Pharmacokinetics and Safety of Boosted Elvitegravir in Subjects with Hepatic Impairment

Joseph M. Custodio, Martin Rhee, Gong Shen, Kah Hiing J. Ling, Brian P. Kearney, Srinivasan Ramanathan
Gilead Sciences, Inc, Foster City, California, USA

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 (AUCτ) was 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.

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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 anticoagu- lants); 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/mm³ and hemoglobin levels of ≥10 g/dl in males and ≥9 g/dl in females.

Subjects in the normal control group were matched with hepati- cally impaired subjects for age (±5 years), sex, and body mass index (BMI) (±15%) and selected based on normal hepatic function with no evidence of 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 (Ccr) 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 psychi- atric 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 an 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, 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 as follows, m/z 448→344 for EVG and m/z 456→344 for IS of EVG. The lower limit of quantitation 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→606 for COBI and m/z 784→614 for the internal standard. The lower limit of quantitation 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,
was −0.3 to 9.7%. The stability of COBI in frozen matrix was 365 days at −60 to −80°C.

Pharmacokinetic analyses. Pharmacokinetic parameters of EVG and COBI were estimated by application of a linear up/log down trapezoidal rule using a noncompartmental method (WinNonlin software, professional edition, version 6.1; Pharsight Corporation, Mountain View, CA). PK parameters estimated included area under the concentration-time curve over the dosing interval (AUCtau), maximum observed plasma concentration (Cmax), observed plasma concentration at the end of the dosing interval (Cmin or C trough), time to reach maximum concentration (Tmax), and terminal elimination half-life (T1/2). 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.

Statistical analyses. Analysis of variance (ANOVA) appropriate for a parallel design was fit to the natural logarithmic transformation of PK parameters (AUCtau, Cmax, and Cmin). Ninety-percent confidence intervals were calculated for the ratio (test/reference) of geometric means (GMR) for each PK parameter for EVG in the moderate hepatic impairment group versus the control group. A total sample size of 8 evaluable subjects in each of the two groups was projected to provide at least 89% power to reject the null hypothesis that subjects with moderate hepatic impairment have an increase of at least 100% in exposure (AUCtau or Cmax) for EVG compared to subjects with normal liver function. The 2-fold or greater increase in exposure (AUCtau or Cmax) was predefined in the study protocol, consistent with FDA guidance for industry on pharmacokinetics in patients with impaired hepatic function for informing on dosing recommendations in labeling (14). Moreover, this 2-fold exposure window is aligned with the robust PK-pharmacodynamic (PD) assessment of historical data of EVG and COBI showing these agents are safe and well tolerated over a wide range of doses (EVG up to 300 mg and COBI up to 400 mg) and exposures (9, 11).

RESULTS

Subject demographics and disposition. Twenty subjects were enrolled in the study (10 per group) and all 20 subjects completed the study. Subjects in the hepatic impairment group (9 males and 1 female) had CPT scores of 7 (n = 3), 8 (n = 4), or 9 (n = 3), with a mean age of 56 years (range, 41 to 68 years). The mean BMI for impaired subjects at screening was 27.7 kg/m² (range, 22.2 to 33.1 kg/m²), and the mean estimated glomerular filtration rate calculated by the Cockcroft-Gault method (eGFRCG) was 116.8 ml/min (range, 78.5 to 163.3 ml/min). Subjects in the matched control group (9 males, 1 female) had a mean age of 56 years (range, 41 to 70 years) and a mean BMI at screening of 28.2 kg/m² (range, 21.1 to 32.2 kg/m²), with a mean estimated glomerular filtration rate calculated by the Cockcroft-Gault method (eGFRCG) of 98.7 ml/min (range, 77.2 to 110.5 ml/min).

Safety. The overall incidence of AEs was comparable between the impaired and control groups. Subjects in the hepatic impairment group reported three grade 1 AEs (mild) and one grade 2 AE (moderate), while subjects in the normal control group reported five grade 1 AEs (mild). Across both groups, no AE occurred in more than one subject except for headache, which occurred in two subjects. There were no occurrences of grade 3 or 4 AEs, and no AEs were observed in the hepatobiliary system organ class. There were no grade 2, 3, or 4 aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin lab abnormalities observed, with the exception of one subject with grade 2 elevated bilirubin levels.

Pharmacokinetics. (i) Elvitegravir. The plasma concentration-time profiles of EVG (n = 20) and corresponding PK parameters following multiple-dose administration of EVG/co in subjects with moderate hepatic impairment or normal matched control subjects are shown in Fig. 1 and Table 1, respectively; GMRs (90% confidence interval [CI]) for impaired versus normal control groups are presented in Table 2 for EVG exposure parameters. EVG AUCtau, Cmax, and Cmin were higher in the subjects with moderate hepatic impairment than in the normal matched control subjects, while the median T1/2 was comparable between the two groups. However, the GMRs for EVG exposure (AUCtau, Cmax, and Cmin) were below the predefined increase of 100% in the subjects with moderate hepatic impairment versus the matched control subjects.

(ii) Cobicistat. The plasma concentration-time profiles of COBI (n = 20) and corresponding PK parameters in subjects with moderate hepatic impairment who received multiple-dose ad-
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 AUCₜₐᵤₜ were comparable in both groups, while Cₜₘᵢₙ 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 AUCₜₐᵤₜ and Cₘₐₓ as a function of CPT scores and individual laboratory components (Fig. 3; data shown for AUCₜₐᵤₜ). No correlation was observed between EVG and COBI AUCₜₐᵤₜ and Cₘₐₓ scores; similar results were obtained for EVG and COBI Cₘₐₓ and Cₜₘᵢₙ 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 heptically 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 AUCₜₐᵤₜ and no change in COBI AUCₜₐᵤₜ 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 expected/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

\[ \text{TABLE 2 Statistical comparison (test/reference ratio) of geometric means and 90% confidence intervals of elvitegravir pharmacokinetic parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or in matched control subjects} \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal matched control group (n = 10)</th>
<th>Moderate hepatic impairment group (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCₜₐᵤₜ (ng · h/ml)</td>
<td>9,840 (37)</td>
<td>9,900 (34)</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/ml)</td>
<td>1,290 (30)</td>
<td>1,150 (33)</td>
</tr>
<tr>
<td>Cₜₘᵢₙ (ng/ml)</td>
<td>41.0 (75)</td>
<td>90.7 (76)</td>
</tr>
<tr>
<td>T₁/₂ (h)</td>
<td>3.0 (2.0, 3.0)</td>
<td>4.0 (3.5, 4.5)</td>
</tr>
</tbody>
</table>

\[ \text{TABLE 3 Cobicistat pharmacokinetic parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or in matched control subjects} \]

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<th>Moderate hepatic impairment group (n = 10)</th>
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<tbody>
<tr>
<td>AUCₜₐᵤₜ (ng · h/ml)</td>
<td>9,360</td>
<td>9,330</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/ml)</td>
<td>33.3</td>
<td>69.2</td>
</tr>
<tr>
<td>Cₜₘᵢₙ (ng/ml)</td>
<td>1,250</td>
<td>1,080</td>
</tr>
</tbody>
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\[ \text{TABLE 4 Statistical comparison (test/reference ratio) of geometric means and 90% confidence interval of cobicistat pharmacokinetic parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or in matched control subjects} \]

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\[ \text{GLSM, geometric least-squares mean.} \]
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 (AUCtau or Cmax) 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 Cmax and no relationship between EVG AUCtau 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 (20), while the AUCtau and concentrations at 12 h after dosing (C12 h) of boosted tipranavir are 30% and 84% higher, respectively (21). In patients with moderate hepatic impairment, darunavir AUCtau values were 20% higher than those in matched controls, despite 2-fold higher RTV Cmin levels, indicating the independent effects of liver impairment on the PK of this agent.

This study, the first clinical evaluation of COBI in liver impairment, showed that COBI AUCtau was unaffected, while Ctrough levels showed a 2-fold increase in impaired subjects versus control subjects. Along with the observed 50% longer T1/2, these data suggest the potential for slower elimination. Relative to COBI Cmax (unchanged with impairment), the Ctrough 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 AUCtau or Cmax 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,


