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, and Srinivasan Ramanathan

Gilead Sciences, Inc., Foster City, CA 94404

Running Title: Elvitegravir Pharmacokinetics in Hepatic Impairment

Informed consent was obtained from all subjects. This study was performed in compliance with current Good Clinical Practice (GCP) and was conducted at Orlando Clinical Research Center, Orlando, FL and APEX GmbH, Munchen, Germany.

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*Corresponding author and requests for reprints:

Joseph M Custodio, Ph.D.

Gilead Sciences, Inc.

333 Lakeside Drive,

Foster City, CA 94404

Phone: (650) 372-7065

Facsimile: (650) 522-1975
Email: jcustodio@gilead.com

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ABSTRACT

Background: 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) was evaluated in subjects with impaired liver function.

Methods: The enrolled subjects had stable moderate liver impairment (N=10; 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 impairment vs control group, with a ≥ 100% increase considered clinically relevant. Protein binding of EVG and COBI was also measured.

Results: All enrolled subjects completed the study. Treatment-emergent adverse events (AEs) incidence was comparable between the groups; all study-drug related AEs were mild. The geometric mean ratio (%) (90% CI) for EVG AUC\textsubscript{tau} and C\textsubscript{max} were 135 (103, 177) and 141 (109, 183), respectively. Corresponding values for COBI were 99.8 (76.0, 131) and 86.1 (65.4, 113), indicating no clinically relevant change in exposure. No correlations were observed between EVG or COBI exposures versus CPT score. EVG and COBI free fraction were similar between groups.
Conclusions: EVG or COBI do not require dose adjustment in moderate or mild liver impairment, as no clinically relevant PK changes are 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.
INTRODUCTION

Antiretroviral (ARV) treatment for HIV-1 infected treatment-naïve 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 (CCR5)- (e.g., maraviroc) and in particular, integrase inhibitors (raltegravir, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet regimen). As a result, life expectancy has improved, approaching that of uninfected individuals, based on a recent analysis of > 4600 asymptomatic treatment-naïve HIV-infected patients in high income countries. The increased longevity, however, also necessitates consideration of increasing incidence of HIV-associated non-AIDS conditions, commonly associated with advancing age and chronic inflammation, including liver disease, among other comorbidities. Chronic liver disease, particularly those 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.

Elvitegravir is the first, once-daily strand transfer inhibitor approved for the treatment of HIV-1 infection as the elvitegravir/cobicistat/emtricitabine/tenofovir DF single tablet regimen (EVG/COBI/FTC/TDF; Stribild™). EVG/COBI/FTC/TDF has demonstrated
non-inferior virologic efficacy and a favorable safety/tolerability profile in Phase 3 studies in treatment-naïve HIV-1 infected patients using EFV/FTC/TDF or atazanavir/r + TDF/FTC as comparators \(^5,6\). Additionally, EVG once-daily was non-inferior to raltegravir twice-daily in a Phase 3 study in treatment-experienced HIV patients, when each was administered as a part of an active background regimen that included a ritonavir (RTV)-boosted protease inhibitor \(^7\).

EVG is metabolized by CYP3A4 and secondarily by glucuronidation via uridine glucuronosyl transferase (UGT) 1A1/3\(^8\). Once-daily coadministration of EVG with ritonavir 100 mg (EVG/r) or cobicistat 150 mg (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-gp, BCRP, OATP1B1 and OATP1B3. Mean EVG trough concentration (C\(_{\text{min}}\) or C\(_{\text{trough}}\)), the best determinant of antiviral activity, is \(~10\)-fold above its \textit{in vitro} protein binding adjusted 95% inhibitory concentration (IC\(_{95}\)) following 150/100 mg elvitegravir/r administration\(^9,10\). COBI, a novel pharmacoenhancer, has demonstrated similar ability as ritonavir to boost various CYP3A substrates in addition to EVG, such as the CYP3A probe midazolam, and 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: 97-98%; EVG: 98-99\%)\(^8\). These attributes render the potential for PK alterations...
in subjects with hepatic impairment. This manuscript 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.

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 (aged 18–
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 ≥ 12 months; laboratory
parameters within 28 days of the first dose of study drug including INR ≤ 2.5 (without
the use of anticoagulants), albumin ≥ 2.0 g/dL; total bilirubin ≤ 10 mg/dL (≤ 171
μmol/L), platelets ≥ 30,000/mm³, ALT value ≤ 20 × upper limit of normal (ULN) on at
least 2 occasions and within 6 months prior to enrollment, and adequate hematologic
function based on absolute neutrophil count ≥ 750/mm³, and hemoglobin in males ≥ 10
g/dL and females ≥ 9 g/dL.
Subjects in the normal control group were matched with a hepatically impaired subjects for age (± 5 years), sex, and body mass index (BMI) (± 15%) and selected based normal hepatic function with no evidence or history of liver disease including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes, alkaline phosphatase, total and direct bilirubin, INR, and albumin values within the normal reference range. Additional major inclusion criteria for control subjects included healthy status based on medical history/physical exams/laboratory evaluations, nonsmoker or consumed ≤ 10 nicotine-containing products per day; body mass index (BMI) of 19 ≤ BMI ≤ 34 kg/m²; creatinine clearance (CLcr) value ≥ 70 mL/min (Cockcroft Gault based on serum creatinine and actual body weight as measured at the screening evaluation); Hepatitis B surface antigen negative; Hepatitis C antibody negative; normal 12-lead electrocardiogram (ECG); 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 or systemic chemotherapeutic agents within 3 months of screening or 6 months of study drug dosing, respectively, 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, 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 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.

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 approximate 8-hour fasting periods prior to the intensive pharmacokinetic blood
sample (see Pharmacokinetic Sampling). Subjects were restricted from food
consumption until after collection of the 4-hour pharmacokinetic sample, relative to study
drug dosing. Subjects were restricted from water consumption one hour before and two
hours 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 preformed 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, 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 (pre-dose), 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 18, 24, 28, 36, 48, 60, 72, and 96 hours postdose. Additional aliquots for determining percent protein binding were collected at pre-dose and at 4 and 5 hours post-dose 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 ethylenediaminetetraacetic acid [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 minutes and centrifuged for 10 minutes at 1000 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 was performed as follows: 50 µL of human plasma was spiked with deuterated internal standard 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 quantitation for EVG was 20 ng/mL. The assay calibration curve was linear from 2 to 10,000 ng/mL. The interassay precision range (%coefficient of variation) for EVG at 2 and 10,000 ng/mL was 2.8 to 8.1. The interassay accuracy range, expressed as %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 was performed as follows: 50 µL 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 (%CVs) for EVG 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 EVG 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...
PK parameters estimated included area under the concentration versus time curve over
the dosing interval (AUC\text{tau}), maximum observed plasma concentration (C_{max}), observed
plasma concentration at the end of the dosing interval, time to reach maximum
concentration (T_{max}), and terminal elimination half life (T_{1/2}). All predose sample times
of less than zero 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 (AUC\text{tau}, C_{max} and C_{min}). Ninety
(90) percent confidence intervals were constructed 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 samples 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 (AUC\text{tau} or C_{max}) for EVG compared to subjects with normal liver
function. The two-fold or greater increase in exposure (AUC\text{tau} or C_{max}) was pre-defined
in the study protocol, consistent with the FDA Guidance for Industry on
Pharmacokinetics in Patients with Impaired Hepatic Function for informing on dosing
recommendations in labeling. Moreover, this two-fold exposure window is aligned with the robust PK-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; COBI up to 400 mg) and exposures. A 25% overage was built into the study sample size to account for potential study discontinuations, thus requiring total enrollment of 20 subjects (10 per group).

Determination of ex vivo protein binding of EVG and COBI in plasma was performed by equilibrium dialysis. Plasma spiked with [14C] EVG or [14C]COBI and the same volume of phosphate buffer were placed into opposite sides of the assembled dialysis cells (5000 molecular weight cut-off dialysis membranes, pre-soaked in 0.133 M potassium phosphate buffer, pH 7.4). Following dialysis, post-dialysis plasma and buffer weights were measured and recorded for recovery and volume shift calculations. Samples were analyzed using via liquid scintillation counting (Model A2800 liquid scintillation analyzer [Packard]).

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, 1 female) had CPT scores of 7 (n=3), 8 (n=4), or 9 (n=3), with a mean age of 56 years (range: 41–68). The mean BMI for impaired subjects at screening was 27.7 kg/m² (range: 22.2-33.1 kg/m²) and the mean estimated glomerular filtration rate calculated by Cockcroft-Gault method (eGFR CG) was 116.8 mL/min (range: 78.5–163.3 mL/min). Subjects in the
matched control group (9 males, 1 female) had a mean age of 56 years (range: 41–70) and a mean BMI at screening of 28.2 kg/m² (range: 21.1–32.2 kg/m²), with a mean estimated glomerular filtration rate calculated by Cockcroft-Gault method (eGFRCG) was 98.7 mL/min (range: 77.2–110.5 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**

**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 Figure 1 and Table 1, respectively; GMR (90% CI) for impaired versus normal control group are presented in Table 2 for EVG exposure parameters. EVG AUCτ, Cmax, and Cmin were higher in the subjects with moderate hepatic impairment relative to normal matched control subjects, while median T1/2 was comparable between the two groups. However, the GMR for EVG
exposure (AUC_{tau}, C_{max}, and C_{min}) were below predefined increase of 100% versus matched control subjects.

**Cobicistat**

The plasma concentration–time profiles of COBI (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 Figure 2 and Table 3, respectively. GMR (90% CI) for impaired versus normal control group are presented in Table 4 for COBI exposure parameters. COBI C_{max} and AUC_{tau} were comparable in both groups, while C_{min} was higher and T_{1/2} longer in the subjects with moderate hepatic impairment relative to normal matched control subjects.

**Elvitegravir and Cobicistat Plasma Protein Binding**

The mean (SD) % free fraction (unbound concentration) for EVG in the normal matched control subjects and subjects with moderate hepatic impairment was 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.

**Elvitegravir and Cobicistat Pharmacokinetics versus CPT Scores and Individual Components**

The relationship between pharmacokinetics and the low range of CPT scores and individual liver function laboratory parameters were explored by plotting steady-state EVG and COBI AUC_{tau} and C_{max} as a function of CPT scores and individual laboratory components (Figure 3; data shown for AUC_{tau}). No correlation was observed for EVG.
DISCUSSION

PK and safety assessment in subjects with liver impairment is recommended for investigational agents, and routinely performed for those cleared hepatically, in order to provide suitable dosing recommendations for this population\textsuperscript{14}. The results of a clinical evaluation of EVG and COBI PK in HIV uninfected subjects with moderate liver impairment, assessed using CPT score, indicated a 35\% increase in EVG AUC\textsubscript{tau} and no change in COBI AUC\textsubscript{tau} compared to matched control subjects with normal liver function. No changes in EVG or COBI plasma free (unbound) fraction were observed, indicating the lack of effect of moderate hepatic impairment on EVG and COBI protein binding. Importantly, the observed safety profile was comparable between 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 NRTIs FTC or TFV\textsuperscript{15} with liver impairment, no dose modifications for EVG/COBI/FTC/TDF single tablet regimen is necessary 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 with moderate hepatic impairment for other HIV integrase inhibitors that are also UGT1A1 substrates such as raltegravir\textsuperscript{16} and
dolutegravir\textsuperscript{17}, as well as for substrates of other UGT isoforms based on in vitro and/or in vivo data\textsuperscript{18}. In the absence of differences in metabolic pathway or changes in protein binding, the modest changes in EVG exposures may have been due to differences in absorption profile between the impaired vs control subjects. Consistent with this hypothesis, no trends/relationships were observed between EVG exposures (AUC\textsubscript{tau} or \(C_{\text{max}}\)) and degree of impairment based on CPT score (Figure 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 naïve 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\textsubscript{tau} and incidence of common AEs\textsuperscript{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\textsuperscript{20}, while the AUC\textsubscript{tau} and \(C_{12\text{ hr}}\) of boosted-tipranavir are 30\% and 84\% higher respectively\textsuperscript{21}. With moderate impairment, darunavir AUC\textsubscript{tau} were 20\% higher versus matched controls, despite two-fold higher RTV \(C_{\text{min}}\), 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\textsubscript{tau} was unaffected, while \(C_{\text{trough}}\) was two-fold higher increase in impaired vs 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 $\text{AUC}_{\text{tau}}$ 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 subjects, treatment-emergent AEs considered study drug-related occurred at similar incidence (2 subjects/cohort). These were diarrhea, dizziness and/or headache in the control cohort, eczema, nausea and/or fatigue in 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 individual agent or as EVG/COBI/FTC/TDF, may be administered without dose adjustment to HIV-infected patients with moderate or mild impairment. There are no data on boosted-EVG in subjects with severe impairment.
REFERENCES


Table 1. Elvitegravir (EVG) pharmacokinetic (PK) Parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or matched control subjects

<table>
<thead>
<tr>
<th>EVG PK Parameter</th>
<th>Normal Matched Control Group (N = 10)</th>
<th>Moderate Hepatic Impairment Group (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{tau} (ng•h/mL)</td>
<td>21,300 (28)</td>
<td>29,800 (41)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>1950 (30)</td>
<td>2820 (34)</td>
</tr>
<tr>
<td>C_{min} (ng/mL)</td>
<td>370 (44)</td>
<td>741 (65)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>4.0 (3.5, 5.0)</td>
<td>4.75 (4.0, 5.0)</td>
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<tr>
<td>T_{1/2} (h)</td>
<td>7.6 (6.7, 8.7)</td>
<td>8.2 (7.1, 11)</td>
</tr>
</tbody>
</table>
Table 2. Statistical comparison (the ratio (test:reference) of geometric means (GMR) and 90% confidence interval (CI) of elvitegravir (EVG) pharmacokinetic (PK) parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or matched control subjects.

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>GLSMs</th>
<th>Reference (N=10)</th>
<th>Test Treatment: Moderate Hepatic Impairment Group (N=10)</th>
<th>GMR (%) (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{tau}$ (ng•h/mL)</td>
<td>20500</td>
<td>27700</td>
<td>135 (103, 177)</td>
<td></td>
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<tr>
<td>C$_{min}$ (ng/mL)</td>
<td>335</td>
<td>602</td>
<td>180 (111, 291)</td>
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<tr>
<td>C$_{max}$ (ng/mL)</td>
<td>1880</td>
<td>2660</td>
<td>141 (109, 183)</td>
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</table>
Table 3. Cobicistat (COBI) pharmacokinetic (PK) Parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or matched control subjects

<table>
<thead>
<tr>
<th>COBI PK Parameter</th>
<th>Normal Matched Control Group (N=10)</th>
<th>Moderate Hepatic Impairment Group (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{τ_{0}} (ng•h/mL)</td>
<td>9840 (37)</td>
<td>9900 (34)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>1290 (30)</td>
<td>1150 (33)</td>
</tr>
<tr>
<td>C_{min} (ng/mL)</td>
<td>41.0 (75)</td>
<td>90.7 (76)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>3.0 (2.0, 3.0)</td>
<td>4.0 (3.5, 4.5)</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>4.0 (3.7, 4.9)</td>
<td>6.1 (4.8, 6.7)</td>
</tr>
</tbody>
</table>
Table 4 Statistical comparison (the ratio (test:reference) of geometric means (GMR) and 90% confidence interval (CI) of elvitegravir (EVG) pharmacokinetic (PK) parameters following administration of cobicistat-boosted elvitegravir in subjects with moderate hepatic impairment or matched control subjects.

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>GLSM</th>
<th>Reference Treatment: Normal Matched Control Group (N=10)</th>
<th>Test Treatment: Moderate Hepatic Impairment Group (N=10)</th>
<th>GMR (%) (90% CI)</th>
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<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (ng•h/mL)</td>
<td>9360</td>
<td>9330</td>
<td>99.7 (76.0, 131)</td>
<td></td>
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<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</td>
<td>33.3</td>
<td>69.2</td>
<td>208 (117, 368)</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1250</td>
<td>1080</td>
<td>86.1 (65.4, 113)</td>
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Figure 1. Mean (± standard deviation) plasma concentration-time profile of elvitegravir (EVG) (inset: concentration profile over 96 hours) following administration of cobicistat-boosted elvitegravir in subjects with moderate liver impairment or matched control subjects (N=10/ cohort).
Figure 2. Mean (± standard deviation) plasma concentration-time profile of cobicistat (COBI) (inset: concentration profile over 96 hours) following administration of cobicistat-boosted elvitegravir in subjects with moderate liver impairment or matched control subjects (N=10/cohort).
Figure 3. Scatter plot of relationship between elvitegravir (EVG) or cobicistat (COBI) $AUC_{\text{tau}}$ and Child-Pugh-Turcotte (CPT) score at baseline in subjects with moderate liver impairment.