CLINICAL PHARMACOLOGY REVIEW ADDENDUM

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

This review is an addendum to the NDA 208215 Clinical Pharmacology review dated 12/7/2015 and includes 1) additional information regarding dosing recommendations for F/TAF when coadministered with efavirenz (EFV) or certain protease inhibitors (atazanavir [ATV], darunavir [DRV], and lopinavir [LPV]); and 2) a summary of clinical pharmacology-related labeling negotiations with the sponsor.

Dosing of F/TAF with EFV

In the initial review of this application, it was noted that TAF AUC was reduced 14% when coadministered with EFV. However, the review did not describe how the requirement for EFV to be taken in the fasted state would lead to further reduced TAF exposure because TAF exposure is reduced in the fasted versus fed state. Relative to coadministration with a high fat meal, TAF (from F/TAF) exposure in the fasted state is reduced 44%. In a TAF monotherapy study, near-maximal (>90% of Emax) antiviral activity was achieved at TAF AUCs of ~≥55 ng*h/mL. Mean TAF AUC when coadministered with EFV is expected to be above this threshold (mean fasting TAF AUC of 146 ng*h/mL – 14% = 126 ng*h/mL). In addition, in a switch study in which subjects received various 3rd agents in addition to either F/TAF or F/TDF, the ratio of active tenofovir diphosphate (TFV-DP) concentrations in peripheral blood mononuclear cells in subjects on EFV (n=8) was 1.7 (90% confidence interval: 0.65, 4.4) in the TAF versus TDF arm. Based on the Emax and TFV-DP data, we agree that the proposed F/TAF dosing of 200/25 mg with EFV is acceptable.

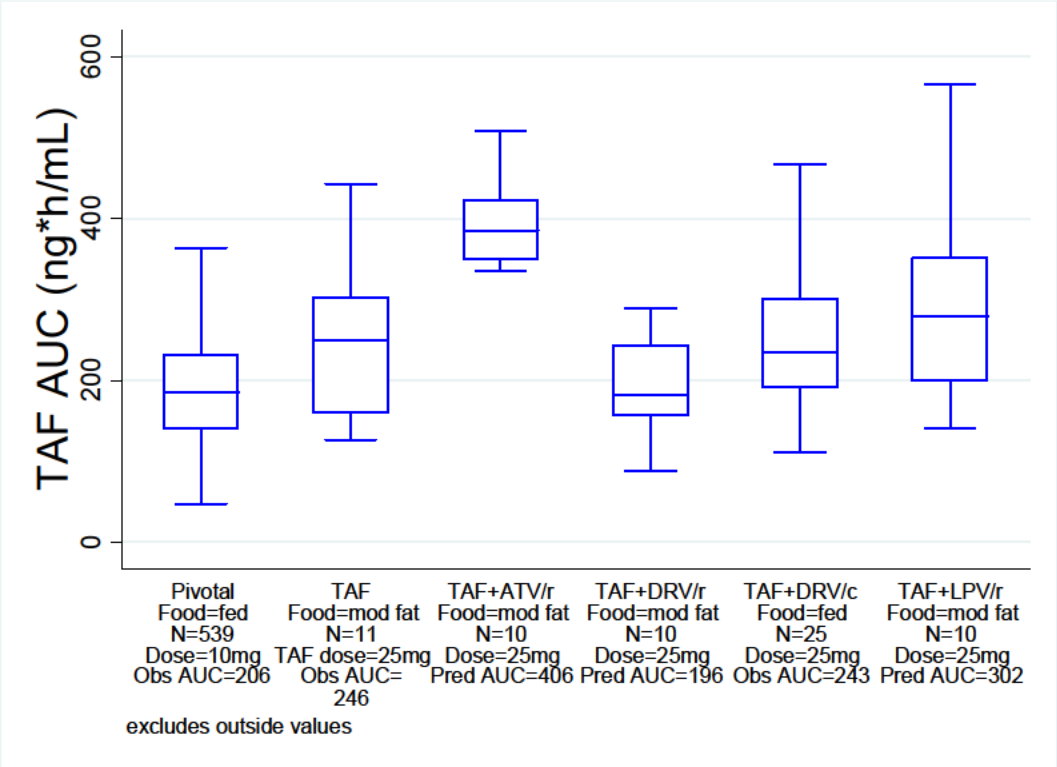
Dosing of F/TAF with ATV, DRV, or LPV

In the initial review of this application, TAF exposure-response (Emax), TFV-DP PK, and phase 2 efficacy (D/C/F/TAF versus D/C/F/TDF in study 299-0102) data were used to conclude that dosing of protease inhibitor (ATV, DRV, and LPV)/CYP3A inhibitor with [redacted] (b) (4) was acceptable. In subsequent discussions with the review team, issues were raised including whether the goal is matching exposures of TAF versus TFV-DP and there were concerns regarding numerically lower efficacy in the TAF versus TDF arm in the phase 2 study. As a

result of these concerns, we considered the possibility of recommending F/TAF dosing of 200/25 mg when coadministered with protease inhibitors/CYP3A inhibitor.

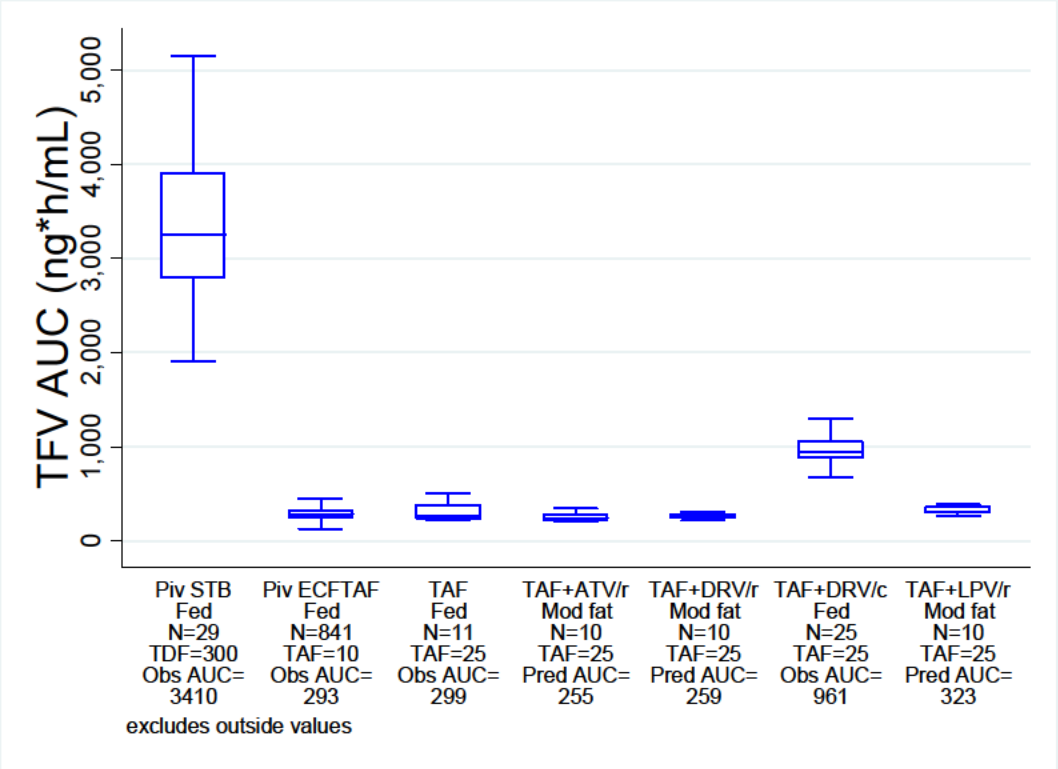
Relative to TAF exposure from the E/C/F/TAF pivotal trials, administration of F/TAF 200/25 mg with protease inhibitors/CYP3A inhibitor is expected to result in TAF AUC increased <2-fold (Figure 1). The maximum predicted TAF exposures occur when coadministered with ATV/r. Although predicted TAF AUCs at a dose of 25 mg when coadministered with ATV/r do not fully overlap with TAF exposures from the pivotal trials, note that no TAF exposure-related safety issues have been identified to date. The primary safety concerns are bone and renal toxicity, which are associated with TFV. Coadministration of CYP3A inhibitor plus ATV, DRV, or LPV with F/TAF 200/25 mg are expected to result in TFV exposures that are ≥72% lower compared to E/C/F/TDF (Figure 2). As there are no safety concerns related to TAF or TFV exposures from administration of F/TAF 200/25 mg with protease inhibitors/CYP3A inhibitor, we recommended an F/TAF dose of 200/25 mg when coadministered with CYP3A inhibitor plus ATV, DRV, or LPV. The sponsor accepted this recommendation.

Figure 1. Predicted and observed TAF AUC for coadministration of F/TAF 200/25 mg with protease inhibitors compared to observed data for E/C/F/TAF.



Prepared by reviewer. Obs AUC = observed AUC; pred AUC = predicted AUC. Predicted AUCs for a TAF dose of 25 mg were obtained by multipling observed AUCs for a TAF dose of 10 mg by 2.5. Pivotal refers to the pivotal E/C/F/TAF trials. TAF 10 mg plus ATV/r, DRV/r, and LPV/r were evaluated in study 120-0118 at a TAF dose of 10 mg. TAF 25 mg plus DRV/c was evaluated in study 311-0101. On the X axis, line 1 = study drug; line 2 = food status; line 3 = number of subjects; line 4 =TAF dose; line 5 = mean observed AUC.

Figure 2. Predicted and observed TFV AUC for coadministration of F/TAF 200/25 mg with protease inhibitors compared to observed E/C/F/TAF and E/C/F/TDF data.



Prepared by reviewer. STB = E/C/F/TDF. Obs AUC = observed AUC; pred AUC = predicted AUC. Predicted AUCs for a TAF dose of 25 mg were obtained by multipling observed AUCs for a TAF dose of 10 mg by 2.5. Pivotal refers to the pivotal E/C/F/TAF trials. TAF 10 mg plus ATV/r, DRV/r, and LPV/r were evaluated in study 120-0118 at a TAF dose of 10 mg. TAF 25 mg plus DRV/c was evaluated in study 311-0101. On the X axis, line 1 = study drug containing TAF or TDF; line 2 = food status; line 3 = number of subjects; line 4 =TDF or TAF dose; line 5-6 = mean observed AUC.

Summary of clinical pharmacology-related labeling negotiations

All clinical pharmacology labeling issues were resolved (Table 1).

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

Section	Issue	FDA edits 12/17/15	Sponsor edits 1/8/16	FDA edits 2/3/16	Sponsor edits 2/11/16	FDA edits 3/2/2016	Sponsor edits 3/4/2016
D&A	Dosing with ATV, DRV, and LPV	(b) (4) (b) (4) (b) (4) F/TAF 200/25 mg with DRV.	(b) (4)	Stated the issue is under review	NA	Change to F/TAF 200/25 mg for ATV, DRV, and LPV. See text for reasoning.	Accepted
DI	Description of drug interaction mechanisms in table of established / potentially significant interactions	(b) (4)	No change	No change	(b) (4)	(b) (4)	Accepted
Lactation	Description of data regarding FTC concentrations in human breast milk	Asked sponsor to include more detail, as specific as possible	(b) (4)	Referred sponsor to agreed upon TRUVADA labeling	(b) (4) Replaced with language from the TRUVADA label stating that FTC is secreted in breast milk.	Accepted	
PK	Inclusion of (b) (4)	Deleted paragraph, stating (b) (4)	(b) (4)	Deleted, citing (b) (4)	Accepted		
PK	Duplication of food effect information in table and text	Deleted, as the data is in the PK properties table	Accepted				
PK	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Accepted		

Prepared by reviewer. D&A=dosing and administration; DI=drug interactions; PK=pharmacokinetics.

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/s/

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03/30/2016

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03/30/2016