# Pharmacokinetics and Bioavailability of an Integrase and Novel Pharmacoenhancer-Containing Single-Tablet Fixed-Dose Combination Regimen for the Treatment of HIV

*Polina German, PharmD, David Warren, MD, Steve West, MSPH, James Hui, PhD, and Brian P. Kearney, PharmD*

**Objective:** This study evaluated the relative bioavailability and pharmacokinetics of elvitegravir (EVG), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and a investigational pharmacoenhancer, cobicistat (GS-9350, COBI) coformulated as a fixed-dose combination tablet (FDC) compared with ritonavir-boosted EVG and FTC + TDF in healthy subjects.

**Methods:** Subjects were randomized to 1 of 2 sequences. All treatments were administered in the morning for 10 days with food, separated by a 2-day washout. Blood samples were collected over 24 hours with the last dose of each treatment.

**Results:** Forty-four subjects enrolled, 42 subjects completed all periods. All study treatments were generally well tolerated. Relative to ritonavir-boosted EVG, the geometric least-squares means ratios (GMR) [90% confidence interval (CI)] for EVG area under plasma concentration–time curve from time zero until the end of the dosing interval $(AUC)_{tau}$, maximum concentration ($C_{max}$), and trough concentration ($C_{tau}$) were 118 (110 to 126), 108 (100 to 116), and 110 (95.3 to 127), respectively, with EVG/COBI 150 mg/FTC/TDF. Relative to FTC + TDF, FTC GMR, and 90% CI were 127 (115 to 140) for $AUC_{tau}$, 121 (107 to 137) for $C_{max}$, and 126 (118 to 136) for $C_{tau}$; tenofovir (TFV) GMR and 90% CI were 118 (114 to 122), 130 (122 to 138), and 124 (119 to 129) for $AUC_{tau}$, $C_{max}$, and $C_{tau}$, respectively, with EVG/COBI 150 mg/FTC/TDF.

**Conclusions:** Fixed-dose combination tablet containing COBI 150 mg resulted in desired high EVG $C_{tau}$ concentrations and clinically equivalent tenofovir and FTC exposures relative to currently approved individual agents and was thus selected for subsequent evaluation.

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Correspondence to: Polina German, PharmD, Gilead Sciences, Inc, 333 Lakeside Drive, Foster City, CA 94404 (e-mail: polina.german@gilead.com).



**Key Words:** elvitegravir, fixed-dose combination, integrase inhibitor, pharmacokinetics, pharmacoenhancer

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## INTRODUCTION

Elvitegravir (EVG) is an investigational HIV integrase inhibitor that selectively inhibits the strand-transfer step of the integration process of viral DNA into host chromosomal DNA.[1] In a 10-day monotherapy study, EVG demonstrated potent antiretroviral activity (mean reductions up to 2 $\log_{10}$ copies/mL) in integrase-naive patients, with exposure-dependent activity described by its plasma trough concentrations ($C_{tau}$).[2]

EVG undergoes metabolism predominantly by cytochrome P450 CYP3A enzymes in the intestine and liver and secondarily by glucuronidation (uridine glucuronosyl 1A1 and 1A3) (data on file at Gilead Sciences, Foster City, CA). In clinical studies, EVG has been coadministered with a low subtherapeutic dose of ritonavir (100 mg), a potent, mechanism-based inhibitor of CYP3A. This results in a marked, 20-fold increased (boosted) systemic EVG exposures area under plasma concentration–time curve from time zero until the end of the dosing interval ($AUC_{tau}$) via increased systemic bioavailability and reduced clearance that provides a robust pharmacokinetic profile allowing for once-daily dosing.[3]

COBI is a new chemical entity in development for use as a pharmacoenhancer (booster) to increase the systemic exposure levels of coadministered agents metabolized by CYP3A enzymes, including EVG and/or HIV protease inhibitors that also require boosting.

Tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) are preferred, once-daily nucleoside (once-daily nucleotide) reverse transcriptase inhibitors (NRTI or N(t)RTI) recommended for initial ARV therapy for HIV-1 infection in adults.[4]

The objective of this study was to evaluate the pharmacokinetics and relative bioavailability of a once-daily, single-tablet antiretroviral regimen of EVG/FTC/tenofovir disoproxil fumarate (TDF)/GS-9350 to identify the dose of

COBI within this FDC tablet that achieves target antiretroviral drug exposures, in particular high $C_{tau}$ of EVG (multiple folds above protein-adjusted $IC_{95}$ against HIV-1 integrase). This study also evaluated tenofovir and FTC exposures as the FDC tablet in comparison to the approved TDF and FTC products.

Development of a new FDC regimen containing an HIV integrase inhibitor, an agent from this new therapeutic class with potent antiviral activity and good tolerability, plus the standard-of-care NRTI/N(t)RTI backbone is desirable and would offer a simple one-tablet, once-daily dosing schedule for the treatment of HIV-1. Simple once-daily antiretroviral regimens demonstrate high levels of adherence and treatment satisfaction and may thus positively affect long-term efficacy.[5–7]

A fixed-dose regimen of EVG/COBI/FTC/TDF may serve as an alternative to protease inhibitor-containing regimens that are often associated with dyslipidemia and gastrointestinal adverse effects or efavirenz/FTC/TDF FDC regimen, which exhibits efavirenz-related central nervous system toxicity, is teratogenic and may not be the regimen of choice for patients that are unable or unwilling to tolerate central nervous system side effects or women of childbearing potential wishing to avoid use of a pregnancy D category medication.

## METHODS

### Study Population

Forty-four healthy, nonsmoking, HIV-1–uninfected male and female subjects (nonpregnant and nonlactating) were enrolled in the study and received study drug treatments. Because this study evaluated the pharmacokinetics of investigational agents, additional precautionary measures were implemented to avoid/minimize the risk of developing pregnancies. Females of childbearing potential and sexually active males were required to use effective barrier contraception from screening onwards while on study and for at least 30 days after the last dose of study drug. Subjects had to be in good health based upon medical history, physical examination (including vital signs), 12-lead electrocardiogram (ECG) and screening laboratory evaluations. Subjects were excluded if they had serious or active medical conditions or if they received prescription medication and/or over-the-counter medications including herbal products within 28 days of commencing study drug dosing with the exception of vitamins and/or acetaminophen, ibuprofen, or hormonal contraceptive medications. Additional restrictions included participation in an investigational trial involving administration of any investigational compounds within 30 days of drug dosing, consumption of illegal or illicit drugs, alcohol, grapefruit juice and grapefruits, Seville orange juice, or calcium-fortified orange juice while on study. Caffeine or methyl xanthine–containing products were prohibited on dosing days. Subjects' participation in the study was periodically re-evaluated to assure ongoing compliance with study restrictions.

Informed consent was obtained from each individual before initiation of any screening procedures. The protocol was approved by an independent Investigational Review Board Inc and conducted at SeaView Research (Miami, FL) in accordance with the clinical research guidelines established by the basic principles defined in the US 21 CFR Part 312.20 and the principles enunciated in the Declaration of Helsinki.

### Study Design

This was an open-label, multidose, partial-crossover, adaptive study to evaluate the bioavailability and pharmacokinetics of a fixed-dose combination tablet (FDC) containing EVG 150 mg, FTC 200 mg, TDF 300 mg, and COBI at 100 mg. Based on the level of EVG boosting achieved with COBI 100 mg, an evaluation with a lower (75 mg) or a higher (150 mg) dose of COBI were to be conducted (Fig. 1). Subjects were randomized to 1 of 2 treatment sequences and assigned a subject number after eligibility confirmation. A randomization scheme was provided to the study center. EVG pharmacokinetics was assessed relative to its coadministration with ritonavir [ritonavir-boosted EVG (EVG 150 mg, ritonavir 100 mg)], a dosing regimen that is currently in phase 3 testing. FTC and tenofovir pharmacokinetics were assessed versus coadministration of FTC 200 mg capsules plus TDF 300 mg tablets.

The duration of study was 60 days in total and consisted of 4 periods of 10 days of dosing. Ten days of treatment were selected to assess pharmacokinetics of all components under clinically relevant, steady-state conditions, in particular evaluation of trough EVG concentrations. Study periods were separated by a 2-day drug washout period. (Fig. 1)

All doses were administered in the morning within 5 minutes of consuming a meal. On pharmacokinetic assessment days, this meal (breakfast) contained approximately 400 kcal and 13 grams of fat. Mouth checks were performed to ensure doses were taken and the time of dosing was recorded. On the days of pharmacokinetic assessments, study drugs were administered after an overnight fast, and the subjects were restricted from food intake until after collection of the 4-hour blood sample.

Serial blood samples were collected on the last day of each treatment (days 10, 22, 34, and 46) at the following time points: 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 14, 16, 20, and 24 hours postdose. Timing of blood samples was based on known concentration–time profiles of each drug to accurately assess their pharmacokinetics. Blood samples were centrifuged, and plasma collected was frozen at

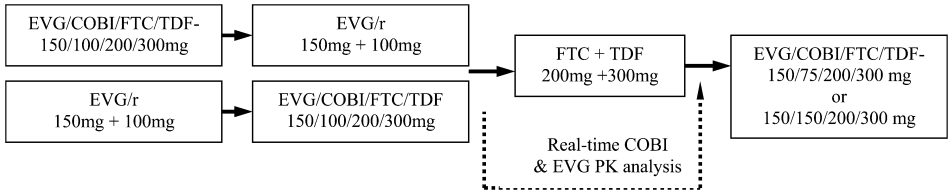


**FIGURE 1.** Study schema.

−80°C until analysis. Plasma samples from periods 1 and 2 were analyzed during period 3 dosing for the assessment of EVG and COBI exposures to allow selection of the FDC tablet containing 75 mg or 150 mg of COBI for an evaluation in the adaptive fourth period of the study.

## Safety Assessments

Safety assessments [laboratory analysis, vital signs, ECGs, physical examinations, and recording of adverse events (AEs)] were conducted at screening and at various time points during the study, with the follow-up visit carried out on day 60. Study drug dosing was to be suspended if 6 or more subjects receiving FDC discontinued due to treatment-emergent, drug-related grade 3 or 4 AEs or laboratory/ECG abnormalities. Assessment of AEs and concomitant medications continued throughout the study. AEs were summarized according to the last dosed treatment relative to the AE onset up to the end of the follow-up period. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 11.0). AEs were graded as grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = life-threatening according to Gilead Sciences Modified NIAID Common Toxicity Grading Scale.[8] Subject replacement was allowed for subjects who failed to complete all treatments in a sequence.

## Bioanalytical Procedures

EVG, RTV, FTC, tenofovir, and COBI concentrations in human plasma were determined by validated liquid chromatography tandem mass spectrometric (LC-MS/MS) methods. The assays for EVG and ritonavir were performed by QPS, Inc (Newark, DE), whereas assays for the other analytes were conducted at Gilead Sciences (Durham, NC).

For EVG and RTV analyses, 50 μL of human plasma was spiked with respective deuterated internal standards and processed by solid phase extraction. The compounds were detected by MS/MS in the selected reaction monitoring mode using electrospray ionization with positive polarity, and the following ion transitions were monitored: m/z 448 → 344 for EVG, m/z 456 → 344 for IS of EVG, m/z 721 → 268 for RTV, and m/z 728 → 274 for IS of RTV. The lower limits of quantitation for EVG and RTV were 20 and 5 ng/mL, respectively. For validation of both analytes, interassay and intra-assay precision was less than 10% and accuracy was within ±10%.

For FTC and tenofovir analyses, 100 μL of human plasma was deproteinized using 400 μL of methanol solution containing the 2 internal standards (lamivudine for FTC, adefovir for tenofovir). The compounds were detected by MS/MS in the selected reaction monitoring mode using electrospray ionization with positive polarity, and the following ion transitions were monitored as follows: m/z 248 → 130 for FTC, m/z 288 → 176 for tenofovir, m/z 230 → 112 for 3TC, and m/z 274 → 162 for adefovir. The lower limits of quantitation for FTC and tenofovir were 5 and 10 ng/mL, respectively. For validation of both analytes, interassay and intra-assay precision was less than 10%, and accuracy was within ±10%.

For assay of COBI, 50 μL of human plasma was spiked with a deuterated internal standard and then extracted using protein precipitation with methanol. The compounds were detected using electrospray ionization in the positive-ion mode, and the following ion transitions were monitored as follows: m/z 776 → 606 for COBI and m/z 784 → 614 for the internal standard. Interassay and intra-assay precision during validation for COBI was <15%, and accuracy was within 15%.

## Pharmacokinetic Analysis

The PK analysis set for each analyte used in the statistical comparisons consisted of all randomized subjects who received study drug and completed both test and reference treatments. All predose sample times of less than zero were assigned a value of zero. Concentration values below the lower limit of quantitation of the bioanalytical assays that occurred before the achievement of the first quantifiable concentration were assigned a value of zero to prevent overestimation of the initial AUC. Samples that were below the lower limit of quantitation at all other time points were treated as missing data to avoid bias in the estimation of the terminal elimination rate constant.

Pharmacokinetic parameters for all analytes were estimated by application of a linear up/log down trapezoidal rule using a noncompartmental method (WinNonlin software, version 5.2; Pharsight Corporation, Mountain View, CA) to estimate the ($AUC_{tau}$), maximum concentration ($C_{max}$), time of $C_{max}$ ($T_{max}$), ($C_{tau}$), and terminal elimination half-life ($T_{1/2}$).

## Statistical Analysis

A total samples size of 34 subjects (17 per sequence) was projected to achieve 90% power to reject the null hypothesis of lack of equivalence (test/reference geometric least-squares means ratio is <80% or >125%) in favor of the alternative hypothesis that the means of 2 treatments were equivalent with respect to $C_{max}$, $AUC_{tau}$, and $C_{tau}$, assuming each of the 2 1-sided comparison is made at the 5% level for all analytes. Calculations were based on the parameters of interest using the highest within-subject variability of the parameter of interest (SD = 0.269; EVG $C_{tau}$). An approximate 30% overage was built into the study sample size to account for potential study discontinuations, resulting in a total enrollment of 44 subjects (22 per sequence).

Demographic data and pharmacokinetic parameters were summarized using descriptive statistics. A parametric (normal theory) analysis of variance was fitted to the raw and natural-log transformed values of the primary pharmacokinetic parameters using a mixed-effects model. The model included treatment, sequence, and period as fixed effects and subject within sequence as a random effect. The comparisons between test and reference treatments of the primary pharmacokinetic parameters were analyzed using SAS PROC MIXED.

# RESULTS

## Subject Demographics and Disposition

Forty-four healthy HIV-uninfected adult subjects (22 males and 22 females) received study treatments. The mean

(SD) age at baseline was 35 (7.6) years, mean (SD) weight at screening was 72.0 (8.92) kg, mean (SD) height at screening was 166.1 (8.82) cm, and mean (SD) body mass index was 26.09 (2.62) kg/m$^2$.

Forty-two subjects completed all study periods and were included in the pharmacokinetic analysis set. One subject experienced severe acute appendicitis (grade 3) that was unrelated to drug administration and was discontinued from the study. The same subject later experienced moderate (grade 2) postsurgical pain that was considered unrelated to study drugs. Another subject was discontinued from the study per protocol due to a confirmed grade 3 alanine aminotransferase (ALT) enzyme elevation while receiving EVG/COBI 100 mg/FTC/TDF (day 3 of period 2).

## Safety

Safety data from this study demonstrated that the FDC of EVG/COBI/FTC/TDF was generally well tolerated at both 100 mg and 150 mg doses of COBI. Similar numbers of subjects reported treatment-emergent AEs with EVG/r (34.1%), EVG/COBI 100 mg/FTC/TDF (29.5%) and EVG/COBI 150 mg/FTC/TDF (30.2%). Slightly fewer treatment-emergent AEs (20.9%) and no treatment-related AEs were reported when FTC + TDF were administered. The incidence of treatment-related AEs was similar for the other 3 treatments occurring in 13.6% of subjects when receiving EVG/r, 11.4% when receiving EVG/COBI 100 mg/FTC/TDF and 11.6% of subjects with EVG/COBI 150 mg/FTC/TDF. The most frequent treatment-related AEs were constipation (5 subjects), headache (4 subjects), diarrhea (2 subjects), and acute hepatitis (2 subjects). Except for 2 cases of asymptomatic acute hepatitis, all treatment-related AEs were mild in severity.

Two subjects experienced acute asymptomatic hepatitis, defined by elevations in ALT while receiving FDC containing COBI 100 mg on the same day of study (day 3 of period 2). One subject with a confirmed grade 3 ALT elevation was discontinued from the study per protocol the next day. The event resolved 22 days later. A second subject with a confirmed grade 2 ALT elevation continued with study treatments. ALT elevation resolved 14 days later, and the subject completed the study. In both subjects, total bilirubin values remained within the reference range at all time points. No subjects experienced grade 2 or grade 3 elevations of liver function tests upon administration of the 150 mg COBI containing FDC.

The incidence of grade 1 treatment-emergent laboratory abnormalities in total cholesterol was similar for EVG/r, FTC + TDF, and FDC containing COBI 150 mg occurring in 13.6%, 14%, and 11.6% of subjects, respectively. The incidence was 22.7% when receiving EVG/COBI 100 mg/FTC/TDF treatment. The incidence of grade 2 total cholesterol increases was 9.1% for EVG/r, 7.0% for FTC + TDF, 4.5% for FDC containing 100 mg of COBI, and 2.3% for FDC containing 150 mg of COBI. Grade 1 increases in serum creatinine were observed in 2.3% of subjects (n = 1), each when receiving EVG/COBI/FTC/TDF with 100 mg and 150 mg of COBI treatments.

## Pharmacokinetics

The pharmacokinetic analysis set included 42 subjects. EVG, tenofovir, and FTC mean (SD) plasma concentration–time profiles are presented in Figures 2–4. Plasma pharmacokinetic parameters of EVG, FTC, tenofovir, and COBI are presented in Table 1.

Administration of a FDC tablet containing COBI 100 mg resulted in bioequivalent exposures of EVG by $AUC_{tau}$ and $C_{max}$ but a lower $C_{tau}$ ($P < 0.0001$), relative to EVG/r. Because efficacy of EVG is strongly associated with $C_{tau}$, we chose to evaluate the FDC with a higher 150 mg dose of COBI. EVG $AUC_{tau}$ and $C_{max}$ were modestly higher with this FDC tablet ($P < 0.03$); importantly, EVG $C_{tau}$ were numerically greater ($P = 0.27$) than those achieved with ritonavir-boosted EVG. Based on the finding of desired EVG exposures within the 150 mg containing COBI fixed-dose FDC, analyses of tenofovir and FTC were then limited to this formulation. Relative to tenofovir and FTC pharmacokinetics after administration of TDF plus FTC, administration of FDC tablet containing GS-9350 150 mg resulted in bioequivalent $AUC_{tau}$, higher $C_{max}$ and $C_{tau}$ ($P < 0.0001$) estimates for tenofovir and modestly higher FTC $AUC_{tau}$ ($P = 0.0003$), $C_{max}$ ($P = 0.01$), and $C_{tau}$ ($P < 0.0001$). Overall, the strict definition of bioequivalence was met for EVG $C_{max}$ and tenofovir $AUC_{tau}$. As expected, COBI

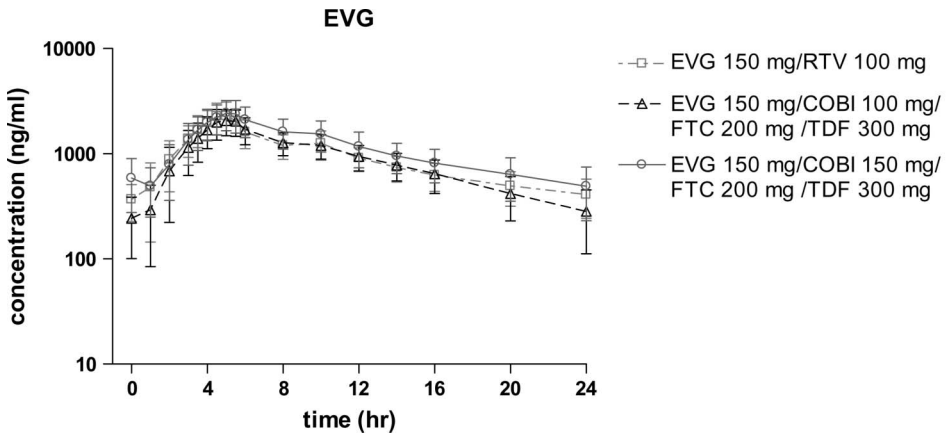


**FIGURE 2.** EVG plasma time–concentration profile.

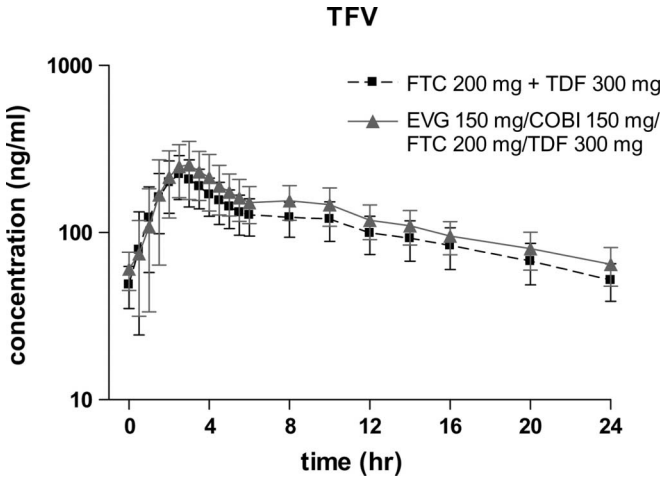


**FIGURE 3.** Tenofovir plasma time–concentration profile.

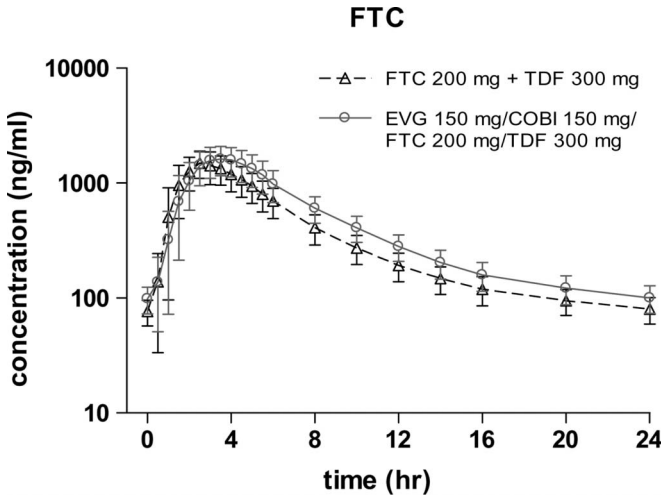


**FIGURE 4.** FTC plasma time–concentration profile.

$AUC_{tau}$, $C_{max}$, and $C_{tau}$ increased in greater than proportional manner with respect to dose (Table 1). Statistical comparisons of EVG, FTC, and tenofovir are presented in Table 1.

## DISCUSSION

The results from this study support the further evaluation of a new integrase inhibitor and novel pharmacoenhancer plus standard-of-care NRTI/NtRTI-containing, FDC once-daily, single-tablet regimen for the treatment of HIV infection. Specifically, this adaptive pharmacokinetic study demonstrated the ability of COBI, administered as the FDC tablet EVG/COBI/FTC/TDF, to boost EVG to desired exposures and similar to those observed with EVG/r. Administration of the FDC containing the lower COBI dose of 100 mg resulted in lower EVG $C_{tau}$ than those observed with EVG/r. Because EVG efficacy is related to its high $C_{tau}$ (multiple folds above the protein-adjusted $IC_{95}$ against HIV-1 integrase), the FDC containing the higher 150 mg COBI dose was selected for subsequent evaluation and shown to achieve target EVG exposures.

Tenofovir systemic exposure, $AUC_{tau}$, was bioequivalent but $C_{max}$ and $C_{tau}$ were 30% and 24% higher, respectively, in the FDC tablet relative to TDF plus FDC administration; FTC $AUC_{tau}$, $C_{max}$, and $C_{tau}$ were modestly higher within the FDC tablet. No differences in the tenofovir and FTC half lives were observed in the setting of the FDC versus TDF and FTC concomitant administration. Because the clearance mechanisms of tenofovir and FTC differ versus COBI and EVG (renal versus hepatic) and the lack of clinically significant interactions between tenofovir, FTC, and many hepatically eliminated drugs, an interaction at the biotransformation level is

**TABLE 1.** Summary and Statistical Comparisons of EVG, Tenofovir, FTC, COBI Pharmacokinetic Parameters

| N = 42 | Treatment | $C_{max}$ (ng/mL) | $T_{max}$ (hr) | $C_{tau}$ (ng/mL) | $AUC_{tau}$ (ng·h·mL$^{-1}$) | $T½$ (hr) |
|---|---|---|---|---|---|---|
| Tenofovir | EVG/COBI 150 mg/FTC/TDF | 332 (28.9) | 2.50 (2.00, 3.50) | 64.7 (26.0) | 3010 (20.4) | 12.7 (11.4, 14.2) |
| | TDF + FTC | 252 (24.9) | 2.50 (2.00, 2.50) | 52.0 (25.4) | 2,550 (22.6) | 12.5* (11.2, 14.1) |
| | GM Ratio (90% CI)† | 130 (122, 138) | — | 124 (119, 129) | 118‡ (114, 122) | — |
| FTC | EVG/COBI 150 mg/FTC/TDF | 1860 (22.5) | 3.25 (2.50, 4.00) | 101 (26.8) | 11,500 (19.4) | 11.0§ (8.92, 11.6) |
| | TDF + FTC | 1600 (26.1) | 2.50 (2.50, 3.00) | 80.1 (25.9) | 9,330 (22.1) | 12.3§ (10.9, 15.0) |
| | GM Ratio (90% CI)† | 121 (107, 137) | — | 126 (118, 136) | 127 (115, 140) | — |
| EVG | EVG/COBI 100 mg/FTC/TDF | 2,250 (26.3) | 5.00 (4.50, 5.50) | 282 (60.4) | 21,100 (25.4) | 5.94‖ (5.30, 6.74) |
| | EVG/COBI 150 mg/FTC/TDF | 2660 (27.6) | 5.00 (5.00, 5.50) | 490 (52.9) | 27,000 (29.4) | 9.15‖ (7.70, 12.4) |
| | EVG/r | 2,500 (32.1) | 5.00 (4.50, 5.00) | 410 (40.5) | 22,500 (23.4) | 11.2‖ (8.87, 13.0) |
| | GM Ratio (90% CI)† | 108‡ (100, 116) | — | 110 (95.3, 127) | 118 (110, 126) | — |
| COBI | EVG/COBI 100 mg/FTC/TDF | 855 (27.6) | 4.00 (2.50, 5.00) | 7.60 (124) | 5150 (31.7) | 3.35 (2.95, 3.86) |
| | EVG/COBI 150 mg/FTC/TDF | 1570 (29.7) | 4.50 (3.50, 5.50) | 22.7 (107.2) | 10,400 (35.2) | 2.99 (2.67, 3.63) |

Data are presented as mean (%CV - coefficient of variation) except for $T_{max}$, $T_{last}$ and $T½$, which are presented as median (Q1, Q3). Data presented in 3 significant figures.
*TDF + FTC (n = 41).
†FTC and tenofovir comparisons: test treatment: EVG/COBI 150 mg/FTC/TDF; reference treatment: FTC plus TDF. EVG comparison: test treatment: EVG/COBI 150 mg/FTC/TDF; reference treatment: EVG/r.
‡Comparison meeting the definition of bioequivalence.
§EVG/COBI 150 mg/FTC/TDF (n = 39); TDF + FTC (n = 37).
‖EVG/COBI 100 mg/FTC/TDF (n = 41); EVG/COBI 150 mg/FTC/TDF (n = 40); EVG/r (n = 38).
CI, confidence interval; GM, geometric least squares means.

unlikely.[9–12] Increases in tenofovir and FTC exposures may thus be the result of a higher relative bioavailability of these components as the FDC tablet. In particular, the increase in tenofovir exposures may be mediated by transient inhibition of the intestinal efflux transporter P-glycoprotein. COBI, like ritonavir and other protease inhibitors, are weak substrates/inhibitors of P-glycoprotein and do not inhibit this efflux transporter at pharmacologically relevant concentrations in the systemic circulation.[13–18] These agents may reach sufficient local concentrations to inhibit this transporter in the intestine during drug absorption.[15,19]

Similar increases in tenofovir concentrations have also been documented after co-administration with lopinavir/ritonavir or atazanavir.[20,21] A potential mechanism for this interaction was hypothesized to be gut inhibition of P-glycoprotein by these protease inhibitors that resulted in an increase in tenofovir absorption.[13,18,22,23] No adjustment in TDF is recommended in the setting of lopinavir/ritonavir or atazanavir/ritonavir because clinical trials have not indicated a high risk for TDF-associated AEs, including renal abnormalities.[10,24–26] Nevertheless, monitoring for TDF-associated AEs, including renal disorders, is warranted.[10,27,28]

The mechanism for higher FTC exposure from the FDC is unknown; however, given the established, favorable long-term safety profile of FTC, the exposures within FDC were considered suitable for further evaluation.[29–31] The safety and efficacy of these drug exposures will be assessed in phases 2 and 3 studies using the FDC.

Multiple doses of all study drugs were generally well tolerated when given as individual components or as a single tablet. Similar percentages of treatment-related AEs were reported for subjects receiving FDC tablets and ritonavir-boosted EVG.

In conclusion, a FDC EVG/COBI/FTC/TDF achieved desired tenofovir, FTC, and EVG exposures and represents the first integrase inhibitor–boosted and nonritonavir-boosted complete regimen for the treatment of HIV-1 infection. Currently Atripla, a FDC tablet of efavirenz, FTC, and TDF is the only available complete single-tablet regimen for the treatment of HIV-1; no such single-tablet regimens exist for protease inhibitor-containing or integrase inhibitor–containing therapy. Pending safety and efficacy evaluation in phases 2 and 3 trials, EVG/COBI/FTC/TDF, may serve as an option for treatment-naive HIV-1 patients.

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