Pharmacokinetics and Safety of Boosted Elvitegravir in Subjects with Hepatic Impairment

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Elvitegravir (EVG), an HIV strand transfer integrase inhibitor, is metabolized primarily via cytochrome P450 3A4 (CYP3A) and secondarily via glucuronidation. The pharmacokinetics (PK) and safety of cobicistat (COBI)-boosted EVG (EVG/co) were evaluated in subjects with impaired liver function. The enrolled subjects had stable moderate liver impairment (n = 10; Child-Pugh-Turcotte [CPT] class B) or were healthy controls (n = 10) matched for age (±5 years), gender, and body mass index (±15%). EVG/co (150/150 mg) was administered once daily for 10 days, followed by pharmacokinetic (PK) sampling. Safety was assessed throughout the study. EVG and COBI exposures were compared between the impairment and control groups, with a ≥100% increase considered clinically relevant. EVG and COBI protein binding was also measured. All enrolled subjects completed the study. The treatment-emergent adverse event (AE) incidences were comparable between the groups; all study drug-related AEs were mild. The geometric mean ratio (90% confidence interval [CI]) for EVG area under the concentration-time curve over the dosing interval (AUCtau) and maximum observed plasma concentration (Cmax) were 135% (103%, 177%) and 141% (109%, 183%), respectively. The corresponding values for COBI were 99.8% (76.0%, 131%) and 86.1% (65.4%, 113%), respectively, indicating no clinically relevant change in exposure. No correlations were observed between the EVG and COBI exposures versus CPT score. The EVG- and COBI-free fractions were similar between groups. EVG and COBI do not require dose adjustment in moderate or mild liver impairment, as no clinically relevant PK changes were observed for EVG or COBI in this special population. No PK or safety data are available for EVG or COBI in subjects with severe hepatic impairment.

A ntiretroviral (ARV) treatment for HIV-1-infected treatment-naive and -experienced patients has substantially improved over the past 10 years with the approval of several new drugs from existing classes, such as protease inhibitors (e.g., darunavir), and novel classes, such as chemokine inhibitors (CCR5) (e.g., maraviroc), and, in particular, integrase inhibitors (raltegravir and elvitegravir–cobicistat–emtricitabine–tenofovir disoproxil fumarate [EVG/COBI/FTC/TDF] single-tablet regimen [Stribild]). As a result, life expectancy has improved, approaching that of uninfected individuals, based on a recent analysis of >4,600 asymptomatic treatment-naive HIV-infected patients in high-income countries (1). The increased longevity, however, also necessitates consideration of the increasing incidence of HIV-associated non-AIDS conditions, commonly associated with advancing age and chronic inflammation, including liver disease, among other comorbidities (2, 3). Chronic liver disease, particularly due to viral hepatitis (B or C), is common in HIV patients. As such, there are potential implications for dosing recommendations of HIV therapy upon the progression of liver disease. Since several ARVs from multiple commonly used classes, except nucleos(t)ide reverse transcriptase inhibitors, undergo hepatic metabolism, changes in liver function due to impairment and consequent alterations in enzyme activity (e.g., cytochrome P450 [CYP]), hepatic blood flow, and/or anatomy can affect the pharmacokinetics (PK) of the ARVs and in turn, their efficacy and safety profile (4).

Elvitegravir is the first, once-daily strand transfer inhibitor approved for the treatment of HIV-1 infection as a component within the EVG/COBI/FTC/TDF single-tablet regimen (Stribild). EVG/COBI/FTC/TDF has demonstrated noninferior virologic efficacy and a favorable safety/tolerability profile in phase 3 studies in treatment-naive HIV-1-infected patients using efavirenz (EFV)/FTC/TDF or atazanavir with ritonavir (RTV) (atazanavir/r) plus TDF/FTC as comparators (5, 6). Additionally, once-daily EVG was noninferior to twice-daily raltegravir in a phase 3 study in treatment-experienced HIV patients when each was administered as a part of an active background regimen that included an RTV-boosted protease inhibitor (7).

EVG is metabolized by CYP3A4 and secondarily by glucuronidation via uridine glucuronosyl transferase 1A1/3 (UGT1A1/3) (8). Once-daily coadministration of EVG with ritonavir (100 mg) (EVG/r) or cobicistat (150 mg) (COBI-boosted EVG [EVG/co]), both potent and irreversible mechanism-based inhibitors of CYP3A4, causes a substantial increase in EVG plasma exposure. In addition, COBI is an inhibitor of CYP2D6 and the transporters P-glycoprotein (P-gp), BCRP, organic anion-transporting polypeptide 1B1 (OATP1B1), and OATP1B3. For EVG, the mean trough concentration (Cmin or Ctrough), the best determinant of antiviral activity, is ~10-fold above its in vitro protein binding–adjusted 95% inhibitory concentration (IC50) following elvitegravir/r (150/100 mg) administration (9, 10). COBI, a novel pharmacoenhancer, has demonstrated ability similar to that of ritonavir to boost various CYP3A substrates in addition to EVG, such as the CYP3A probe midazolam, and the HIV protease inhibitors atazanavir and darunavir (11–13). COBI is metabolized predominantly by CYP3A, consistent with its mechanism-based inhibition of this enzyme.

EVG and COBI undergo primarily hepatic biotransformation,
with minimal renal elimination (COBI, 8% of dose for COBI; EVG, none) and are highly protein bound (COBI, 97 to 98%; EVG, 98 to 99%) (8). These attributes render the potential for PK alterations in subjects with hepatic impairment. This article presents the findings of a clinical study that evaluated the safety, PK, and associated dosing recommendations of COBI-boosted EVG (EVG/co) (and thus EVG/COBI/FTC/TDF in HIV-uninfected subjects with liver impairment).

MATERIALS AND METHODS

Study population and study design. This was a phase 1, open-label, parallel-group study evaluating the steady-state pharmacokinetics of EVG and COBI in HIV-uninfected subjects with moderate hepatic impairment versus control subjects with normal hepatic function. Eligible subjects included male and nonpregnant, nonlactating female subjects (ages 18 to 70 years, inclusive). Subjects in the hepatic impairment group were selected based on a diagnosis of stable hepatic impairment with documentation of findings consistent with a Child-Pugh-Turcotte (CPT) score of 7 to 9 (CPT Classification B), with no clinically significant changes within 120 days prior to screening. Additional major inclusion criteria for impaired subjects were an expected survival period of ≥12 months; laboratory parameters within 28 days of the first dose of study drug, including an international normalized ratio (INR) of ≤2.5 (without the use of anticoagulants); albumin at ≥2.0 g/dl; total bilirubin at ≤10 mg/dl (≤171 μmol/liter); ≥30,000 platelets/mm³; alanine aminotransferase (ALT) at ≤20× the upper limit of normal (ULN) on at least 2 occasions and within 6 months prior to enrollment; and adequate hematologic function based on an absolute neutrophil count of ≤750/μm³ and hemoglobin levels of ≥10 g/dl in males and ≥9 g/dl in females.

Subjects in the normal control group were matched with hepatitis impaired subjects for age (±5 years), sex, and body mass index (BMI) (±15%) and selected based on normal hepatic function with no evidence of or history of liver disease, as determined by parameters including levels within the normal reference ranges for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes, alkaline phosphatase, total and direct bilirubin, INR, and albumin. Additional major inclusion criteria for the control subjects included healthy status based on medical history/physical exams/laboratory evaluations, status as a nonsmoker or consumer of ≤10 nicotine-containing products per day, a body mass index (BMI) of 19 to 34 kg/m² inclusive, a creatinine clearance (CrCl) value of ≥70 ml/min (Cockcroft-Gault value based on serum creatinine and actual body weight as measured at the screening evaluation), hepatitis B virus surface antigen-negative status, hepatitis C virus antibody-negative status, a normal 12-lead electrocardiogram (ECG) result, and use of at least two forms of contraception, including an effective barrier method.

Major exclusion criteria included serious or active medical or psychiatric conditions, use of hepatotoxic drugs within 3 months of screening or systemic chemotherapeutic agents within 6 months of study drug dosing, use of CYP3A and/or P-glycoprotein inducers or inhibitors within 30 days of study drug dosing, prior clinical evidence of a hepatic mass suggestive of hepatocellular carcinoma, significant drug sensitivity or drug allergy, and history of alcohol or substance abuse. Subjects in the impairment group were excluded if they required paracentesis >1 time per month. Subjects in the control group were excluded if they received any prescription medications or over-the-counter medications, including herbal products and antacids, within 28 days of commencing study drug dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications.

The study protocol and informed consent document were reviewed and approved by the study center’s institutional review board, and all subjects provided written informed consent before study participation. The present study was done in HIV-uninfected subjects to avoid the need for short-term changes to their ARV regimen for the purposes of PK assessment and the additional complexity of identifying age/gender/body mass index-matched control HIV-1-infected subjects. The study was performed in compliance with current good clinical practice (GCP) and was conducted at the Orlando Clinical Research Center, Orlando, FL, and APEX GmbH, Munich, Germany.

A total of 20 eligible subjects were enrolled, 10 subjects in the moderate hepatic impairment group and a parallel cohort of 10 subjects in the normal matched control group. Each subject received EVG (150 mg) plus COBI (150 mg) once daily for 10 days, followed by a 11-day follow-up period.

On days 1 through 10, EVG and COBI were coadministered, under the supervision of study personnel, in the morning immediately after a meal with 240 ml water at the same time each day. Mouth checks were performed to ensure doses were taken and the time of dosing was recorded. Subjects were restricted from food consumption (water allowed), starting from midnight on the evening of day 9, to ensure an approximately 8-hour fasting period prior to the intensive pharmacokinetic blood sample (see “Pharmacokinetic sampling,” below). Subjects were restricted from food consumption until after collection of the 4-h pharmacokinetic sample, relative to study drug dosing. Subjects were restricted from water consumption 1 h before and 2 h after dosing, except for the 240 ml given with the study treatment.

Safety assessments. Safety was evaluated by complete physical examinations or symptom-directed physical examinations with vital signs (temperature, blood pressure, heart rate, and respiration rate) performed at screening, baseline, and on days 3, 7, 10, 14, and 21. Clinical laboratory tests were performed at screening, baseline, and on days 3, 7, and 14, while urine/ alcohol testing and pregnancy testing for females of childbearing potential were conducted on day 5 and upon admission to the clinic on day 9. ECG assessment was performed at screening and baseline and on days 3, 7, and 14. Subjects were monitored for adverse events (AEs) throughout the study.

Pharmacokinetic sampling. On day 10, PK blood sampling was performed at 0 h (predose) and 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 18, 24, 28, 36, 48, 60, 72, and 96 h postdose. Additional aliquots for determining the percentage of protein binding were collected at predose and at 4 and 5 h postdose on day 10. Timing of blood samples was based on known concentration-time profiles of each drug to accurately assess their PK. Blood samples were collected in a Vacutainer Plus plastic whole-blood tube (Becton, Dickinson, Franklin Lakes, NJ) containing anticoagulant (spray-dried K₂ EDTA [EDTA]) and inverted several times to mix the blood and the anticoagulant. Tubes were kept in a covered container to limit light exposure and were kept on ice for 30 min and centrifuged for 10 min at 1,000 relative centrifugal force (RCF) in a refrigerated centrifuge set at 4°C to harvest plasma. Plasma samples were frozen at −70°C until analysis.

Bioanalytical procedures. Concentrations of EVG and COBI in plasma samples were determined using validated high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) bioanalytic assays with electrospray ionization in the positive-ion mode.

Sample analyses for EVG were performed as follows. Fifty microliters of human plasma was spiked with deuterated internal standard (IS) and processed by solid-phase extraction. The following ion transitions were monitored, m/z 448→344 for EVG and m/z 456→344 for IS of EVG. The lower limit of quantification for EVG was 20 ng/ml. The assay calibration curve was linear from 2 to 10,000 ng/ml. The interassay precision range (percent coefficient of variation [%CV]) for EVG at 2 and 10,000 ng/ml was 2.8 to 8.1%. The interassay accuracy range, expressed as the percent relative error (%RE), was −8.2 to 5.7%. The stability of EVG in frozen matrix was 585 days at −70°C.

Sample analyses for COBI were performed as follows. Fifty microliters of human plasma was spiked with a deuterated internal standard and then extracted using protein precipitation with methanol. The following ion transitions were monitored as follows, m/z 776→600 for COBI and m/z 784→614 for the internal standard. The lower limit of quantification for COBI was 5 ng/ml. The assay calibration curve was linear from 5 to 2,500 ng/ml. The interassay precision range (%CV) for COBI at 5 and 2,500 ng/ml was 3.9 to 8.3%. The interassay accuracy range, expressed as %RE,
ministration of EVG/co or normal matched control subjects are shown in Fig. 2 and Table 3, respectively. The GMRs (90% CIs) for subjects with impaired liver function versus the normal control group are presented in Table 4 for COBI exposure parameters. COBI Cmax and AUCtau were comparable in both groups, while Cmin was higher and T1/2 longer in the subjects with moderate hepatic impairment relative to the normal matched control subjects.

(iii) Elvitegravir and cobicistat plasma protein binding. The mean (standard deviation [SD]) percentage free fractions (unbound concentrations) for EVG in the normal matched control subjects and subjects with moderate hepatic impairment were 1.15% (0.14%) and 1.22% (0.23%), respectively. Corresponding values for COBI were 2.71% (0.56%) and 3.23% (0.63%), respectively.

(iv) Elvitegravir and cobicistat pharmacokinetics versus CPT scores and individual components. The relationships between pharmacokinetics and the low range of CPT scores and individual liver function laboratory parameters were explored by plotting steady-state EVG and COBI AUCtau and Cmax as a function of CPT scores and individual laboratory components (Fig. 3; data shown for AUCtau). No correlation was observed between EVG and COBI AUCtau and CPT scores; similar results were obtained for EVG and COBI Cmax and CPT scores (data not shown).

DISCUSSION

PK and safety assessments in subjects with liver impairment are recommended for investigational agents and are routinely performed for those cleared hepatically in order to provide suitable dosing recommendations for this population (14). The results of a clinical evaluation of EVG and COBI PK in HIV-uninfected subjects with moderate liver impairment, assessed using CPT scores, indicated a 35% increase in EVG AUCtau and no change in COBI AUCtau compared to matched control subjects with normal liver function. No changes in EVG or COBI plasma free (unbound) fractions were observed, indicating the lack of effect of moderate hepatic impairment on EVG and COBI protein binding. Importantly, the observed safety profiles were comparable in the two cohorts. As such, the modest EVG exposure changes are not considered to be clinically relevant and do not necessitate dose modifications for EVG/co. Further, based on the lack of observed changes in the PK of the nucleoside reverse transcriptase inhibitors (NRTIs) emtricitabine (FTC) and tenofovir (TFV) (15) with liver impairment, no dose modifications for the EVG/COBI/FTC/TDF single-tablet regimen are necessary for patients with moderate or mild liver impairment.

Since EVG is administered with COBI, a potent CYP3A inhibitor, potential changes in EVG systemic clearance due to impairment-based alterations in CYP3A activity were not expected. When boosted, the net metabolism of EVG is through glucuronidation via UGT1A1/3, which is a high-capacity metabolic pathway. For instance, no clinically meaningful changes have been observed in subjects with moderate hepatic impairment receiving an HIV integrase inhibitor that is also a UGT1A1 substrate, such as raltegravir (16) or dolutegravir (17), as well as substrates of other UGT isoforms based on in vitro and/or in vivo data (18). In the absence of differences in metabolic pathways or changes in

<table>
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<tr>
<th>Table 2</th>
<th>Statistical comparison (test/reference ratio) of geometric means and 90% confidence intervals of elvitegravir pharmacokinetic parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or in matched control subjects</th>
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<tbody>
<tr>
<td><strong>GLSM</strong> values for:</td>
<td><strong>Test treatment,</strong> normal matched group (n = 10)</td>
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<tr>
<td><strong>EVG PK parameter</strong></td>
<td><strong>COBI PK parameter</strong></td>
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<td></td>
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<tr>
<td>EVG PK</td>
<td>COBI PK</td>
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<tr>
<td>AUCtau</td>
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<tr>
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<tr>
<td>Cmin</td>
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<tr>
<td>Cmin</td>
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*GLSM, geometric least-squares mean.

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<th>Table 3</th>
<th>Cobicistat pharmacokinetic parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or in matched control subjects</th>
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<tr>
<td><strong>GLSM</strong> values for:</td>
<td><strong>Test treatment,</strong> moderate hepatic impairment group (n = 10)</td>
</tr>
<tr>
<td><strong>COBI PK parameter</strong></td>
<td><strong>AUCtau (ng ⋅ h/ml)</strong></td>
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<td></td>
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<tr>
<td>AUCtau</td>
<td>9,900 (34)</td>
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<tr>
<td>Cmax</td>
<td>1,150 (33)</td>
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<tr>
<td>Cmin</td>
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<td>T1/2</td>
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<tr>
<td>AUCtau</td>
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<tr>
<td>Cmax</td>
<td>208 (117, 368)</td>
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<tr>
<td>Cmin</td>
<td>86.1 (65.4, 113)</td>
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*GLSM, geometric least-squares mean.

FIG 2 Mean (± standard deviation) plasma concentration-time profile of cobicistat (COBI) (inset, concentration profile over 96 h) following administration of cobicistat-boosted elvitegravir in subjects with moderate liver impairment or matched control subjects (n = 10/cohort).

FIG 3 Mean (± standard deviation) plasma concentration-time profile of cobicistat (COBI) (inset, concentration profile over 96 h) following administration of cobicistat-boosted elvitegravir in subjects with moderate liver impairment or in matched control subjects (n = 10/cohort).
protein binding, the modest changes in EVG exposures may have been due to differences in absorption profiles between the impaired versus control subjects. Consistent with this hypothesis, no trends/relationships were observed between EVG exposures (AUC$_{\text{tau}}$ or C$_{\text{max}}$) and degree of impairment based on CPT score (Fig. 3). Further, no correlation was observed between EVG exposures and the individual laboratory parameters associated with CPT score (data not shown). EVG exposures in the impaired group were in the range of values observed in the long-term phase 2 and 3 studies of EVG/COBI/FTC/TDF in HIV-infected treatment-naive patients. The overall PK/PD analyses from these studies indicated similar efficacy over the range of observed EVG C$_{\text{trough}}$ and no relationship between EVG AUC$_{\text{tau}}$ and incidence of common AEs (19).

Several ARVs have been evaluated in the setting of liver impairment to evaluate potential changes in PK and safety. For RTV-boosted HIV protease inhibitors (PIs), for a given degree of impairment, the exposure changes vary considerably depending on the PI. Boosted-darunavir exposures are unchanged with mild impairment, while the AUC$_{\text{tau}}$ and concentrations at 12 h after dosing (C$_{12\text{h}}$) of boosted tipranavir are 30% and 84% higher, respectively (21). In patients with moderate hepatic impairment, darunavir AUC$_{\text{tau}}$ values were 20% higher than those in matched controls, despite 2-fold higher RTV C$_{\text{min}}$ levels, indicating the independent effects of liver impairment on the PK of these agents.

This study, the first clinical evaluation of COBI in liver impairment, showed that COBI AUC$_{\text{tau}}$ was unaffected, while C$_{\text{trough}}$ levels showed a 2-fold increase in impaired subjects versus control subjects. Along with the observed 50% longer T$_{1/2}$, these data suggest the potential for slower elimination. Relative to COBI C$_{\text{max}}$ (unchanged with impairment), the C$_{\text{trough}}$ values were substantially lower, rendering the observed differences unlikely to be clinically relevant. As expected based on the overall PK data, no correlations/trends were observed between COBI AUC$_{\text{tau}}$ or C$_{\text{max}}$ and CPT scores.

Multiple-dose EVG/co (150/150 mg) administration was well tolerated in both groups, with all enrolled subjects completing the study. In this phase 1 special population study in a small group of subjects, the incidences of treatment-emergent AEs considered study drug related were similar in both groups (2 subjects/cohort). These were diarrhea, dizziness, and/or headache in the control cohort and eczema, nausea, and/or fatigue in the impaired cohort. No hepatobiliary AEs or clinically significant changes in liver function tests were observed. The majority of treatment-emergent laboratory abnormalities were grade 1 or 2, including the graded abnormalities related to liver inflammation or function. Consistent with the overall safety data with EVG and COBI, no clinically significant changes in vital signs, physical examination findings, or ECGs were observed.

In summary, no clinically relevant changes in EVG or COBI PK were observed following multiple-dose administration of EVG/co (150/150 mg) in subjects with moderate liver impairment versus matched control subjects and the study treatments were well tolerated; these findings can be extrapolated to mild hepatic impairment. Accordingly, boosted EVG, as an individual agent or as a component of EVG/COBI/FTC/TDF, may be administered without dose adjustment to HIV-infected patients with moderate or mild hepatic impairment. There are no data on boosted EVG in subjects with severe impairment.

REFERENCES


5. DeJesus E, Rockstroh JK, Henry K, Molina JM, Gathe J, Ramanathan S,


