CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208215Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	April 4, 2016
From	Jeffrey Murray, M.D., M.P.H.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208215
Applicant	Gilead Sciences, Inc.
Date of Submission	April 7, 2015
PDUFA Goal Date	April 7, 2016
Proprietary Name / **Non-Proprietary Name**	Descovy Emtricitabine/tenofovir alafenamide (F/TAF)
Dosage Form(s) / Strength(s)	200 mg/25 mg
Applicant Proposed Indication(s)/Population(s)	In combination with other antiretrovirals for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	In combination with other antiretrovirals for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	William Tauber, M.D.
Statistical Review	Daniel Rubin, Ph.D.
Pharmacology Toxicology Review	Claudia Wrzesinski, DVM, Ph.D. Mark Powley, Ph.D.
OPQ Review	Haripada Sarker, Ph.D. Shrikant Pagay, Ph.D. Ying Wang, Ph.D. Frank Wackes Gerlie Geiser, Ph.D. Stephen Miller, Ph.D.
Microbiology Review	Lisa Naeger, Ph.D.
Clinical Pharmacology Review	Mario Sampson, Pharm.D.
OSI	
CDTL Review	Islam Younis, Ph.D.

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Benefit-Risk Assessment

The Benefit-Risk of Descovy, emtricitabine/tenofovir alafenamide (FTC/TAF), 200 mg/25 mg, for the treatment of HIV infection for use in combination with other antiretroviral drugs is favorable. It is based on previous trials conducted with [redacted] (b) (4) for the four-drug fixed dose combination (FDC) product with the trade name Genvoya (elvitegravir, cobicistat, FTC, TAF). Genvoya is an FDA-approved FDC (complete regimen) that is safe and effective for the treatment of HIV. The TAF dose (25 mg) in the two-drug FDC FTC/TAF (Decovy) is higher than the dose of TAF (10 mg) in Genvoya to account for differences in TAF exposures between the two formulations resulting from a pharmacokinetic drug-drug interaction between TAF and cobicistat (COBI).

In brief, based on the data available in this NDA, the Division of Antiviral Products (DAVP) reached consensus that 200 mg/25 mg is the most appropriate dose for FTC/TAF for combination use with a broad range of antiretrovirals. With respect to efficacy considerations, 25 mg of TAF provides for TAF exposures that match or exceed those observed in patients receiving Genvoya, ensuring adequate antiviral effect. As discussed further below, [redacted] (b) (4) With respect to safety, TAF exposures for FTC/TAF 200 mg/25 mg when used with some boosted protease inhibitors will be higher than that of Genvoya. However, exposures of the active metabolite, tenofovir, will remain substantially lower than that observed with previously approved tenofovir disoproxil fumarate (TDF) formulations such as, Viread (TDF), Truvada (FTC/TDF) and Stribild (Elvitegravir, COBI, FTC, TDF). Thus, safety is supported by formulations with substantially higher TFV exposures. The Division believes that FTC/TAF 200mg/25 mg provides exposures with the best balance of efficacy and safety considerations until further clinical data confirming efficacy with lower TAF exposures are available.

2. Background

TAF is a pro-drug of the active metabolite tenofovir diphosphate. Two approved FDCs contain TAF: Genvoya (mentioned above) and Odefsy (FTC, TAF, rilpivirine). Genvoya was the first product approved containing the new molecular entity TAF. The approval of Odefsy and the FTC/TAF NDA are based on relative bioavailability bridging studies demonstrating comparable TAF exposures to that of the first approved TAF-containing product (Genvoya). Multiple other products include the tenofovir prodrug TDF that preceded the approvals of TAF formulations. The advantage of TAF compared to TDF is the ability of TAF to deliver tenofovir to intracellular sites of viral replication (where tenofovir is phosphorylated to tenfovir diphosphate) with lower doses and with lower systemic exposures of TFV, which has been associated with renal and bone toxicity. TAF with its lower associated plasma TFV exposures is expected to result in less renal and bone toxicity than TDF. In fact, when Genvoya was compared to Stribild (same four drug combination as Genvoya except for TDF in place of TAF), the products were equally efficacious and some markers of renal function and bone density were less adversely affected with Genvoya (TAF FDC) compared to Stribild (TDF FDC).

3. Product Quality

There are no product quality issues precluding approval of this application. For additional details on chemistry, manufacturing and product quality, please review to the review documents prepared by the OPQ review team referred to in the top of this review.

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical pharmacology issues precluding approval of this application.

5. Clinical Pharmacology

The Clinical Pharmacology review team recommends approval of this NDA (Original 1).

Two relative bioavailability studies are the basis of approval for this application (original 1):

(b) (4)

2. Study GS-US-311-1473 was a randomized, open-label, single-dose, two-way cross-over study under fed conditions which compared FTC and TAF exposures of FTC/TAF 200/25 mg FDC to that of EVG/COBI/FTC/TAF (Genvoya).

(b) (4) However, the choice of dosage strengths recommended for use with various concomitant antiretrovirals depends on drug-drug interaction data.

Food Effect

For FTC/TAF, food increases TAF AUC by 77% but does not affect FTC AUC. This food effect on TAF is larger than that observed with EVG/COBI/FTC/TAF (Genvoya) where TAF AUC increased by 18%. In his cross-discipline team leader (CDTL) review, Dr. Younis states that this differential food effect between the two FDCs is not likely due to formulation issues because both products are immediate release with rapid dissolution and are manufactured using standard excipients. The Clinical Pharmacology team agrees with Gilead's hypothesis that this differential food effect is a result of increased TAF bioavailability (estimated to be ~40% in humans) in the presence COBI (a Pgp inhibitor) for Genvoya. Food does not cause a further substantial increase in TAF bioavailability in the presence of COBI. In contrast, when FTC/TAF is administered alone, without a Pgp inhibitor, food leads to a substantial relative increase in TAF bioavailability.

The clinical pharmacology team agrees with the Applicant's proposal to allow the administration of FTC/TAF FDC without regard to food because the reduction in TAF exposure in the fasted state relative to the fed state (44%) is expected to be less (~15%) when

FTC/TAF is combined with a regimen containing ritonavir or cobicistat because of increased bioavailability due to Pgp inhibition.

Administration with Concomitant Antiretroviral Drugs

Gilead conducted several drug-drug interaction studies to evaluate the effect of other antiretroviral drugs on the exposures of TAF. As expected, dolutegravir (DTG), efavirenz (EFV), and rilpivirine (RPV) had no clinically significant effect on the exposure of TAF. On the other hand, darunavir (DRV)/RTV, lopinavir (LPV)/RTV, and atazanavir (ATV)/RTV had variable but significant effects on the PK of TAF. Results are shown in Figure 1 taken from Dr. Younis's CDTL review. A mean TAF AUC of ~200 ng*h/mL (upper dashed line) was observed in the Genvoya clinical efficacy and safety trials. A minimum TAF AUC of ~55 ng*h/mL (lower dashed line) had antiviral activity similar to TDF 300 mg in a short-term TAF monotherapy trial. TAF exposures were substantially less than the desired Genvoya target when TAF 10 mg was administered with ritonavir-boosted darunavir, lopinavir or atazanavir. Administration of TAF with darunavir/ritonavir produces similar exposures as TAF alone, suggesting that darunavir "nullifies" the effect of COBI (or ritonavir) on increasing TAF exposures. Concomitant use of boosted lopinavir and atazanvir (to a lesser degree) also reduced TAF exposures below the Genvoya target. For this reason DAVP recommends 200 mg/25mg as the dose of FTC/TAF that best achieves the exposure target for efficacy as established in clinical trials. Phase 2 clinical trial data (see Section 7) of the 200 mg/100 mg dose of FTC/TAF plus COBI-boosted daruanvir did not alleviate concerns that lower TAF exposures would reliably produce the desired antiviral effect.

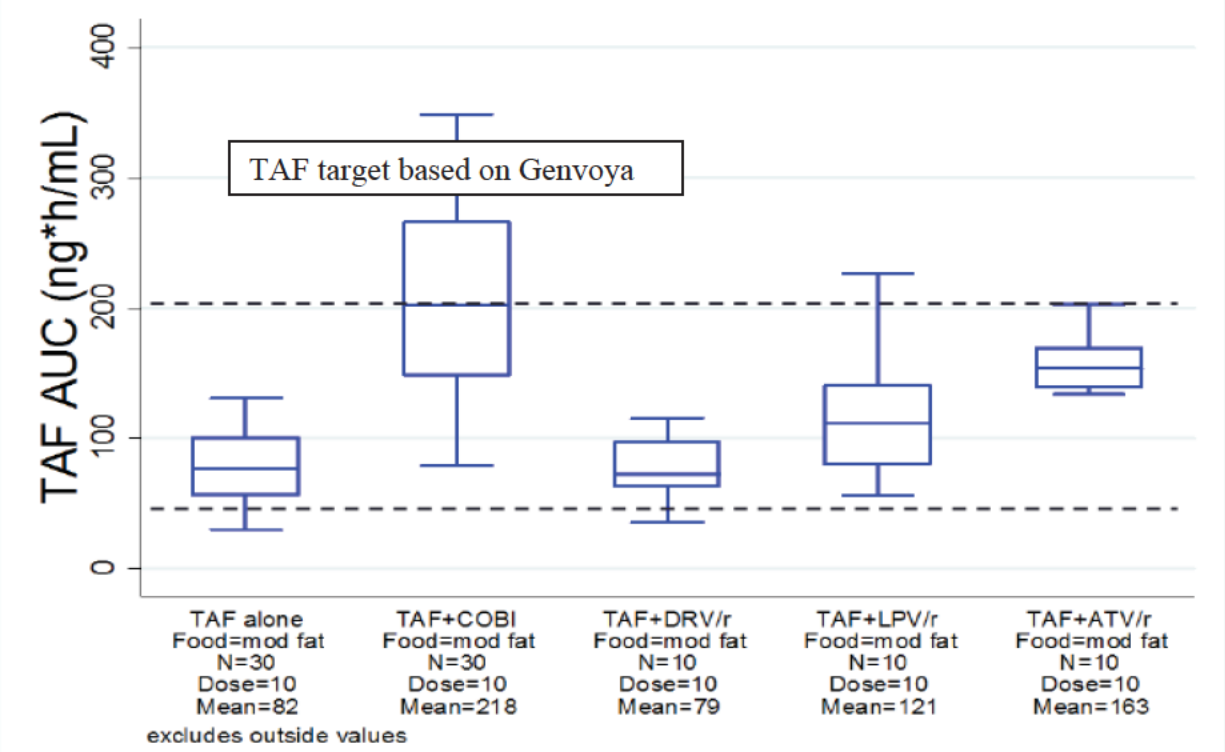

Figure. Distribution of TAF AUC when administered alone and in the presence of COBI or various HIV-1 protease inhibitors combined with RTV. Figure adapted from clinical pharmacology review.

6. Clinical Microbiology

There are no clinical virology issues precluding approval of this application.

7. Clinical/Statistical-Efficacy

Gilead submitted data from Study GS-US-299-0102 which was a phase 2, double-blind, non-inferiority trial in treatment-naïve HIV infected adults. A total of 153 subjects were randomly assigned in a 2:1 ratio to one of the following treatments:

1. (b) (4)
2.

The primary efficacy endpoint was the percentage of subjects with HIV-1 viral loads < 50 copies/mL at 24 weeks. The pre-specified non-inferiority margin was 12% on the risk difference scale. It should be noted that this study was not required for approval of FTC/TAF for use with various other antiretroviral drugs as long as the NDA included exposure links between at least one of the dosage strengths of FTC/TAF and previously approved FTC and TAF formulations (Genvoya for the latter). In addition, for trials supporting approval of new antiretroviral drugs or new indications for treatment naïve patients, DAVP strongly recommends that primary efficacy comparisons be conducted at 48 weeks.

Baseline demographics and disease characteristics were similar between the two treatment arms. Results are shown in Table 1. Although results were similar between the TAF and TDF regimen at 24 weeks, at 48 weeks the TAF regimen was numerically worse by 7 percentage points and the lower confidence bound for the difference between proportion of patients with HIV-RNA < 50 copies/mL was -20%. The Division acknowledges that this was a phase 2 trial that was underpowered for a noninferiority comparison at weeks 24 or 48 and that there were numerically more people who discontinued treatment on the TAF arm due to reasons other than virologic failure. Therefore we cannot definitely conclude that the (b) (4)

Also in the Phase 3 trials supporting the approval of Genvoya, Week 48 virologic success rates in the pooled trials were 800/866 (92%) in the Genvoya group and 784/867 (90%) in the Stribild group. Both treatment arms in phase 2 trial GS-US-299-0102 appeared to underperform compared to the phase 3 trials. Although these are cross-study comparisons, the relevant trials were conducted by the same sponsor over a similar time period, with similar entry criteria, procedures, endpoints, and relatively similar patient characteristics. Gilead presented alternative explanations for the observed efficacy differences, including greater discontinuation rates seen in the phase 2 trial and worse adherence due to the number of pills required to maintain blinding. (b) (4)

(b) (4)

Table 1. Virologic success rates for DRV/COBI/FTC/TAF in GS-US-299-0102. Adapted from biometrics review.

Virologic success	D/C/F/TAF (n = 103)	DRV+COBI+TVD (n = 50)	Difference (95% CI)	P-value
Week 24	77/103 (75%)	37/50 (74%)	3.3% (-11% to 18%)	0.64
Week 48	79/103 (77%)	42/50 (84%)	-6.2% (-20% to 7%)	0.35

8. Safety

There were no new safety issues identified with the use of FTC/TAF 200mg/10mg in phase 2 trial GS-US-299-0102. The safety of FTC/TAF 200 mg/25 mg is primarily supported by data collected in the Genvoya development program. Table 2 shows TAF and TFV AUCs when FTC/TAF 200mg/25 mg is co-administered with three commonly used protease inhibitors. TAF AUC increases compared to Genvoya are expected when TAF 25 mg is concomitantly administered with atazanavir (ATV)/ritonavir and lopinavir (LPV)/ritonavir. The magnitude of TAF AUC increases are considered acceptable with respect to safety, particularly given TFV AUCs are not substantially elevated. Increased TFV exposures relative to Genvoya are expected when TAF 25 mg is concomitantly administered with Darunavir (with ritonavir or

COBI); however, the TFV AUCs are still substantially less (approximately 5 fold) that observed with Stribild. Therefore most of the potential safety advantages of TAF compared to TFV are expected to be preserved.

Table 2. Observed or Predicted TAF and TFV AUC for TAF 25 mg in Combination with Boosted Protease Inhibitors Compared to Genvoya and Stribild

	TAF AUC	TAF AUC Ratio TAF 25mg/Genvoya	TFV AUC	TFV AUC TAF 25 mg/Stribild
Genvoya	210	1.0	290	0.07
Stribild	N/A	N/A	4400	1.00
Darunavir/COBI +TAF	239	1.1	935	0.21
Lopinavir/r +TAF*	303	1.4	333	0.08
Atazanvir/r + TAF*	408	1.9	255	0.06

AUC: ng/h/mL
*Values for this row are predicted and not observed

9. Advisory Committee Meeting

An advisory committee was not convened for this NDA. This application is an FDC of previously approved drugs with established efficacy and safety profiles.

10. Pediatrics

Pediatric trials with F/TAF in children ages weeks and up are deferred and are postmarketing requirements as outlined in the approval letter.

11. Other Relevant Regulatory Issues

This application was (b) (4) There are no outstanding regulatory issues.

12. Labeling

Important labeling issues included the description of drug-drug interaction with various antiretroviral drugs and with other concomitant medications. Drug interactions with TAF are not necessarily the same as those with the other approved tenofovir prodrug, TDF. The label adequately addresses these concerns.

13. Postmarketing

There are no Postmarketing Risk Evaluation and Mitigation Strategies associated with this application and the only postmarketing requirements are those under PREA as stated in section 10 of this review.

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/s/

JEFFREY S MURRAY
04/04/2016