

Cross-Discipline Team Leader Review

NDA	208351
Submission Type	505(b)(1)
Applicant	Gilead Sciences, Inc.
Submission Date	07/01/2015
Generic Name	Emtricitabine (FTC)/Rilpivirine (RPV)/Tenofovir alafenamide (TAF)
Trade Name	ODEFSEY
Dosage Form (Strength)	FDC Tablet (FTC 200 mg / RPV 25 mg/ TAF 25 mg)
Proposed Indication	Treatment of HIV-1 infection in adults and pediatrics patients 12 years of age and older.
CDTL	Islam R. Younis, Ph.D.
Recommendation	Approval

1. Introduction

Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor (NRTI) approved (initial approval in 2003) for treatment of HIV-1 in combination with other antiretroviral agents in adults and pediatrics 0 month through 17 years of age. Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved (initial approval in 2011) in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adults and pediatric patients 12 years of age and older with HIV-1 RNA less than or equal to 100,000 copies/mL. RPV is also approved as part of the fixed dose combination COMPLERA[®] (FTC/RPV/ tenofovir disoproxil fumarate (TDF), initial approval in 2011). COMPLERA[®] is a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients 12 years of age and older with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL or who are virologically suppressed to replace their current antiretroviral treatment regimen. Tenofovir alafenamide (TAF) is a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir (TFV) approved (initial approval in 2015) as part of the fixed dose combination GENVOYA[®] (Elvitegravir (EVG)/Cobicistat (COBI)/FTC (200 mg)/TAF (10 mg)). GENVOYA[®] is indicated for treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL).

2. Background

The Applicant developed a fixed dose combination (FDC) tablet containing FTC 200 mg, RPV 25 mg, and TAF 25 mg. The proposed indication is to use the FDC as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients 12 years of age and older with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL or who are virologically suppressed to replace their current antiretroviral treatment regimen.

The Applicant is seeking approval of the current application based on the results of a single relative bioavailability (Study GS-US-366-1159) where the exposure of FTC/RPV/TAF were compared following the administration of RPV single agent and EVG/COBI/FTC/TAF FDC vs. the administration of FTC/RPV/TAF FDC. A clinical trial to evaluate the efficacy and safety of FTC/RPV/TAF FDC was not required because the efficacy and safety of RPV, FTC, and TAF was established previously.

The efficacy of RPV, FTC, and TAF in the treatment of HIV-1 infection in adults as initial therapy in those with no antiretroviral treatment history and to replace a stable antiretroviral regimen in those who are virologically-suppressed was established in trials of:

1. RPV + FTC and TDF in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (n=550) and to replace a first or second stable antiretroviral regimen containing a protease inhibitor and ritonavir in those who were virologically-suppressed and either on their first or second antiretroviral regimen with no history of virologic failure for at least 6 months with no known resistance substitutions (n=317). The virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) in these two populations was 77% at Week 96 and 89% at Week 48, respectively.
2. FTC + TAF with EVG+COBI in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (n=866) and to replace a stable antiretroviral regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions (n=799). At Week 48, 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL.

The efficacy of RPV, FTC, and TAF in the treatment of HIV-1 infection in pediatric patients aged 12 to less than 18 years old and greater than 35 kg as initial therapy in those with no antiretroviral treatment history and to replace a stable antiretroviral regimen in those who are virologically-suppressed was established in trials of antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years old with:

1. RPV and other antiretrovirals in 36 adolescents. The virologic response rate was 72% at Week 48.

2. FTC + TAF and EVG+ COBI in 23 adolescents weighing at least 35 kg. The virologic response rate was 91% at Week 24.

The efficacy of FTC + TAF combined with EVG + COBI in the treatment of HIV-1 infection in patients with creatinine clearance greater than 30 mL minute was established in 248 HIV-1 infected patients with creatinine clearance greater than 30 mL per minute. Of the 248 patients, 6 were treatment naïve and 242 were virologically suppressed (HIV-1 RNA less than 50 copies per mL for at least 6 months before switching to FTC+TAF with EVG+COBI). At Week 24, 83% (5/6) of treatment naïve and 95% (236/248) of virologically suppressed subjects had HIV-1 RNA less than 50 copies per mL. It should be noted that COMPLERA® should not be administered in patients with creatinine clearance below 50 mL per minute.

3. Chemistry, Manufacturing, and Control

The NDA is recommended for approval from CMC perspective. Satisfactory information and responses have been submitted to support the quality of the drug substances and drug product, including establishment of a post-marketing commitment (PMC) for the RPV dissolution time point. All manufacturing facilities have been determined to be in acceptable status. Please refer to the Office of Pharmaceutical Quality review dated 02/03/2016 for full details.

Drug Substance: The manufacturing and quality attributes of the all active pharmaceutical ingredient components (FTC, RPV, and TAF) of the FDC are acceptable because they were previously reviewed and approved by FDA in the cross-referenced NDAs.

Drug Product: The drug product consists of gray capsule-shaped film-coated (b) (4) tablets debossed with “GSI” on one side and “255” on the other. The tablet is produced using (b) (4) processes. The specifications include tests for appearance, identity, water, assay, degradants, uniformity, dissolution, and microbial limits. The specification is largely conventional for an immediate release solid oral dosage form and a satisfactory justification is provided. After extensive discussion the (b) (4) NMT (b) (4) % because stability data (b) (4). The degradants are toxicologically qualified at the proposed limits. The analytical methods are described in reasonable detail and have been validated and shown to be reasonably robust. Satisfactory batch analyses are provided for 12 batches of (b) (4).

Stability data support a 24 month expiration dating period with the storage statement: “Store below 30°C”. Stability data indicated an increase in TAF impurities (b) (4) and total TAF impurities with time and temperature.

Dissolution: The proposed dissolution methods for FTC and TAF components are acceptable. The biopharmaceutics review team concluded that RPV dissolution data do not support the proposed acceptance criterion of $Q = \text{(b)}_{(4)}\%$ at $\text{(b)}_{(4)}$ minutes. The provided dissolution data supported a dissolution acceptance criterion of $Q = \text{(b)}_{(4)}\%$ at 30 minutes. FDA informed the Applicant that the acceptance criterion should be revised. A teleconference between FDA and the Applicant was held on 12/3/15 to discuss the FDA recommendations and the Applicant proposed a revised dissolution acceptance criterion of $Q = \text{(b)}_{(4)}\%$ at $\text{(b)}_{(4)}$ minutes. An agreement on the acceptance criteria could not be reached. The Applicant agreed to an interim RPV dissolution specification of $Q = \text{(b)}_{(4)}\%$ at $\text{(b)}_{(4)}$ minutes and to a PMC to compare dissolution results from all commercial batches at the 30-minute and 45-minute time points. The Applicant also agreed to provide the requested information as a supplement 18 months post NDA approval.

Packaging: The tablets are packaged 30 counts in 75 mL white HDPE bottles containing $\text{(b)}_{(4)}$ of silica gel desiccant and a polyester coil. The bottles are capped with $\text{(b)}_{(4)}$ screw caps and an induction seal. The commercial in-process packaging configurations were clearly defined in Applicant's response. The Applicant also provided data to support the stability of all three actives in the given bulk configurations, as well as confirming consistency between intended commercial bulk packaging and ongoing bulk hold stability studies.

4. Nonclinical Pharmacology/Toxicology

The NDA is recommended for approval from pharmacology and toxicology perspective. Please refer to the pharmacology and toxicology review dated 11/23/2015 for full details.

All nonclinical information for the current NDA is cross-referenced to the original NDAs and INDs and no additional nonclinical toxicology information is included in the submission package. The information was deemed sufficient during the review of the referenced NDAs. The target organs of toxicity are different for the three drugs; therefore, administration of FTC, RPV and TAF in combination is unlikely to exacerbate known toxicities of the individual agents. There are no unique impurities or degradants in the FTC/RPV/TAF FDC tablets. The impurities and degradation products present in FTC, RPV, and TAF and in FTC/RPV/TAF tablets have been qualified through toxicology studies.

5. Clinical Pharmacology

The NDA is recommended for approval from clinical pharmacology perspective. Please refer to the clinical pharmacology review dated 12/01/2015 for full details.

The pivotal trial for this NDA was a randomized, open-label, single-dose, three-way, six-sequence, cross-over study which evaluated the relative bioavailability of FTC/RPV/TAF (200/25/25 mg) FDC to EVG/COBI/FTC/TAF (150/150/200/10 mg) FDC and RPV (25 mg) under fed conditions in 95 healthy subjects (Study GS-US- 366-1159). As shown in Figure 1, similar exposures of FTC, RPV, and TAF between FTC/RPV/TAF, RPV, and E/C/F/TAF were demonstrated which supports approval of FTC/RPV/TAF.

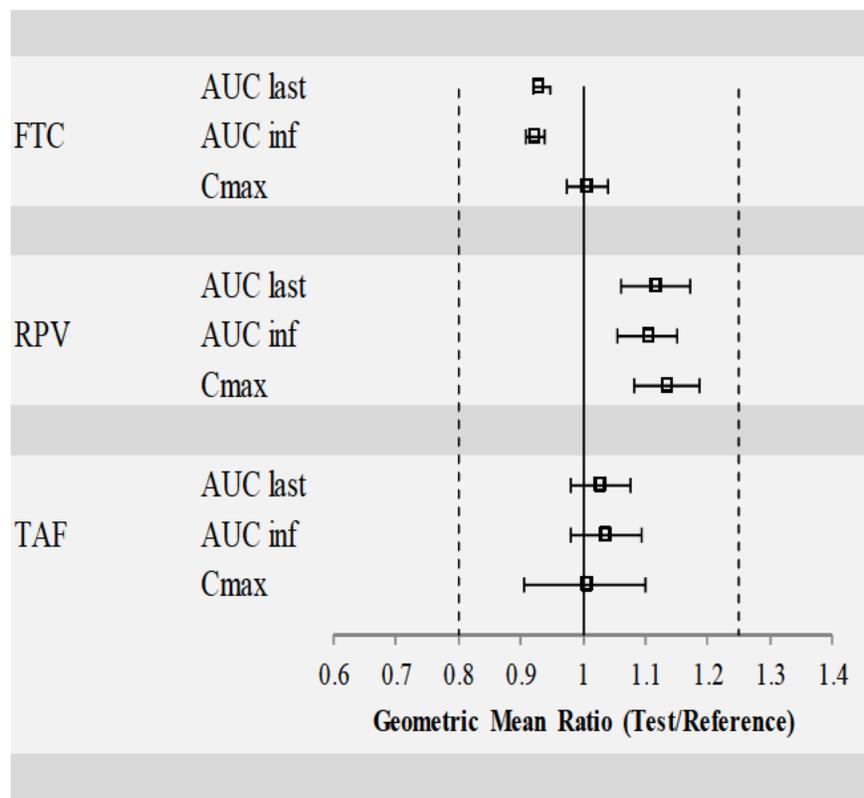


Figure 1. Statistical comparison of FTC/RPV/TAF pharmacokinetic parameters in study GS-US-366-1159. Points represent the ratio of the geometric mean (test/reference) and error bars represent the 90% confidence interval. Figure adapted from the clinical pharmacology review.

The Applicant evaluated the effect of food on the FTC/RPV/TAF FDC. As shown in Table 1 RPV and TAF AUC are significantly increased when the FDC is coadministered with food. The clinical pharmacology review team recommended that FTC/RPV/TAF should be labeled to “be taken with a meal” because low RPV exposure is associated with virologic failure and RPV efficacy trials were conducted under fed conditions. This recommendation differs from the sponsor’s recommendation of (b) (4). The clinical pharmacology review team rationale for the recommendation is that to most people the term “meal” signifies a substantial

Table 1. Effect of food on the components of FTC/RPV/TAF FDC. Table adapted from the clinical pharmacology review.

Analyte	Geometric mean AUC ratio (Fed/Fasted) (90% CI)	
	Moderate-Fat	High-Fat Meal
FTC	91 (89, 93)	88 (85, 90)
RPV	113 (103, 123)	172 (149, 199)
TAF	145 (133, 158)	153 (139, 169)

The Applicant conducted two drug-drug interaction studies as follows:

1. Study MC278-TiDP6 evaluated the drug-drug interactions between RPV and omeprazole at the clinical dose of RPV (25 mg) with RPV given 1.5 hours or 12 hours after omeprazole or with a higher RPV dose of 50 mg given 1.5 hours after omeprazole. When administered 1.5 hours after omeprazole, mean RPV AUC was decreased 63% (RPV 25 mg) and 12% (RPV 50 mg). Also, RPV administered 12 hours after omeprazole resulted in a mean RPV AUC decrease of 32%. The clinical pharmacology review team agrees with the Applicant's proposal to contraindicate the co-administration of FTC/RPV/TAF FDC and omeprazole because low RPV exposure is associated with virologic failure. This is consistent with current RPV single agent labeling which contraindicates the coadministration of omeprazole and RPV based on the findings of a prior RPV-omeprazole drug-drug interaction study that utilized a 150 mg RPV dose.
2. Study GS-US-366-1689 evaluated two-way drug interactions between the components of FTC/RPV/TAF FDC and ledipasvir/sofosbuvir (LDV/SOF). No clinically significant increases in TAF and TFV exposure were observed; other components of the study drugs were unaffected. The clinical pharmacology team agrees with the Applicant's clinical recommendation proposal of "no dose adjustment is needed when FTC/RPV/TAF FDC is coadministered with LDV/SOF".

Inspections of the clinical and bioanalytical sites for Study GS-US-366-1159 were requested and only the clinical site inspection was conducted. The Office of Study Integrity and Surveillance (OSIS) recommended accepting the bioanalytical data without an on-site inspection because the bioanalytical site had been inspected recently, relative to the timing of the inspection request, and the nature of identified issues does not warrant another inspection. Please refer to OSIS memorandum dated 08/17/2015 for full details. Clinical site inspection did not identify any significant issues and OSIS recommended accepting the clinical data from Study GS-US-366-1159. Please refer to OSIS memorandum dated 01/05/2016 for full details.

6. Clinical Microbiology

The NDA is recommended for approval from clinical virology perspective. Please refer to the clinical virology review dated 12/02/2015 for full details. The Applicant did not conduct any new clinical virology studies for this submission.

7. Clinical Efficacy and Safety

The NDA is recommended for approval from clinical perspective. Please refer to the clinical review dated 12/01/2015 for full details.

The Applicant did not conduct any new clinical efficacy trials to support this application. The approval of this application is based on the pivotal relative bioavailability study (see clinical pharmacology). There were no new safety concerns observed for the FTC/RPV/TAF FDC in the pivotal relative bioavailability study, the food effect study, and the drug-drug interaction studies. There were no deaths or serious adverse events. There was a single discontinuation due to adverse event of colitis in the drug-drug interaction study (Study GS-US-366-1689) in the combined FTC/RPV/TAF + LDV/SOF arm. The data from all studies indicates a possible association between constipation and RPV usage, including an individual with grade 2 constipation. This potential link to RPV must be tempered by the knowledge that study subjects were physically confined to the study center for the duration of the study. Their diet and activity at the center may have differed from that of their home environment.

8. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

9. Pediatrics

There are no pediatric data in the application. In the Agreed Initial Pediatric Study Plan submitted on 04/23/2015 for FTC/RPV/TAF FDC the Agency agreed with the Applicant on the following:

1. A partial waiver of the requirements to evaluate FTC/RPV/TAF FDC in pediatrics < 6 years of age weighing less than 25 mg was granted because (b) (4) and necessary studies are highly impracticable
2. Defer the development of FTC/RPV/TAF FDC in pediatrics > 6 years to < 12 years of age until because pediatric trials with RPV and TAF are currently ongoing.

10. Other Relevant Regulatory Issues

Financial disclosures were obtained for the pivotal relative bioavailability study for all of the clinical investigators and were reviewed by Dr. Tauber. All investigators reported having no disclosed financial interests/arrangements and therefore, financial disclosure information does not affect approvability of this application. Please refer to Dr. Tauber memorandum dated 02/03/2016 for full details.

11. Labeling

The proposed proprietary name ODEFSEY for FTC/RPV/TAF FDC was considered acceptable by DMEPA and DAVP. Review and discussions with the Applicant regarding of the contents of this product prescribing information (PI) are ongoing at the time of this review. DAVP recommended that the summary of essential safety and efficacy information for use of FTC/RPV/TAF FDC should be contained directly in the PI to meet the requirements of 21CFR 201.56(a)(1). DAVP recommended minimizing the reference to GENVOYA[®] PI and COMPLERA[®] PI because it may be confusing to healthcare providers to refer to different PIs and it may not be clear to healthcare providers what aspects of the other PI to review.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action: Approval

12.2 Risk Benefit Assessment: The risk-benefit profile of FTC/RPV/TAF FDC is acceptable based on the assessment of the review team. Because FTC/RPV/TAF FDC combination produced similar exposure to the RPV single agent and FTC/TAF in EVG/COBI/FTC/TAF FDC the risks and benefits of the FTC/RPV/TAF FDC is considered similar to those of the RPV single agent and FTC/TAF in EVG/COBI/FTC/TAF FDC. Efficacy and safety of FTC, RPV, and TAF were established previously in clinical trial in HIV-1 patients.

12.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies:

None

12.4 Recommendation for other Postmarketing Requirements and Commitments:

1. A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan.

2. A PMC will be issued to reach an agreed upon dissolution specifications for the RPV component of the TAF/RPV/FTC FDC.

12.5 Recommended Comments to Applicant: None

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

/s/

ISLAM R YOUNIS
02/03/2016