Bioequivalence of Two Co-formulations of Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combinations with 200/10 mg and 200/25 mg

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Abstract

Emtricitabine/tenofovir alafenamide (FTC/TAF) is the next advancement in nucleotide reverse transcriptase inhibitor (NRTI) backbone for the treatment of HIV-1 in adults. Tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir (TFV), is a preferred NRTI, but it is also associated with nephrotoxicity and reduced bone mineral density (BMD). TDF has been replaced by TAF, a novel prodrug of TFV with a unique metabolic pathway leading to >90% lower circulating plasma of TFV. Less nephrotoxicity, less BMD reduction in treatment-naïve subjects, and BMD increase in virologically suppressed patients on TAF in clinical trials. The two studies presented here were conducted in healthy subjects. Study 1472 evaluated the pharmacokinetics (PK) and bioequivalence (BE) of the components of FTC/TAF 200/10 mg fixed-dose combination (FDC) administered with elvitegravir 150 mg and cobicitabist 150 mg tablets to elvitegravir (E)cobicistat (C)/FTC (F)/TAF (150/150/200/10 mg) single-tablet regimen (STR). Study 1473 evaluated the PK and BE of the components of FTC/TAF 200/25 FDC to E/C/F/TAF STR. One-hundred and 116 subjects were randomized into the single-dose, open-label, 2-way, crossover Phase 1 Study 1472 and Study 1473, respectively; two subjects did not complete Study 1472. Serial blood samples were obtained over 144 hours after administration of each treatment, and pharmacokinetic parameters were calculated. Formulation bioequivalence was assessed by 90% confidence intervals (CIs) for the geometric least-squares mean (GLSM) ratios of pharmacokinetic parameter $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ for each component of FTC/TAF FDC to FTC and TAF administered as E/C/F/ TAF STR. The test and reference treatments were generally well tolerated. The 90% CIs for the GLSM ratios of the primary pharmacokinetic parameter $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ for test versus reference treatments were within the protocol-specified bioequivalence boundary of 80% to 125% for FTC and TAF; FTC/TAF 200/10 mg and 200/25 mg are the next advancement in NRTI backbone for the treatment of HIV-1 adults and adolescents, with an emphasis on safety while maintaining the efficacy and convenience of its predecessor.

Keywords: Bioequivalence; Tenofovir alafenamide; Emtricitabine; Pharmacokinetics; Fixed-dose combination; HIV-1; TAF

Introduction

Tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir (TFV), is the nucleotide reverse transcriptase inhibitor (NRTI) in the majority of Department of Health and Human Services (DHHS) recommended regimens for antiviral agents in HIV-1-infected adults and adolescents [1]. However, TDF is associated with nephrotoxicity and reduced bone mineral density (BMD) [1,2]. Tenofovir alafenamide (TAF) is a novel prodrug of TFV. TAF has been selected for clinical development because it has a different metabolic pathway from TDF that enhances lymphocyte delivery of TFV; this unique metabolic pathway results in 91% lower circulating plasma concentrations of TFV while maintaining similar intracellular levels of the active phosphorylated metabolite TFV-diphosphate (TFV-DP) when TAF 10 mg is administered as elvitegravir (EVG; E)cobicistat (COBI; C)/FTC/TAF (E/C/F/TAF) [3]. In a Phase I b study, there were 97% and 86% lower circulating plasma concentrations of TFV with TAF 8 mg and 25 mg, respectively, than TDF 300 mg [4]. Due to lower TFV exposure, TAF has demonstrated less nephrotoxicity, less bone mineral density (BMD) decreases in treatment-naïve patients, and BMD increases in virologically suppressed patients in pivotal trials of TAF-containing single-tablet regimen (STR) of E/C/F/TAF when compared to TDF-containing regimens. TAF has been co-formulated with FTC, referred to as F/TAF, and if approved, will allow clinicians to combine F/TAF with other antiretroviral (ARV) agents. Furthermore, a fixed-dose combination (FDC) reduces the pill burden, an important consideration to improve adherence [1].

The recommended TAF dose (10 or 25 mg) is based on whether or not the coadministered third agent has any clinically relevant effect on TAF exposures. This ensures that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg or with TAF 10 mg when administered as E/C/F/ TAF. Pharmacokinetic (PK) enhancers, like COBI and ritonavir (RTV), substantially increase TAF exposure by inhibiting intestinal p-glycoprotein-mediated efflux of TAF [5-9]. Thus, the TAF 10 mg dose is utilized with RTV/COBI-boosted regimens, and TAF 25 mg dose is utilized with unboosted regimens.

The two studies presented here were conducted to establish the bioequivalence (PK comparability) between F/TAF 200/10 mg (Study 1472) and F/TAF 200/25 mg (Study 1473) and the reference product of E/C/F/TAF, which is supported by extensive clinical safety and efficacy data. E/C/F/TAF has been approved by US and EU Regulatory Authorities and has been designated a recommended regimen for treatment-naïve and virologically suppressed individuals in the United States.

Methods

Study population

Healthy male and nonpregnant, nonlactating female subjects,

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between 18 and 45 years of age (inclusive), with a body mass index (BMI) between 19 and 30 kg/m² (inclusive), in general good health, and a creatinine clearance ≥ 70 mL/minute (using the Cockcroft-Gault formula and actual body weight) were enrolled in the F/TAF 200/10 mg (N=100) and F/TAF 200/25 mg (N=116) bioequivalence studies, respectively.

A negative serum pregnancy test was required for female subjects of childbearing potential. Screening laboratory evaluations (hematology, chemistry, and urinalysis) had to be within the normal range. Inclusion criteria included having a normal 12-lead electrocardiogram (ECG). Subjects who had a history of recurring syncope, palpitations, or recurring, unexplained dizziness; who had an implanted defibrillator or pacemaker; or who had any serious or active medical or psychiatric illness were excluded. They were also excluded if they took any prescription medications or over-the-counter medications including herbal products within 28 days of commencing study drug dosing; exceptions were vitamins, acetaminophen, ibuprofen, and/or hormonal contraceptive medications. Additionally, subjects treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months of study screening were excluded. Subjects with current alcohol or substance abuse that could potentially interfere with compliance, as judged by the investigator, were excluded. Subjects were restricted, both before and through discharge, from consuming alcohol-containing products; using nicotine-containing products; consuming grapefruit and Seville orange juice. Consuming caffeine and other methyl-xanthines-containing products were prohibited only on dosing days.

Informed consent was obtained from each subject before initiation of study procedures. The protocol was reviewed and approved by a central institutional review board (Schulman and Associates, Research Triangle Park, NC). The study was performed in accordance with the principles of the Declaration of Helsinki and adhered to the basic principles of Good Clinical Practice as outlined in the US Code of Federal Regulations (CFR) Title 21, Part 312.

Study methods

Both studies were randomized, single-dose, open-label, 2-way, crossover Phase 1 studies in healthy adults under fed conditions (moderate calorie/ moderate fat meal) after an overnight fast for at least 10 hours. In the F/TAF 200/10 mg bioequivalence study, Treatment A contained a 200 mg of FTC and 10 mg of TAF FDC tablet administered simultaneously with elvitegravir (EVG) 150 mg and cobicistat (COBI) 150 mg tablets orally; Treatment B contained a 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (EVG/COBI/FTC/TAF) STR. In the F/TAF 200/25 mg bioequivalence study, Treatment A was a F/TAF 200/25 mg FDC tablet; Treatment B was an EVG/COBI/FTC/ TAF (150/150/200/10 mg) STR.

Subjects were randomized to 1 of 2 treatment sequences (AB, BA). A single dose of study drug(s) was administered on Days 1 and 7 within 5 minutes of completing a standardized moderate fat/moderate calorie breakfast (approximately 600 calories and approximately 27% fat). Following study drug administration, subjects were restricted from food intake until after the 4-hour PK blood sampling time point. Subjects were discharged on Day 13, with a follow-up phone call on Day 21 (± 2).

Serial blood samples for PK assessments were collected at the following time points: 0 (predose), 5 minutes, 15 minutes, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, 48, 72, 96, 120, and 144 hours after administration of each treatment. The samples at the 144th hour were collected predose on Day 7. The number, frequency, and timing of blood samples were based on the concentration-time profiles of the individual drugs to assess bioequivalence accurately based on maximum concentration (Cmax) and area under the concentration-time curve (AUC).

Bioanalytic methods

Concentrations of FTC and TAF in human plasma samples were determined using fully validated high-performance liquid chromatography-tandem mass spectrometry (LC/MS/MS) bioanalytical methods. All samples were analyzed within the timeframe supported by frozen stability storage data. Briefly, the methodology for FTC and TAF was as follows: 100 µL and 50 µL of human plasma were spiked with internal standards [13C₃,15N] -emtricitabine and [H₃]-GS-7171 (tenofovir derivative), respectively. The FTC sample was then processed by protein precipitation with methanol. The TAF sample was then processed by protein precipitation with acetonitrile-formic acid. After this processing, the organic solvent was evaporated, and an aliquot of the reconstituted sample extract was injected into the LC/MS/MS system.

For each method, the results of within-run (intra-assay) and between-run (inter-assay) precision assessments were reported as the coefficients of variation, each expressed as %CV, and the results of accuracy assessments were reported as the relative error values expressed as %RE. For FTC, the calibrated range of the method was 5 to 3000 ng/mL; all %CV values were <8.6% and all %RE values were within ± 9.8% of 100%. For TAF, the calibrated range of the method was 1 to 1000 ng/mL; all %CV values were <9.6% and all %RE values were within ± 7.8% of 100%.

Safety assessments

Safety was evaluated throughout each study and included physical examination, vital sign measurement, clinical laboratory test, evaluation of adverse events (AEs), and review of concomitant medications. Treatment-emergent AEs were defined as any AEs with an onset date of on or after the date of the first dose of study drug and on or before the date of the last dose of study drug plus 30 days, or any AEs that led to premature discontinuation of study drug. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.0. The severity of AEs and laboratory abnormalities was graded according to the Gilead Sciences, Inc. (GSI) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (grades 1-4).

Pharmacokinetic analysis

The PK analysis sets for FTC and TAF included all randomized subjects who received at least 1 dose of study drug and had at least 1 plasma concentration data reported by the PK lab. Samples below the limit of quantification (BLQ) of bioanalytical assays that were taken before study drug administration were given a value of 0 to prevent overestimation of the initial AUC. For AUC, samples that are BLQ at all other time points were treated as missing data in WinNonlin. For summary statistics, values that are BLQ at postdose time points were treated as one-half the value of the lower limit of quantitation (LLOQ). Furthermore, subjects with predose concentration values >5% of the maximum observed plasma concentration of drug (Cmax) for either period were excluded from the corresponding PK analysis set.

PK parameters were estimated using standard of non-compartmental methods [Phoenix WinNonlin®, version 6.4; Certara USA, Inc., Princeton, NJ] from the plasma concentration-time data.
of FTC and TAF after administration of a single dose(s) of test and reference treatments. The primary PK parameters are area under the plasma concentration versus time curve extrapolated to infinity ($\text{AUC}_{\text{inf}}$), area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration ($\text{AUC}_{\text{last}}$), and $\text{C}_{\text{max}}$ of FTC and TAF. The following PK parameters were calculated for FTC, TAF, COBI, and EVG: $\text{AUC}_{\text{inf}}$, $\text{AUC}_{\text{last}}$, half-life ($t_{1/2}$), $\text{C}_{\text{max}}$, and time to maximum concentration ($t_{\text{max}}$).

### Statistical analysis

The primary endpoints were the PK parameters $\text{AUC}_{\text{inf}}$, $\text{AUC}_{\text{last}}$, and $\text{C}_{\text{max}}$ of FTC and TAF. Bioequivalence of FTC and TAF in the F/TAF FDC to the FTC and TAF components in E/C/F/TAF STR was concluded if the 90% confidence interval (CI) of the geometric least-squares mean (GLSM) ratio of the PK parameters for each analyte between the 2 formulations is within the boundaries of 80% and 125%.

The primary hypothesis of F/TAF’s bioequivalence to E/C/F/TAF STR was tested using a Two One-Sided Tests (TOST) method with a 5% significance level for each test. Approximately 104 evaluable subjects were estimated to conduct a TOST with 80% power for the 90% CI of the GLSM ratio of test vs. reference treatments with regard to AUC and $\text{C}_{\text{max}}$, to be contained within 0.80 and 1.25; this assumed a GLSM ratio of 1.05. If the true GLSM ratio was 1.0, the TOST with 104 evaluable subjects would have at least 98% power. A total enrollment of 116 subjects was planned for a 10% overage. SAS software (SAS Institute, Cary, North Carolina, USA) was used to perform the statistical summaries and analyses.

Subject demographic data, baseline characteristics, plasma concentrations, and PK parameters were summarized by treatment using descriptive statistics. For each analyte (FTC and TAF), the natural logarithmic transformation of PK parameters ($\text{AUC}_{\text{inf}}, \text{AUC}_{\text{last}}, \text{C}_{\text{max}}$) were compared between the test and reference treatments by an analysis of variance (ANOVA) using a mixed-effects model with treatment, period, and sequence as fixed effects and subject within sequence as a random effect. SAS’ PROC MIXED (SAS Institute, Cary, NC) code was used to calculate the treatment comparisons and corresponding 90% CIs. The safety analysis set included all randomized subjects who received at least 1 dose of study drug.

### Results

#### Subject demographics and disposition

In Study 1472, evaluating F/TAF 200/10 mg, there were 100 subjects randomized and received at least 1 dose of study drug, and there were 116 subjects in Study 1473, evaluating F/TAF 200/25 mg. The majority of subjects was male (52% and 66%) and white (85% and 53%) in both studies, respectively. At baseline, the median age was 32 years (range: 18-45) and 33 (18-45), median BMI was 26.4 kg/m$^2$ (interquartile range [IQR]: 23.5-28.1) and 25.9 (24.0-27.9), and median creatinine clearance by Cockcroft-Gault method was 135.4 mL/min (IQR: 116.8-150.2) and 25.9 (24.0-27.9), and median creatinine clearance 18-45) and 33 (18-45), median BMI was 26.4 kg/m$^2$.

#### Pharmacokinetics

In both bioequivalence studies, the PK analysis sets of plasma FTC and TAF included all subjects who were randomized and received at least 1 dose of study drug. Mean (SD) FTC and TAF plasma concentration-time profiles are presented in Figure 1 (F/TAF 200/10 mg) and Figure 2 (F/TAF 200/25 mg). In both studies, the plasma concentrations of FTC and TAF were similar after administration of the test or reference treatment throughout the monitoring period (Treatments A and B [144 hours]). Plasma PK parameters for FTC and TAF after administration of the test or reference treatment are presented in Table 1.

The statistical analyses of FTC and TAF PK parameters between test and reference treatments are presented in Table 2. The 90% CIs for the GLSM ratios of the primary PK parameters $\text{AUC}_{\text{inf}}, \text{AUC}_{\text{last}}, \text{C}_{\text{max}}$ for test versus reference treatments were within the protocol-specified bioequivalence boundary of 80% to 125% for FTC and TAF, in both studies. FTC and TAF component of F/TAF FDCs, at both dose strengths, were bioequivalence to FTC and TAF component of E/C/F/TAF.
Safety

In both bioequivalence studies, all treatments were generally well tolerated by the study subjects. There were no deaths or Grade 4 AEs reported in either study. The one serious Grade 3 AE of peritoneal hemorrhage was reported with F/TAF 200/25 mg and considered by the investigator as not related to the study drug. No laboratory abnormalities were considered clinically significant in either study. In the F/TAF 200/25 mg bioequivalence Study 1473, one subject had Grade 4 lipase, but did not exhibit clinical symptoms. In both bioequivalence studies, no clinically relevant changes in median values for hematology and chemistry parameters were observed.

In the F/TAF 200/10 mg bioequivalence Study 1472, the majority of AEs were Grade 1 in severity with one case of Grade 3 arthralgia, no Grade 4 AEs, and only one subject discontinued therapy due to a treatment-related AE - Grade 2 macular rash with E/C/F/TAF. Treatment-related Grade 2 AEs reported by more than 1 subject consisted of only headache - 3 subjects with F/TAF 200/10 mg+EVG+COBI and 4 subjects with E/C/F/TAF. The most frequently reported AEs (>2.5%) with F/TAF 200/10 mg+EVG+COBI were headache and nausea (9.1% each), diarrhea (4.0%); pruritus, papular rash, feeling hot, and anxiety (3.0% each) and with E/C/F/TAF were headache (10.0%) and nausea (6.0%).

In the F/TAF 200/25 mg bioequivalence Study 1473, the majority of AEs were Grade 1 in severity with no Grade 4 AEs reported. The only treatment-related Grade 2 AEs reported was nausea and vomiting in 1 subject with E/C/F/TAF. The most frequently reported AEs with F/TAF 200/25 mg were nausea (4.3%), constipation, and headache (2.6% each) and with E/C/F/TAF were nausea (5.2%), vomiting, and headache (2.6% each).

Discussion

The results of the bioequivalence Study 1472 demonstrate that

Table 1: Summary of FTC and TAF pharmacokinetic parameters.

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<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt; (ng·h/mL)</td>
<td>10535.1 (27.0)</td>
<td>10294.4 (15.8)</td>
<td>351.8 (31.0)</td>
<td>354.1 (32.9)</td>
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<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt; (ng·h/mL)</td>
<td>10159.2 (17.2)</td>
<td>10086.8 (15.9)</td>
<td>336.6 (33.9)</td>
<td>340.2 (33.8)</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1660.8 (20.6)</td>
<td>1662.6 (19.1)</td>
<td>301.6 (48.8)</td>
<td>310.3 (48.7)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>18.1 (46.8)</td>
<td>19.1 (57.0)</td>
<td>0.41 (39.5)</td>
<td>0.43 (35.4)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.0 (1.5, 3.0)</td>
<td>2.0 (1.5, 3.0)</td>
<td>1.5 (1.0, 1.5)</td>
<td>1.0 (0.8, 1.0)</td>
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AUC<sub>inf</sub> = Area Under the Plasma Concentration Versus Time Curve Extrapolated to Infinity, AUC<sub>last</sub> = Area Under the Plasma Concentration Versus Time Curve from Time 0 to the Last Quantifiable Concentration, C<sub>max</sub> = Maximum Observed Plasma Concentration of Drug, t<sub>1/2</sub> = Elimination Half-Life of the Drug in Plasma, T<sub>max</sub> = Time to Maximum Concentration.

| n=80 |
| n=84 |
| n=95 |
| f=97 |
under fed conditions F/TAF 200/10 mg administered simultaneously with EVG and COBI is bioequivalent to E/C/F/TAF STR. Furthermore, the results of the bioequivalence Study 1473 demonstrate that under fed conditions F/TAF 200/25 mg, without a PK enhancer, is bioequivalent to the FTC and TAF components of E/C/F/TAF STR that includes a PK enhancer. The selection of the TAF dose (10 or 25 mg) is based on whether or not the third ARV agent requires a PK enhancer (i.e., COBI or RTV) that results in increased TAF absorption due to the inhibition of intestinal p-glycoprotein-mediated efflux of TAF [9]. Specifically, F/TAF 200/25 mg is recommended with third agents that do not have clinically relevant effect on TAF exposure (e.g., efavirenz [EFV], rilpivirine [RPV], dolutegravir [DTG]). F/TAF 200/10 mg is recommended with third agents that substantially increase TAF exposure (e.g., atazanavir+RTV, lopinavir/RTV, EVG+COBI [as E/C/F/TAF]). The development of these two once daily F/TAF FDCs is supported by these critical bioequivalence findings as well as the long intracellular half-lives of FTC-triphosphate (~39 hours) and TFV-DP (~150 hours) [10,11].

Formal bioequivalence evaluations are an essential part of the regulatory approval strategy in the development of FDCs when supportive clinical trial data of the components exists. This strategy expedites the approval process since clinical evaluations with the FDC can continue after the submission of the marketing application to the proper regulatory authorities. To date, 3 of the 4 available antiretroviral STRs (EFV/FTC/TDF [Atripla], RPV/FTC/TDF [Complera/Eviplera], and DTG/lamivudine/abacavir [Triumeq]) have been approved by regulatory authorities for the treatment of HIV-1 infection based on such a bioequivalence strategy that compared the PK of the test coformulation to the PK of the approved antiretroviral components [12-14]. The two bioequivalence studies presented here are unique in that they bridge the safety and efficacy data of the approved E/C/F/TAF STR, evaluated in numerous registrational trials, to the NRTI components of the FDC, F/TAF, at two different doses.

The E/C/F/TAF clinical development program is the largest to date for an antiretroviral, consisting of 23 clinical trials with >3000 subjects, and has led to the approval of E/C/F/TAF in November 2015 by the US Food and Drug Administration. In the pooled analysis of such a bioequivalence strategy that compared the PK of the test coformulation to the PK of the approved antiretroviral components [12-14]. The two bioequivalence studies presented here are unique in that they bridge the safety and efficacy data of the approved E/C/F/TAF STR, evaluated in numerous registrational trials, to the NRTI components of the FDC, F/TAF, at two different doses.

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