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Bioequivalence of the Rilpivirine/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen

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Abstract

Rilpivirine/emtricitabine/tenofovir alafenamide (RPV/FTC/TAF) is the next advancement in once-daily antiretroviral single-tablet regimen (STR) for the treatment of HIV-1 in adults. Tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir (TFV), is a preferred nucleotide reverse transcriptase inhibitor, but it is also associated with nephrotoxicity and reduced bone mineral density (BMD). TDF has been replaced by tenofovir alafenamide (TAF), a novel, oral prodrug of TFV with a different metabolic pathway leading to 91% lower circulating plasma concentrations of TFV. Differences with TAF have resulted in less nephrotoxicity and less reduction or increase in BMD in clinical trials. This study evaluated the pharmacokinetics and bioequivalence of the components of RPV/FTC/TAF (25/200/25 mg) STR to the references of RPV (25 mg) single tablet and elvitegravir (E)/cobicistat (C)/FTC (F)/TAF (150/150/200/10 mg) in healthy subjects. Ninety-six subjects were randomized in a single-dose, open-label, 3-way, 6-sequence, crossover Phase 1 study; two subjects did not complete the study. Serial blood samples were obtained over 336 hours for RPV/FTC/TAF and RPV and over 144 hours for E/C/F/TAF following oral 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 RPV/FTC/TAF compared to RPV and E/C/F/TAF. The test and reference treatments administered under fed conditions 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, RPV, and TAF. RPV/FTC/TAF is the next advancement in once-daily STR for the treatment of HIV-1 in adults. Once approved, it will add to the armamentarium of STRs available for efficacious and safe therapies.

Keywords: Bioequivalence; Rilpivirine; Tenofovir alafenamide; Emtricitabine; HIV-1; Pharmacokinetics; Single-tablet regimen

Introduction

The Department of Health and Human Services (DHHS) guidelines for use of antiretroviral agents in HIV-1-infected adults and adolescents has designated the combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) as a preferred nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbone [1]. However, safety concerns with TDF, an oral prodrug of tenofovir (TFV), include nephrotoxicity and reduced bone mineral density (BMD) [2]. Advances in antiretroviral therapy (ART) have resulted in increased life expectancies for HIV-infected patients and a refocused attention on the safety profile of ART as patients age given the increased prevalence of comorbidities at a younger age than their HIV-negative counterparts [3]. Tenofovir alafenamide (TAF), a novel, oral prodrug of TFV, has a different metabolic pathway from TDF that enhances lymphocyte delivery of TFV, resulting in 91% lower circulating plasma concentrations of TFV while maintaining similar intracellular levels of the active phosphorylated metabolite TFV-diphosphate (TFV-DP) [4]. These differences seen with TAF have translated into reduced risk of nephrotoxicity and smaller decrease and even increase of BMD in pivotal trials of the TAF-containing single-tablet regimen (STR) of elvitegravir (EVG; E)/cobicistat (COBI; C)/FTC (F)/TAF (E/C/F/TAF) compared to E/C/F/TDF [4-7].

Rilpivirine (RPV)/FTC/TAF STR is a fixed-dose combination (FDC) product of three antiretrovirals, RPV 25mg, FTC 200 mg, and TAF 25 mg. RPV/FTC/TAF represents the next advancement in non-nucleoside reverse transcriptase inhibitor (NNRTI)-based STRs with expected improvements in renal and bone safety resulting from replacing the TDF component with the new TFV prodrug, TAF, while maintaining the adherence-enhancing convenience of one pill, once daily dosing.

The development of FDCs can be supported by formal bioequivalence evaluations when substantial clinical data for the FDC components exist. The bioequivalence strategy, which compares the pharmacokinetics (PK) of the test coformulation to the PK of the approved antiretroviral components, expedites the approval process since clinical evaluations with the STRs may not be necessary at the time of filing given the ability to extrapolate to often robust and long-term safety and efficacy data. To date, 3 of the 5 available antiretroviral STRs (efavirenz [EFV]/FTC/TDF [Atripla], RPV/FTC/TDF [Complera/Eviplera], and dolutegravir/lamivudine/abacavir [Triumeq]) have been approved by regulatory authorities for the treatment of HIV-1 infection based on a bioequivalence strategy [8-10]. As such, this study was conducted to establish the bioequivalence (PK comparability) between components of the RPV/FTC/TAF STR and the reference products for each component that are supported by clinical safety and efficacy data (RPV and E/C/F/TAF).

Methods

Study population

A total of 96 HIV-negative male and nonpregnant, nonlactating female subjects, between 18 and 45 years of age (inclusive), with a body mass index (BMI) between 19 and 30 kg/m^2 (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 bioequivalence study.

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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; and consuming grapefruit juice, grapefruits, and Seville orange juice. Consuming caffeine and other methyl-xanthines-containing products are 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 design

This was a randomized, single-dose, open-label, 3-way, 6-sequence, crossover Phase 1 study in healthy adults under fed conditions due to RPV's food requirement (moderate fat meal after at least a 10-hour fasting period). Treatment A contained 25 mg of RPV, 200 mg of FTC, and 25 mg of TAF (RPV/FTC/TAF) STR. Treatment B was a 25 mg tablet of RPV (Edurant). Treatment C contained 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF as a STR (E/C/F/TAF). The duration of the study was either 35 days or 43 days depending on the subject's sequence and included 3 dosing periods. Period 1 and 2 doses were followed by a 14-day washout. Following period 3 dosing, subjects received a follow-up phone call 7 (± 2) days after discharge from the study clinic.

Subjects were randomized to 1 of 6 treatment sequences (ABC [1], ACB [2], BAC [3], BCA [4], CAB [5], and CBA [6]) as described in Table 1. Subjects on treatment sequences 1 and 3 were discharged on Day 35 while subjects on treatment sequences 2, 4, 5, and 6 ending with RPV-based treatment were discharged on Day 43. A single dose of study drug was administered on Days 1, 15, and 29 within 5 minutes of completing a standardized breakfast (approximately 600 calories and approximately 27% fat). Following study drug administration, subjects were restricted from food intake until after the 4-hour pharmacokinetic blood sampling time point. For Treatment A (RPV/FTC/TAF), Treatment B (RPV), and Treatment C (E/C/F/TAF) serial blood samples for PK assessments were collected at the following time points: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours after administration of the treatment. For Treatment A (RPV/FTC/TAF) and Treatment B (RPV), serial blood samples were also collected at the following time points: 168, 192, 216, 240, 264, 288, 312, and 336 hours after administration. Plasma PK sampling occurred over 14 days after dosing for RPV-based treatments to fully characterize the drug components due to RPV's long half-life of ~50 hours [11].

Bioanalytic methods

Concentrations of RPV, FTC, and TAF in human plasma samples were determined using fully validated high-performance liquid chromatography-tandem mass spectroscopy (LC/MS/MS) bioanalytical methods. All samples were analyzed within the timeframe supported by frozen stability storage data. Briefly, the methodology for RPV, FTC, and TAF was as follows: 50 µL, 100 µL, and 50 µL of human plasma were spiked with internal standards [$^{2}H_{6}$]-rilpivirine; [$^{13}C_{1}$],[$^{15}N_{2}$]-emtricitabine; and [$^{2}H_{7}$]-GS-7171 (tenofovir derivative), respectively. The RPV sample was then processed by liquid-liquid extraction with methyl *tert*-butyl ether. 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 RPV, the calibrated range of the method was 1 to 500 ng/mL; all %CV values were <11% and %RE values were within ± 6.6% of 100%. For FTC, the calibrated range of the method was 5 to 3000 ng/mL; all %CV values were <13.6% and all % RE values were within ± 7.3% 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 the study and included physical examination, vital sign measurement, clinical laboratory tests, evaluation of adverse events (AEs), and review of concomitant medications. Treatment-emergent AEs were defined as any AEs with an onset date on or after the study drug start date and up to 30 days after the permanent discontinuation of study drug. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.1. 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, RPV, and TAF included all randomized subjects who received at least 1 dose of study drug and had at least 1 plasma concentration data point for each analyte. The sample at the 336th hour for Treatments A and B before Days 15 and 29 served as the time 0 (predose) sample for these days. Samples below the limit of quantitation (BLQ) of bioanalytical assays that were taken before study drug administration were given a value of 0 to prevent overestimation of the initial under the plasma concentration-time curve (AUC). 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). For AUC, samples that are BLQ at all other time points were treated as missing data in WinNonlin. Furthermore, subjects with predose concentration values >5% of the maximum observed plasma concentration of drug (C_{max}) for any period were excluded from the corresponding PK analysis set.

Pharmacokinetic parameters were estimated using standard of noncompartmental methods [Phoenix WinNonlin®, version 6.4.0; Certara USA, Inc., Princeton, NJ] from the plasma concentration-time data of the three treatments. The primary PK parameters are area under the plasma concentration versus time curve extrapolated to infinity (AUC_{inf}), area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration (AUC_{last}), and C_{max} of FTC, RPV, and TAF. The following PK parameters were calculated for FTC, RPV, TAF, COBI, and EVG: AUC_{inf}, AUC_{last}, C_{max}, time to maximum concentration (T_{max}), and terminal elimination half-life of the drug in plasma ($t_{1/2}$).

Statistical analysis

The primary endpoints were the PK parameters AUC_{last}, AUC_{inf}, and C_{max} of RPV, FTC, and TAF. Bioequivalence of the test (RPV/FTC/TAF) and reference treatments was concluded if the 90% confidence interval (CI) of the geometric least-squares mean (GLSM) ratio of the PK parameters for each analyte is within the boundaries of 80% and 125%.

The primary hypothesis of RPV/FTC/TAF's bioequivalence to E/C/F/TAF STR and RPV (Edurant) tablet was tested using a Two One-Sided Tests (TOST) method with a 5% significance level for each test. Approximately 78 evaluable subjects or 13 evaluable subjects per sequence 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 C_{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 78 evaluable subjects would have at least 94% power. A total of 96 subjects or 16 subjects per sequence were enrolled for a 20% 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, RPV, TAF), the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, and C_{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, and safety data were collected starting on the date of the first dose of study drug through 30 days after the last dose of study drug. Safety data (including AEs, laboratory data, and vital signs) were summarized by treatment and the incidence of graded AEs and laboratory abnormalities calculated.

Results

Subject demographics and disposition

A total of 96 subjects were randomized and received at least 1 dose of study drug. Of the 96 subjects, most were male (71.9%) and white (68.8%). At baseline, the median age was 32 years (range of 19 to 45 years), median [interquartile range (IQR)] BMI was 26.4 kg/m^2 (23.8-28.3), and median (IQR) creatinine clearance by Cockcroft-Gault method was 120.5 mL/min (106.2-137.2) mL/min. Two subjects did not complete the study: 1 subject did not complete study drug dosing and withdrew consent, and 1 subject completed study drug dosing and withdrew consent.

Pharmacokinetics

The PK analysis sets for FTC and TAF included all 96 subjects while 95 subjects were included in the RPV PK analysis set. Mean (SD) RPV, FTC and TAF plasma concentration-time profiles are presented in Figure 1 (A-C, respectively). The plasma concentrations of FTC, RPV, and TAF were similar after administration of the test or reference treatment throughout the monitoring period (Treatments A and B [336 hours], Treatment C [144 hours]). Plasma PK parameters for FTC, RPV, and TAF after administration of the test or reference treatment are presented in Table 2.

FTC and TAF administered as RPV/FTC/TAF (25/200/25 mg) STR met the primary endpoints of the study and demonstrated bioequivalence to E/C/F/TAF (150/150/200/10 mg) STR under fed conditions (moderate fat). RPV administered as RPV/FTC/TAF STR also demonstrated bioequivalence to RPV 25 mg (Edurant) tablet under fed conditions. The 90% CIs for the GLSM ratios of the primary PK parameters 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, RPV, and TAF. FTC and TAF administered as

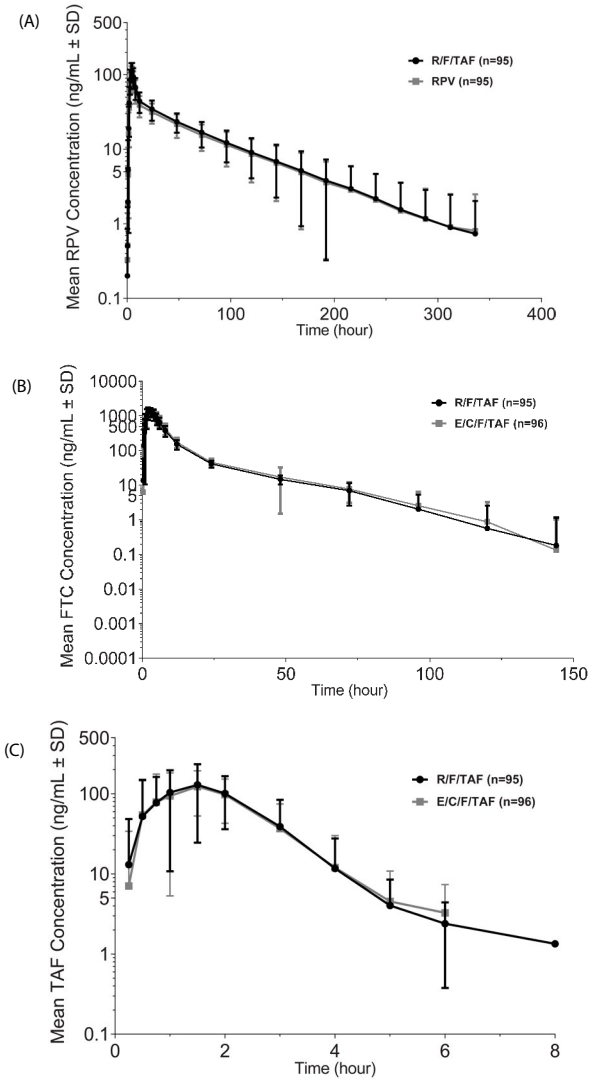

Figure 1A-1C: Mean (SD) RPV, FTC and TAF plasma concentration-time profiles are presented.

Treatment Sequence	Day 1	Day 2-14	Day 15	Day 16-28	Day 29	Discharge
1	RPV/FTC/TAF	Washout	RPV	Washout	E/C/F/TAF	Day 35
2	RPV/FTC/TAF		E/C/F/TAF		RPV	Day 43
3	RPV		RPV/FTC/TAF		E/C/F/TAF	Day 35
4	RPV		E/C/F/TAF		RPV/FTC/TAF	Day 43
5	E/C/F/TAF		RPV/FTC/TAF		RPV	Day 43
6	E/C/F/TAF		RPV		RPV/FTC/TAF	Day 43

Table 1: Summary of treatment sequences.

	FTC		RPV		TAF	
PK Parameter[a]	Test: RPV/FTC/TAF (N=95)	Reference: E/C/F/TAF (N=96)	Test: RPV/FTC/ TAF (N=95)	Reference: RPV (N=95)	Test: RPV/FTC/TAF (N=95)	Reference: E/C/F/TAF (N=96)
AUC_{last} (ng•h/mL)	9381.9 (21.7)	10159.4 (21.5)	3698.6 (34.9)	3373.4 (40.0)	250.0 (43.4)	238.4 (36.5)
AUC_{inf} (ng•h/mL)	9603.2 (21.6)	10387.1 (21.5)	3843.1 (36.2)	3540.7 (43.0)	263.6 (42.0)	247.4 (36.1)
$t_{1/2}$ (h)	18.71 (15.05, 25.27)	18.90 (15.89, 26.43)	51.65 (36.83, 66.88)	52.51 (39.29, 66.79)	0.42 (0.39, 0.49)	0.41 (0.37, 0.48)
C_{max} (ng/mL)	1608.6 (26.5)	1583.8 (23.8)	121.4 (26.1)	108.0 (28.7)	198.0 (57.7)	191.5 (48.2)
T_{max} (h)	2.00 (1.50, 3.00)	2.00 (2.00, 3.00)	4.00 (4.00, 5.00)	4.00 (4.00, 5.00)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)

a. Data are mean (%CV) except for T_{max} and $t_{1/2}$, which are reported as median (first quartile, third quartile)

Table 2: Summary of FTC, RPV, and TAF pharmacokinetic parameters.

	FTC		RPV		TAF	
	GLSM Ratio (Test/ Reference) (%)	90% CI (%)	GLSM Ratio (Test/ Reference) (%)	90% CI (%)	GLSM Ratio (Test/ Reference) (%)	90% CI (%)
AUC_{last} (ng•h/mL)	92.2	90.8, 93.7	111.7	106.3, 117.4	102.9	98.2, 107.8
AUC_{inf} (ng•h/mL)	92.4	90.9, 93.8	110.5	105.8, 115.4	103.9	98.3, 109.7
C_{max} (ng/mL)	100.8	97.5, 104.2	113.5	108.4, 118.9	100.8	91.6, 110.9

Table 3: Statistical comparisons of FTC, RPV, and TAF PK parameters for test vs. reference treatments.

RPV/FTC/TAF and E/C/F/TAF had similar median T_{max} and $t_{1/2}$ values. Rilpivirine administered as RPV/FTC/TAF and RPV (Edurant) tablet also had similar median T_{max} and $t_{1/2}$ values. The statistical analyses of FTC, RPV, and TAF PK parameters between test and reference treatments are presented in Table 3.

Safety

All treatments were generally well tolerated by the study subjects. All AEs were Grade 1 in severity. The most frequently reported AEs were constipation (9.4%), nausea, and headache (6.3% each). Treatment-related AEs included nausea and vomiting (4 subjects each) and headache (1 subject) with E/C/F/TAF, and nausea (1 subject) with RPV. No treatment-related AEs were reported with RPV/FTC/TAF. Overall, no deaths or serious AEs were reported, and no AEs led to premature study drug discontinuation.

No laboratory abnormality was considered clinically significant. Five of eight subjects with occult blood on urinalysis had confirmed menses and no events were deemed clinically significant. One subject had Grade 3 amylase and Grade 4 lipase, but did not exhibit clinical symptoms. No clinically relevant changes in median values for hematology and chemistry parameters were observed. No clinically relevant changes in vital sign measurements were observed. No pregnancies were reported during the study.

Discussion

The results of this study demonstrate the bioequivalence of RPV/FTC/TAF STR to the reference RPV (Edurant) tablet and E/C/F/TAF STR under fed conditions. The reference of E/C/F/TAF STR was used for the F/TAF components. While this reference contains additional antiretrovirals (EVG and COBI), it allows for the extrapolation to the multiple pivotal registrational trials with E/C/F/TAF that already establish the safety and efficacy of TAF in combination with other ARVs in HIV-1 infected patients. Given this study found the plasma tenofovir alafenamide exposures were bioequivalent for F/TAF 200/25 mg in the unboosted regimen of RPV/FTC/TAF compared to F/TAF 200/10 mg in boosted EVG and COBI regimen (250 vs. 238 ng·h/mL), the RPV/FTC/TAF STR would be expected to have a > 90% decrease in plasma tenofovir exposure similar to that reported in the pooled Phase 3 treatment-naïve studies of E/C/F/TAF [4]. This significant reduction in plasma tenofovir exposures is felt to explain the reduced off-target effects of tenofovir on the bone and kidneys observed in the clinical trials of TAF. The reference for the RPV component was RPV (Edurant) tablet to extrapolate to the registrational RPV studies and Phase 3b studies of RPV/FTC/TDF STR, which established the safety and efficacy of RPV in HIV-1 infected patients.

In the pooled analysis of two randomized, double-blind, phase 3, non-inferiority studies in treatment-naïve, HIV-infected adults, E/C/F/TAF not only demonstrated non-inferior efficacy to E/C/F/TDF at Weeks 48 and 96, but also had significantly less proteinuria, no discontinuations due to renal adverse events (AEs), and significantly less decrease in spine and hip BMD [4,12]. Similarly, in two phase 3 studies of virologically suppressed adults who switched off other antiretroviral regimens, E/C/F/TAF maintained high rates of virologic suppression at Week 48 and resulted in significant improvement in proteinuria, no cases of proximal renal tubulopathy or Fanconi syndrome, and increases in spine and hip BMD [5,6]. Notably, E/C/F/TAF also can be safely administered in patients with mild-moderate renal impairment, defined as an estimated glomerular filtration rate (eGFR) of 30-69 mL/min, whereas TDF-containing STRs cannot be administered in patients with eGFR > 50 mL/min due to the need to dose adjust TDF in renal impairment [2].

The safety and efficacy of the RPV component of this new TAF-based STR has been established in studies of RPV as an individual antiretroviral (Edurant) given with 2 NRTIs and as an STR coformulated with FTC/TDF (Complera/Eviplera). Three randomized, phase 3/3b studies have demonstrated RPV+2 NRTIs and RPV/FTC/TDF STR to have non-inferior efficacy in treatment-naïve, HIV-1-infected adults compared to EFV + 2 NRTIs and EFV/FTC/TDF STR (Atripla) at Weeks 48 and 96 [13-17]. Based on the ECHO and THRIVE data, RPV-based regimens are indicated for treatment-naïve HIV-1 patients with HIV-1 RNA ≤ 100,000 copies/mL [11,18]. RPV/FTC/TDF STR maintained high rates of virologic suppression through Week 48 in virologically-suppressed patients (HIV-1 RNA<50 copies/mL for ≥ 6 months) switching from ritonavir-boosted PI-based regimens or EFV/FTC/TDF who had no history of virologic failure and were sensitive to all components of the STR [19,20]. RPV/FTC/TDF STR was well tolerated with ≤ 2.5% of treatment-naïve or virologically suppressed adults discontinuing due to AEs through Week 48 [16,19]. RPV does not require dose adjustment in patients with mild or moderate renal impairment [11,18].

A survey of HIV-infected patients revealed that the top HIV regimen attributes that impact adherence in descending order are: 1) total pills per day, 2) dosing frequency, 3) adverse effects, 4) diet restrictions, 5) pill size, 6-9) monthly number of refills, copayments, prescriptions, medication bottles, and 10) requirement of bedtime dosing [21]. The RPV/FTC/TAF STR effectively addresses 9 of the 10 regimen attributes contributing to adherence, with the exception being the requirement to take it with food. RPV/FTC/TAF STR has the flexibility of being dosed with food any time during the day. The long plasma (RPV ~50 hours) and intracellular (FTC ~39 hours and TFV-DP ~150 hours) half-lives supported the development of a once daily single-tablet regimen of RPV/FTC/TAF [11,22,23]. STRs provide patients with convenient regimens that improve adherence and eliminate selective non-adherence, and consequently, may lead to improved long-term virological suppression. When approved by Regulatory Authorities, RPV/FTC/TAF will be the smallest commercially available STR measuring approximately 15.4 mm x 7.3 mm x 5.9 mm, which provides an advantage over other STRs for those patients where pill size is a concern.

The third most important attribute impacting adherence in the survey was the occurrence of adverse events. In addition to the differences in adverse events between TDF and TAF, RPV/FTC/TAF may benefit from RPV's tolerability profile compared to EFV [13-20,24]. RPV-based STRs have the additional advantages of minimal drug interactions compared to RTV- or COBI-boosted regimens and approximately 5 years of clinical experience with RPV [1,11].

In conclusion, RPV/FTC/TAF STR is bioequivalent to its references, RPV (Edurant) tablet and E/C/F/TAF STR. Importantly, the safety and efficacy data from the registrational trials of RPV and E/C/F/TAF, as well as the phase 3b clinical trials with RPV/FTC/TDF, can be extrapolated to RPV/FTC/TAF STR. This bioequivalence study also demonstrated that the RPV/FTC/TAF STR provides therapeutic plasma concentrations of its component antiretroviral agents, which was the basis for initiating 2 on-going Phase 3 safety and efficacy studies of RPV/FTC/TAF to further support its clinical use [clinicaltrials.gov NCT02345226 and NCT02345252]. It is anticipated that these BE results will support the registration of the RPV/FTC/TAF STR to add to the armamentarium of STRs available for efficacious, safe, convenient, and well-tolerated therapies for the treatment of HIV-1 infection.

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