hours post-dose were 19.1, 21.5, 19.7, and 20.3 percent, respectively. Variability in fraction unbound values was greater in the severe hepatic impairment group (Figure 30). TAF fraction unbound in both groups was not associated with time after dose or TAF concentration (Figure 30, Figure 31).

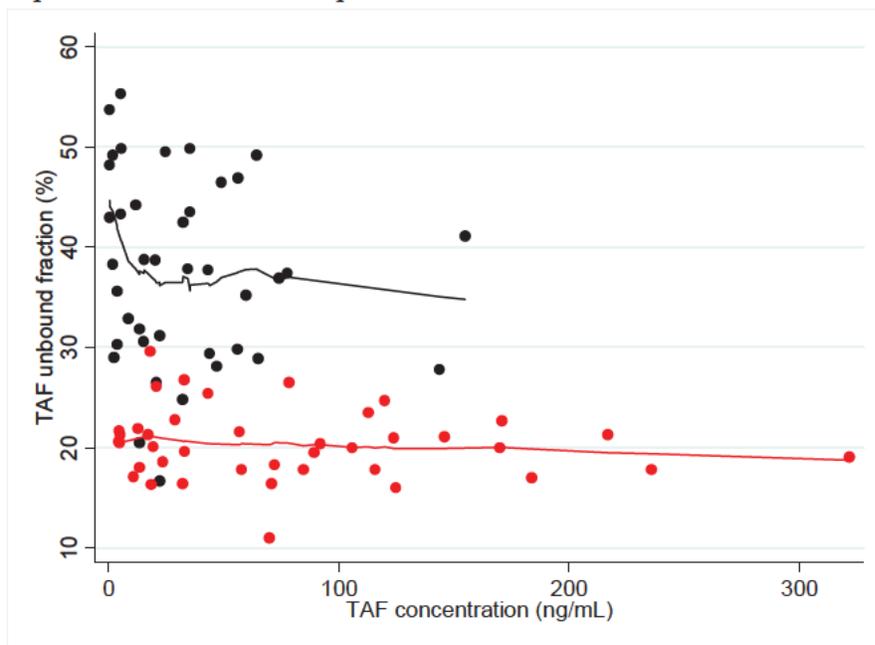
## CLINICAL PHARMACOLOGY REVIEW

**Figure 30.** TAF fraction unbound versus time after dose in subjects with severe hepatic impairment and normal hepatic function.



Source: Prepared by reviewer. Black lines = subjects with severe hepatic impairment; black line = lowest of severe hepatic impairment data; Red lines = subjects with normal hepatic function; Red line = lowest of normal hepatic function data.

**Figure 31.** TAF fraction unbound versus TAF concentration in subjects with severe hepatic impairment and normal hepatic function.

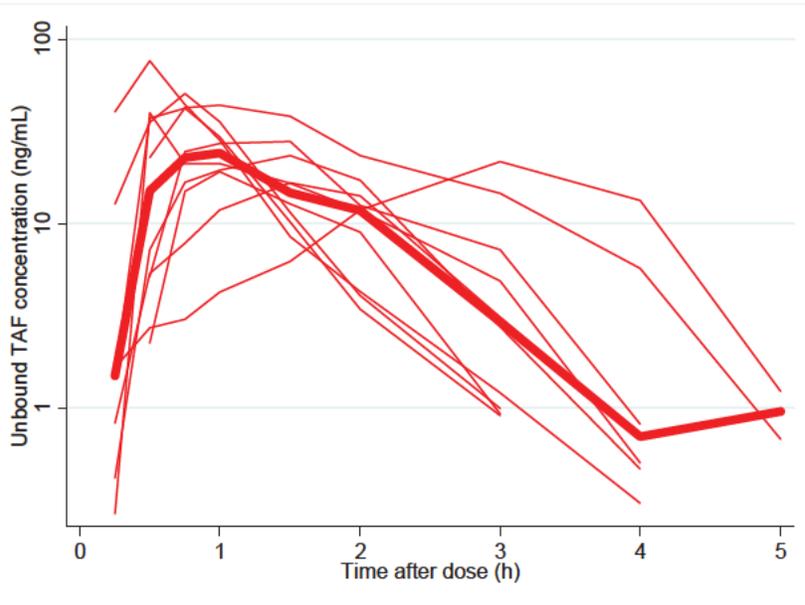


Source: Prepared by reviewer. Black circles = subjects with severe hepatic impairment; Black line = lowest of severe hepatic impairment data; Red circles = subjects with normal hepatic function; Red line = lowest of normal hepatic function data.

## CLINICAL PHARMACOLOGY REVIEW

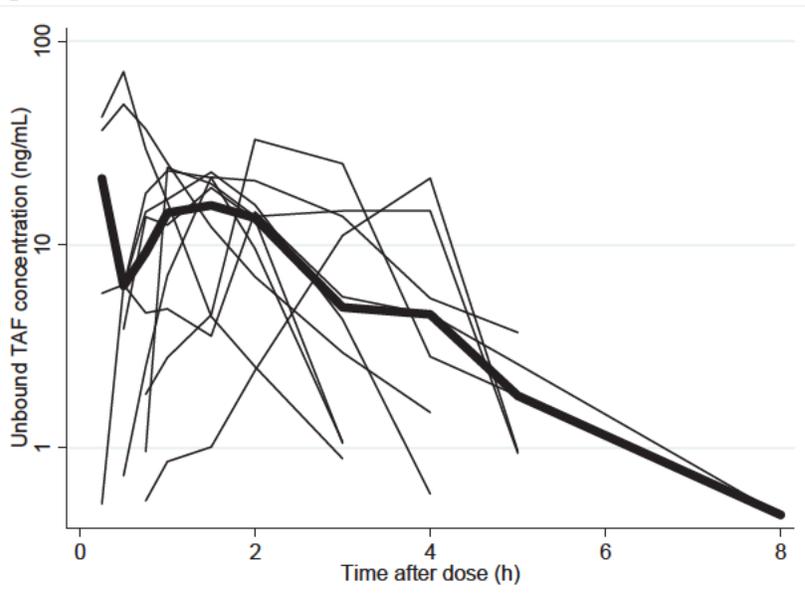
There was significant variation in the shape of unbound TAF concentration-time profiles in both groups (Figure 32, Figure 33). Unbound TAF exposures were not significantly different between groups: geometric mean ratios (90% confidence intervals) [normal/severe hepatic impairment] of unbound TAF C<sub>max</sub> and AUC<sub>last</sub> were 0.82 (0.57, 1.19) and 0.93 (0.73, 1.20), respectively.

**Figure 32.** Unbound TAF concentration-time profiles in subjects with normal hepatic function.



Source: Prepared by reviewer. Thick line = median.

**Figure 33.** Unbound TAF concentration-time profiles in subjects with severe hepatic impairment.

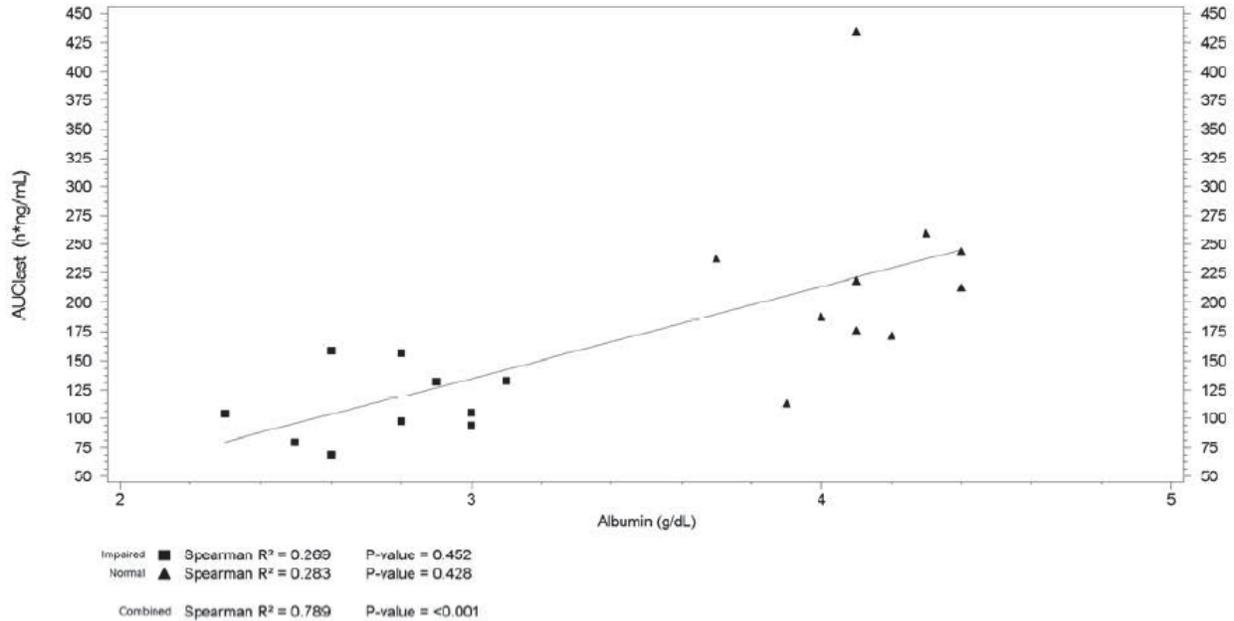


Source: Prepared by reviewer. Thick line = median.

# CLINICAL PHARMACOLOGY REVIEW

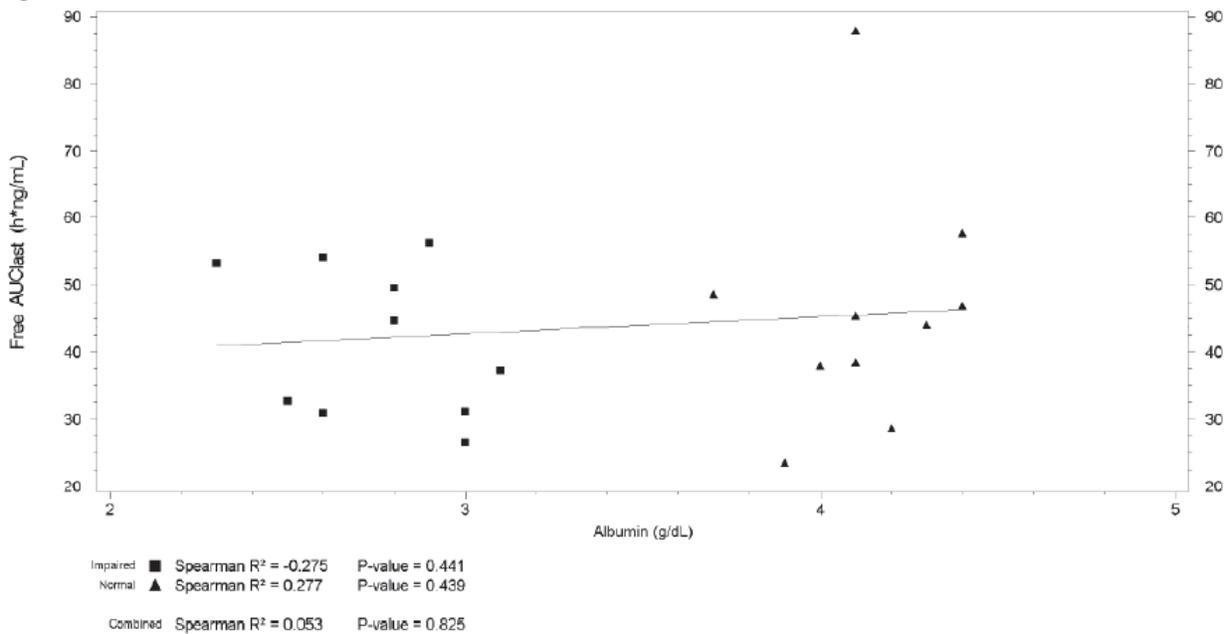
Total TAF AUC was associated with baseline measures of liver function (albumin, total bilirubin, prothrombin time) while unbound TAF AUC was not associated with these parameters (Figure 34, Figure 35).

**Figure 34.** Total TAF AUC versus baseline albumin concentrations.



Source: CSR.

**Figure 35.** Unbound TAF AUC versus baseline albumin concentrations.

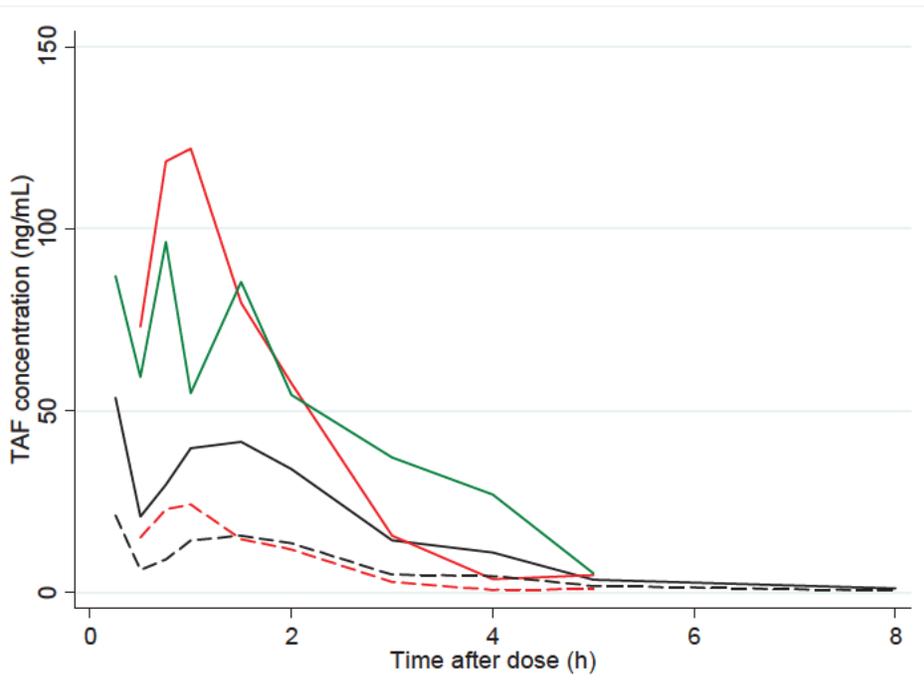


Source: CSR.

## CLINICAL PHARMACOLOGY REVIEW

In summary, relative to subjects with normal hepatic function and HBV-infected subjects, total TAF exposures were lower in subjects with severe hepatic impairment while unbound exposures were similar between subjects with severe hepatic impairment and subjects with normal hepatic function (Figure 36, Figure 37). Exposures were comparable between HBV-infected subjects and subjects with normal hepatic function.

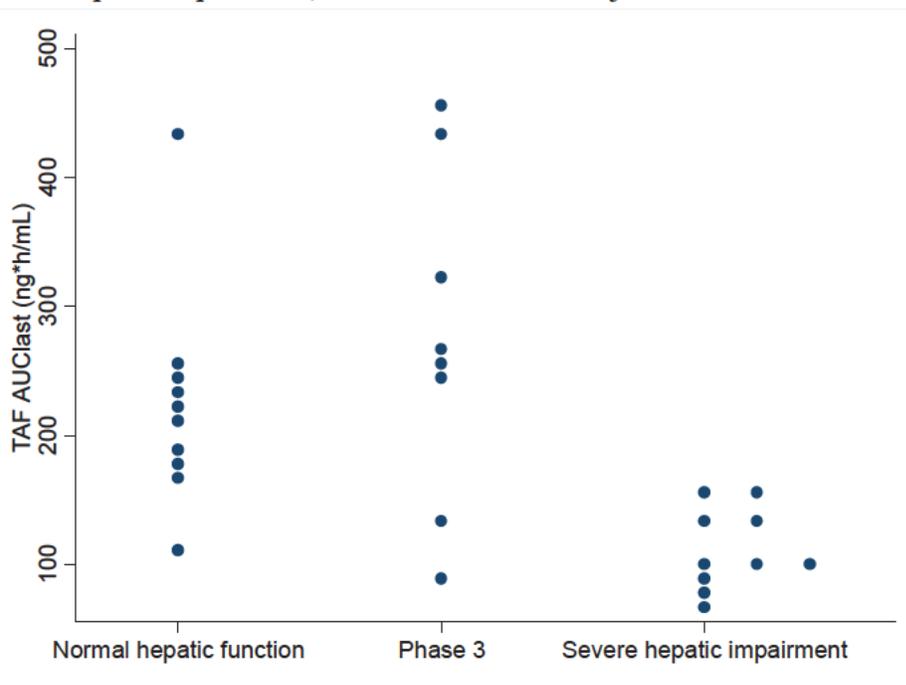
**Figure 36.** Comparison of total and unbound TAF concentration-time profiles between subjects with normal hepatic function, severe hepatic impairment, and HBV-infected subjects.



Source: Prepared by reviewer. Lines are medians. Red = normal hepatic function; Black = severe hepatic impairment; Green = phase 3 studies 0108 and 0110; Solid lines = total concentrations; Dashed lines = unbound concentrations.

## CLINICAL PHARMACOLOGY REVIEW

**Figure 37.** Comparison of total TAF AUC between subjects with normal hepatic function, severe hepatic impairment, and HBV-infected subjects.



Source: Prepared by reviewer. Phase 3 = studies 0108 and 0110 in HBV-infected subjects. Median AUC = 216 ng\*h/mL in subjects with normal hepatic function, AUC = 259 ng\*h/mL in Phase 3 subjects, and AUC = 105 ng\*h/mL in subjects with severe hepatic impairment.

### TFV pharmacokinetics

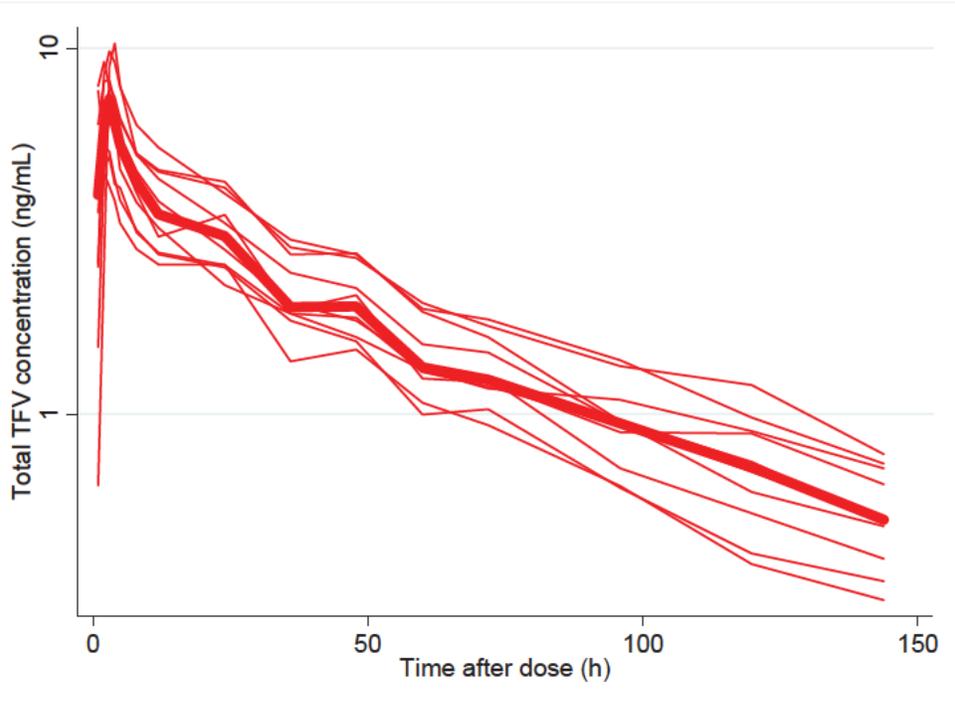
#### *Total concentrations*

Despite wide variation in the shape of TAF concentration-time profiles, TFV concentration-time profiles were consistent within each group (Figure 38, Figure 39). More secondary peaks were observed in the normal hepatic function group. Relative to subjects with normal hepatic function and HBV-infected subjects, total TFV exposures were lower in subjects with severe hepatic impairment (Figure 38, Figure 39).

Total TFV C<sub>max</sub> was not affected by hepatic impairment while TFV AUC was significantly lower in subjects with severe hepatic impairment: geometric mean ratios (90% confidence intervals) [severe hepatic impairment/normal] of TFV C<sub>max</sub> and AUC<sub>inf</sub> were 0.90 (0.65, 1.25) and 0.63 (0.43, 0.93), respectively.

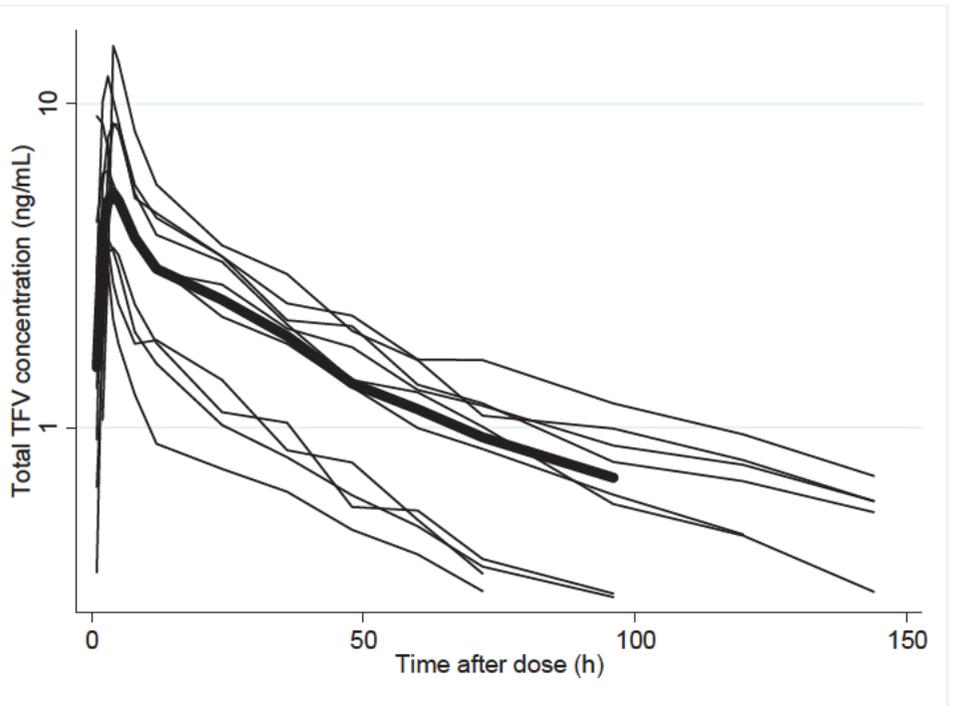
# CLINICAL PHARMACOLOGY REVIEW

**Figure 38.** Total TFV concentration-time profiles in subjects with normal hepatic function.



Source: Prepared by reviewer.

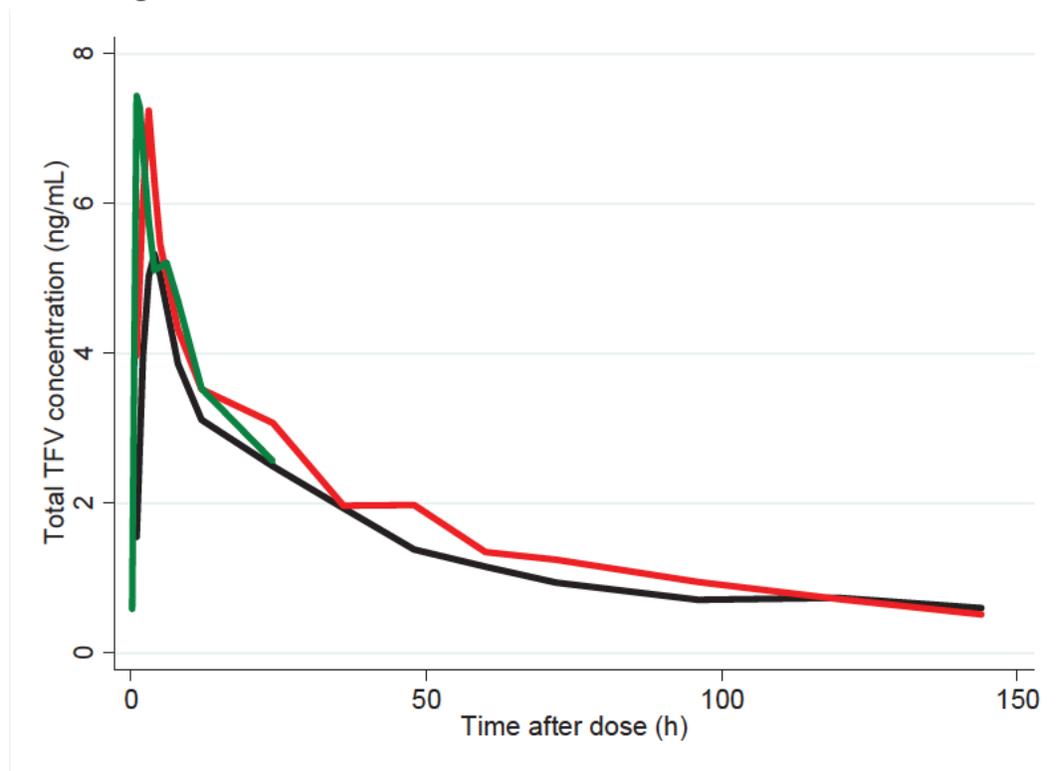
**Figure 39.** Total TFV concentration-time profiles in subjects with severe hepatic impairment.



Source: Prepared by reviewer.

## CLINICAL PHARMACOLOGY REVIEW

**Figure 40.** Comparison of total TFV concentration-time profiles between subjects with normal hepatic function, severe hepatic impairment, and HBV-infected subjects after a single dose of TAF 25 mg.



Source: Prepared by reviewer. Lines = medians. Red = normal hepatic function; Black = severe hepatic impairment; Green = HBV-infected subjects in antiviral activity study 0101.

Total TFV exposures were not associated with baseline albumin or total bilirubin concentrations.

TFV concentrations in urine samples were not analyzed.

### *Unbound TFV concentrations*

TFV fraction unbound was high in all subjects (>95%) regardless of hepatic status. PK analyses were not conducted using unbound TFV concentrations.

### Safety

Adverse events occurring in  $\geq 2$  subjects in either group included mild nausea (n=2) and mild headache (n=2). One severe adverse event of hepatic decompensation was reported in a subject in the severe hepatic impairment group. This event occurred on days 27-29 post-dose. There were no deaths in the study. No subjects discontinued study drug or the study due to adverse events.

# CLINICAL PHARMACOLOGY REVIEW

## DISCUSSION/REVIEWER'S COMMENTS

There were no reported significant protocol deviations.

The concomitant medications section of the protocol was not clear in that the first section did not allow prescription medications (with few exceptions) and did not specify which group it applied to, while the following sections were specific to subjects with severe hepatic impairment. It is likely the first section was intended to be specific to subjects with normal hepatic function. Clarifying this was not important because the list of concomitant medications used in the trial did not include medications expected to interact with TAF.

One limitation to measurement of TAF protein binding was that recovery data was not provided, which would enable assessment of nonspecific binding to the filter membrane. Methods used to determine TAF and TFV concentrations were acceptable. Total TAF concentration-time profiles were highly variable in both groups. TFV concentration-time profiles were less variable than TAF profiles for both groups. However, TFV profiles were more variable in the severe hepatic impairment group. In the TFV profiles, fluctuating concentrations suggestive of enterohepatic recirculation were observed. We speculate this may be due to hepatic uptake (OATP) and excretion (Pgp) of TAF, followed by reabsorption of TAF from the intestine. Finally, we note that the 40% lower TFV AUC in the severe hepatic impairment group calculated from the statistical analysis is less apparent when median concentration-time profiles are compared between groups.

Baseline total bilirubin and albumin concentrations were significantly different between subjects in the phase 3 studies of TAF in HBV-infected subjects compared to study 1615 in subjects with severe hepatic impairment (Table 14). Thus safety and efficacy data from the phase 3 studies does not inform use of TAF in subjects with hepatic impairment.

**Table 14.** Comparison of baseline total bilirubin and albumin values between subjects with severe hepatic impairment and HBV-infected subjects in phase 3 TAF trials.

Baseline laboratory value	Severe hepatic impairment	Phase 3 study 0108	Phase 3 study 0110
Total bilirubin (mg/dL)	3.6 (1.5, 4.8)	0.6 (0.5, 0.9)	0.6 (0.5, 0.9)
Albumin (g/dL)	2.8 (2.6, 3.0)	4.3 (4.1, 4.5)	4.2 (4.0, 4.5)

Source: Prepared by reviewer. Values are median (Q1, Q3). Data from phase 3 trials are for subjects in the TAF arms.

TAF is primarily eliminated by conversion to TFV. Conversion to TFV occurs through unidentified processes in plasma in addition to intracellular enzymes (cathepsin A in lysosomes, CES1 in hepatocytes). Lower total TAF exposures in subjects with hepatic impairment may result from a higher unbound fraction and thus higher clearance of free TAF.

Current FDA guidance emphasizes exposure matching in subjects with and without liver disease based on plasma concentrations (PK in patients with impaired hepatic function, FDA, 2003). However, the assumption that unbound plasma drug concentrations mirror unbound hepatocyte concentrations has been called into question and the ability to predict hepatocyte drug

## CLINICAL PHARMACOLOGY REVIEW

concentrations is currently limited (Chu et al, 2013, CPT). Exposure matching also assumes similar exposure-response relationships in subjects with or without liver disease. This assumption was not supported in the case of sofosbuvir, where parent and metabolite systemic total exposures were increased 2-fold and unchanged in HCV-infected subjects with hepatic impairment (moderate and severe relative to non-cirrhotic), respectively, while the degree of hepatic impairment was inversely associated with antiviral activity (Lawitz et al, 2012, EASL 47<sup>th</sup> Annual Meeting).

The stage of liver disease in phase 3 studies was classified as compensated or decompensated, apparently based on clinical judgment; Child-Pugh category was not determined. Patients with liver disease in the phase 3 trials are thought to be Child-Pugh A. In the small number of subjects in phase 3 studies with cirrhosis, efficacy rates appeared to be similar to the overall population (Table 15).

**Table 15.** Efficacy rates (fraction of subjects with HBV DNA <29 IU/mL) in subjects with cirrhosis in phase 3 studies 108 and 110.

	Study 108 (HBeAg-Negative)		Study 110 (HBeAg-Positive)	
	VEMLIDY (N=285)	tenofovir disoproxil fumarate (N=140)	VEMLIDY (N=581)	tenofovir disoproxil fumarate (N=292)
Overall	94%	93%	64%	67%
Subjects with Cirrhosis	92% (22/24)	93% (13/14)	63% (26/41)	67% (16/24)

(b) (4)

### LABEL RECOMMENDATIONS

(b) (4)

(b) (4) In section 2 and 8, we propose to state that no dose adjustment is needed in mild hepatic impairment, and use in patients with moderate to severe hepatic impairment is not recommended. In addition, in section 8 we propose to add that safety and efficacy has not been established in patients with moderate to severe hepatic impairment. Labeling negotiations are ongoing.

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## 3.8 QP 2015-1004 TAF ESRD – Prediction of TFV exposures in subjects on dialysis administered TAF

Prediction of Pharmacokinetic Exposures for Tenofovir following Administration of Tenofovir Alafenamide in End Stage Renal Disease Subjects with HBV Undergoing Hemodialysis	
Report date	12/9/2015
Link	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\esrd-hd\esrd-hd.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\esrd-hd\esrd-hd.pdf</a>

### STUDY DESIGN

This is a simulation study conducted to make predictions of TFV concentration-time profiles in subjects on dialysis with a CrCL of 5 mL/min. The final TFV population PK model was used to make predictions. The subject dataset was generated by random sampling from a dataset of 907 HBV-infected subjects from TAF phase 3 studies (0108 and 0110) and the TAF antiviral activity study (0101). All subjects were assigned a CrCL value of 5 mL/min. Typical TFV hemodialysis clearance was assigned a value of 9.302 L/hr with intersubject variability of 0.0564. These values were obtained from study GS-01-919, where nine subjects with ESRD on high-flux hemodialysis were administered 300 mg TDF after dialysis.

### RESULTS

Predicted TFV exposures in subjects with ESRD dialysis administered TAF are shown below (Table 16).

**Table 16.** Predicted TFV PK following administration of TAF in ESRD subjects undergoing hemodialysis.

TFV PK Parameter	Mean	Median	CV%	Range	Percentiles (5-95)
$C_{max,ss}$ (ng/mL)	110	107	27.9	46.7 – 234	66.9 – 167
$C_{min,ss}$ (ng/mL)	90.0	87.8	27.1	39.7 – 188	55.4 – 133
$AUC_{0-\tau}$ (ng•hr/mL)	2360	2300	26.7	1040 – 4810	1460 – 3510

The PK parameters are reported for 312-336 hours for maximum TFV exposures.  
CV% = percent coefficient of variation

Source: CSR.

### DISCUSSION/REVIEWER'S COMMENTS

It is unclear why a typical TFV dialysis CL value of 9.3 L/h was used because the reported median TFV dialysis CL value was 134 ml/min (8.04 L/h) (Kearney et al, 2006, Clin PK).

TFV concentrations were reported to increase 50% over the 8 hours after dialysis was stopped (Kearney et al, 2006, Clin PK). This rebound was attributed to distribution from tissues. This rebound phenomenon was not incorporated into the model.

## CLINICAL PHARMACOLOGY REVIEW

The fraction of a TAF dose administered to humans that is excreted in urine as TAF is <1%. Relative to subjects with normal renal function, after a single TAF dose to subjects with severe renal impairment (CrCL of 5-29 mL/min), TAF C<sub>max</sub> and AUC were increased 79 and 92%, respectively, and TAF renal clearance was 88% lower. As renal elimination is not a clinically significant route of TAF elimination (the primary route is metabolism to TFV), it is unclear what mechanisms resulted in higher TAF exposures in subjects with severe renal impairment.

(b) (4)

TAF is mainly cleared by nonrenal elimination, there is evidence that drug absorption, distribution, and metabolic pathways can be altered in ESRD patients (Velenosi et al, 2014, Exp Opin Drug Metab Toxicol). For this reason a TAF study in ESRD patients on dialysis is needed to derive dosing recommendations. Such a study is ongoing (GS-US-292-1825) in HIV-infected patients using the TAF-containing product (GENVOYA).

### LABEL RECOMMENDATIONS

(b) (4)

(b) (4) This was accepted by the applicant.

## CLINICAL PHARMACOLOGY REVIEW

### 3.9 AD-120-2042 – Effect of OATP inhibitor on TAF uptake into human hepatocytes

<b>Effect of an OATP Inhibitor on Uptake of TAF into Primary Human Hepatocytes</b>	
<b>Study #</b>	AD-120-2042
<b>Report date</b>	8/5/2015
<b>Link to study report</b>	<a href="\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biostat\5322-rep-hep-metab-interact-stud\ad-120-2042\report-body.pdf">\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biostat\5322-rep-hep-metab-interact-stud\ad-120-2042\report-body.pdf</a>

<b>STUDY DESIGN</b>	
Study description	Following pre-incubation of primary human hepatocytes from four donors with 20 µM rifampicin or vehicle (2.5% DMSO) for 30 min, cells were incubated with 0.5 µM TAF or bosentan (positive control) for 2, 15, and 60 min and intracellular concentrations of TFV-DP or cell-associated bosentan levels were determined, respectively.
Population	Hepatocytes were obtained from four donors aged 44-55 years who died from anoxia or stroke.
Study Rationale	The effect of an OATP inhibitor, rifampicin, on TAF uptake was examined by measuring the intracellular levels of TFV-DP in primary human hepatocytes to assess the potential for drug-drug interactions.

<b>RESULTS</b>	
<p>Intracellular TFV-DP levels were unable to be quantified at 2 and 15 min in cells from certain donors. levels at 60 min were used for assessments for both TAF and bosentan.</p> <p>A mean of 13% inhibition of TAF uptake by rifampicin was observed. Rifampicin inhibited accumulation of cell-associated levels of bosentan by approximately 38%.</p>	

<b>REVIEWER'S COMMENTS AND CONCLUSION</b>	
Discussion / reviewer's comments	We agree with the applicant's assessment that the effect of rifampicin on bosentan uptake was likely underestimated due to nonspecific binding, while this is not an issue for TAF because TFV-DP is formed intracellularly. We also agree that TAF enters hepatocytes by passive diffusion in addition to OATP-mediated uptake. This is also the conclusion reached in a Gilead publication (Murakami et al, AAC, 2015).
Labeling recommendations	We agree with the current statement in section 12.4 of labeling: "Tenofovir alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3"

# CLINICAL PHARMACOLOGY REVIEW

## 4 Appendix

### 4.1 Criteria for evaluation of bioanalytical methods and study sample analyses

	<b>Characteristic</b>
Validation	<ul style="list-style-type: none"><li>▪ Calibration and quality control samples range and number</li><li>▪ Accuracy and precision of the calibration curve and quality control samples</li><li>▪ Chromatograms provided</li><li>▪ Analyte (especially LLOQ) can be detected with adequate signal to noise</li><li>▪ Analyte can be detected without interference due to internal standard, carryover, sample extraction, concomitant medications, etc</li><li>▪ Overall performance</li><li>▪ Method fully validated</li></ul>
Study Samples Analysis	<ul style="list-style-type: none"><li>▪ Fully validated method used</li><li>▪ Samples analyzed within the established stability period</li><li>▪ Accuracy and precision of the calibration curve and quality control samples</li><li>▪ Sufficient number of quality control samples</li><li>▪ Incurred samples analysis</li><li>▪ Chromatograms provided</li><li>▪ Analyte (especially LLOQ) can be detected with adequate signal to noise</li><li>▪ Analyte can be detected without interference due to internal standard, carryover, sample extraction, concomitant medications, etc</li><li>▪ Incurred samples analysis</li><li>▪ Overall performance</li></ul>

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/s/  
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