

# Pharmacokinetic Interaction Between Boceprevir and Etravirine in HIV/HCV Seronegative Volunteers

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**Objective:** The primary aim of this study was to determine the bioequivalence of boceprevir, an HCV protease inhibitor and etravirine, an HIV non-nucleoside reverse transcriptase inhibitor; area under the concentration time curve ( $AUC_{0,7}$ ); maximum concentration ( $C_{max}$ ); and trough concentration ( $C_8$  or  $C_{min}$ ) when administered in combination versus alone.

**Design:** Open-label crossover study in healthy volunteers.

**Methods:** Boceprevir, etravirine, and the combination were administered for 11–14 days with intensive sampling between days 11 and 14 of each sequence. Boceprevir and etravirine were quantified using validated liquid chromatography coupled with tandem mass spectrometry and high-performance liquid chromatography/ultraviolet assays, respectively and pharmacokinetics determined using noncompartmental methods. Geometric mean ratios (GMRs) and 90% confidence interval (CI) for the combination versus each drug alone were evaluated using 2 one-sided *t* tests. The hypothesis of equivalence was rejected if 90% GMR CI was not contained in the interval (0.8–1.25).

**Results:** Twenty subjects completed study. GMRs (90% CI) for etravirine  $AUC_{0,7}$ ,  $C_{max}$ , and  $C_{min}$  were 0.77 (0.66 to 0.91), 0.76 (0.68 to 0.85), and 0.71 (0.54 to 0.95), respectively, in combination versus alone. Boceprevir GMRs (90% CI) for  $AUC_{0,7}$ ,  $C_{max}$ , and  $C_8$  were 1.10 (0.94 to 1.28), 1.10 (0.94 to 1.29), and 0.88 (0.66 to 1.17), respectively, in combination versus alone. All adverse events (*n* = 112) were mild or moderate. Six subjects discontinued: 4 due to rash, 1 due to central nervous system effects, and 1 for a presumed viral illness.

**Conclusions:** Etravirine  $AUC_{0,7}$ ,  $C_{max}$ , and  $C_{min}$  decreased 23%, 24%, and 29%, respectively, with boceprevir. Boceprevir  $AUC_{0,7}$  and  $C_{max}$  increased 10% and  $C_8$  decreased 12% by etravirine. Additional research is needed to elucidate the mechanism(s) and therapeutic implications of the observed interaction.

**Key Words:** boceprevir, etravirine, interaction, pharmacokinetic, bioequivalence

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## INTRODUCTION

In the United States, approximately 30% of persons infected with the human immunodeficiency virus (HIV) are coinfecting with the hepatitis-C virus (HCV).<sup>1</sup> In the presence of HIV, individuals with HCV have a more frequent and accelerated progression to fibrosis, cirrhosis, and end-stage liver disease than their HCV monoinfected counterparts.<sup>2,3</sup> Additionally, HIV infection has been associated with persistent HCV viremia, higher HCV viral load, and reduced response to interferon-based HCV therapy.<sup>4</sup> These complications highlight the salient need for effective HCV therapy in persons coinfecting with HIV and HCV.

Contrary to HIV, HCV can be cured as defined by an absence of detectable HCV RNA 24 weeks after stopping treatment [sustained virological response (SVR)]. Coinfected patients achieve SVR with pegylated interferon plus ribavirin (P/R) at a rate of 27%–29%.<sup>5–7</sup> This is significantly lower than in the HCV monoinfected population.<sup>8–10</sup> Augmenting P/R with an NS3/4A protease inhibitor, either boceprevir (Victrelis, Whitehouse Station, NJ) or telaprevir (Incivek, Cambridge, MA), improves SVR rates. In the treatment naive HCV monoinfected population, SVR is increased approximately 30% with the addition of boceprevir or telaprevir to P/R.<sup>11–13</sup> Although NS3/4A protease inhibitors are not yet approved for HIV/HCV-coinfecting patients, interim analyses have shown promising results with SVR at 61% (vs. 27% for P/R alone) for boceprevir and 74% (vs. 45% for P/R alone) for telaprevir.<sup>14,15</sup> Non-nucleoside reverse transcriptase inhibitors, including etravirine, were not included in the phase 2 boceprevir coinfection study based on CYP3A induction of boceprevir metabolism by efavirenz. However, etravirine has different pharmacology and a different drug–drug interaction profile compared with efavirenz. Non-nucleoside reverse transcriptase inhibitors are an important component of antiretroviral therapy<sup>16</sup>; excluding their use in coinfecting patients is detrimental. Evaluating the

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interaction potential between boceprevir and etravirine, and management of any discovered interactions, will fill an important gap in the treatment of coinfecting patients.

Etravirine is a substrate for cytochrome P450 (CYP) 3A, CYP2C9, CYP2C19, and uridine glucuronosyl transferases.<sup>17</sup> It is also a weak inhibitor of CYP2C9 and CYP2C19 and an inducer of CYP3A4.<sup>18</sup> Etravirine is not a substrate for the drug transporter p-glycoprotein (P-gp), but is a weak inhibitor of this transporter.<sup>18</sup> Boceprevir is metabolized by aldoketoreductases 1C3 and 1C2, is a substrate of CYP3A and P-gp<sup>19</sup> and an inhibitor of CYP3A. The overlapping pharmacology through the CYP3A enzyme and P-gp transporter provides a platform for drug interactions to occur. Efavirenz, a potent CYP3A4 enzyme inducer, causes a 44% reduction in minimum concentration ( $C_{\min}$ ) of boceprevir.<sup>19</sup> In addition, boceprevir increases the area under the concentration time curve (AUC) of oral midazolam (a sensitive substrate of CYP3A4) by 5.3-fold.<sup>19</sup>

The primary objective of this study was to determine the bioequivalence of boceprevir and etravirine by estimating AUC over the dosing interval ( $AUC_{0,\tau}$ ), maximum concentration ( $C_{\max}$ ), and trough concentration [ $C_{\min}$  for etravirine and 8 hour postdose concentration ( $C_8$ ) for boceprevir], when administered alone and in combination in HIV/HCV seronegative healthy volunteers. Secondary objectives included estimating changes in other pharmacokinetic parameters and assessing the safety and tolerability of the 2 drugs when used alone and in combination.

## METHODS

The study (NCT01427504) was approved by the Colorado Multiple Institutional Review Board. All participants provided written informed consent. All study procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

## Subjects

Healthy HIV-1/HCV-seronegative men and women between 18 and 60 years of age with hemoglobin, platelet count, absolute neutrophil count, serum creatinine, and hepatic function test results all within normal limits at screening were eligible. All other laboratory tests were accepted if not greater than grade 1 per the 2004 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.<sup>20</sup> Criteria for exclusion from study participation were allergy or sensitivity to boceprevir or etravirine; active dermatitis or urticaria or diagnosis of eczema or psoriasis; active drug or alcohol abuse or dependence; active or chronic gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory, infectious disease, or malignancy requiring pharmacologic treatment or, in the opinion of the investigator, likely to affect study participation or safety or integrity of results; and the use of concomitant medications, including investigational, prescription, and over-the-counter products and dietary supplements within 14 days of study entry with the exception of acetylsalicylic acid, acetaminophen, once-daily multivitamins, mineral supplements, and hormonal oral contra-

ceptives (other than those that contain drospirone). Subjects who participated in any investigational drug study within 30 days before study entry were also excluded. Women who were pregnant or breast-feeding and women and men of reproductive potential engaging in sexual activity or assisted reproductive technology with the intent of pregnancy were also excluded. Because of the potential effects of boceprevir on oral contraceptive concentrations, all men and women of reproductive potential were required to use at least 2 contraceptive methods, including a barrier method (condoms, diaphragm, female condoms, or cervical cap) during the study and for at least 2 weeks after the last dose of study drug.

## Design

This was an open-label, 3-treatment, 3-period, crossover study designed to determine the effect of etravirine on the  $AUC_{0,\tau}$ ,  $C_{\max}$ , and  $C_8$  of boceprevir and to determine the effect of boceprevir on the  $AUC_{0,\tau}$ ,  $C_{\max}$ , and  $C_{\min}$  of etravirine in HIV-1/HCV-seronegative subjects. Subjects received 3 treatment sequences and were randomized to sequence order resulting in 6 possible combinations. The 3 sequences included boceprevir 800 mg every 8 hours for 11–14 days (sequence 1), etravirine 200 mg every 12 hours for 11–14 days (sequence 2), and boceprevir 800 mg every 8 hours plus etravirine 200 mg every 12 hours for 11–14 days (sequence 3). The sequence length of 11–14 days allowed flexibility in scheduling visits. Participants were instructed to take each home dose with food. Two washout periods, at least 14 days in length, occurred between the 3 sequences. Participants underwent intensive 8-, 12-, and 12-hour pharmacokinetic visits on days 11–14 of sequence 1, 2, and 3, respectively. Subjects were fed a standardized moderate fat breakfast (600–700 kcal; 45% carbohydrates, 15% protein, and 40% fat) at all 3 intensive pharmacokinetic visits before study drug(s) administration. Blood samples for pharmacokinetic analysis were collected before dosing and at the following time points after an observed dose of study drug(s): 1, 2, 3, 4, 5, 6, and 8 hours for boceprevir and at these time points plus 10 and 12 hours postdose for sequences that included etravirine. Eligibility laboratories (HIV and HCV antibody, urine pregnancy, comprehensive metabolic panel, and complete blood count) were obtained at screening and safety laboratories (urine pregnancy, comprehensive metabolic panel, and complete blood count) were obtained at the 3 intensive pharmacokinetic visits. Adherence was assessed by participant self-report and by pill count during the 3 intensive pharmacokinetic study visits.

## Bioanalyses

### Boceprevir in Plasma

Blood samples for boceprevir quantification were cooled in an ice bath, approximately 4°C, and then centrifuged within 30 minutes of collection. The samples were centrifuged for 15 minutes at 1500g in a refrigerated centrifuge (4°C). Immediately following centrifugation, 1.5 mL of plasma was placed in prechilled cryovials containing 75  $\mu$ L of

85% phosphoric acid. The vials were capped, mixed well, and kept on wet ice until placed in a freezer for storage at  $-20^{\circ}\text{C}$  or colder.

Boceprevir in plasma was analyzed by PPD (Highland Heights, KY). Boceprevir plasma samples were fortified with 150  $\mu\text{L}$  of internal standard working solution (1.00  $\mu\text{g}/\text{mL}$  503034-d9 and 1.00  $\mu\text{g}/\text{mL}$  629144-d9 in 10% phosphoric acid solution). The prepared samples were then loaded onto a 96-well SPEC-IQe solid phase extraction plate. The analytes and internal standards were eluted from the solid phase extraction plate with 200- $\mu\text{L}$  aliquots of ammonium hydroxide (0.1%) in acetonitrile. The extracts were dried and reconstituted with 250- $\mu\text{L}$  of acetonitrile:water (30:70, v:v). The extract was divided into two plates. The first plate was analyzed for the boceprevir stereoisomers via HPLC with tandem mass spectrometry detection using positive ion atmospheric pressure chemical ionization. The chromatographic separation of boceprevir stereoisomers and the internal standard was accomplished on a Agilent Zorbax SBC18  $2.1 \times 100\text{-mm}$  column with a 3.5  $\mu\text{m}$  particle size. The mobile phase consisted of nonafluoropentanoic acid in water (1%) and ammonium acetate in methanol (10 mM). The linear ranges for the stereoisomers of boceprevir were 5.20–5200 ng/mL for SCH534128 and 4.8–4800 ng/mL for SCH534129. A linear, 1 per square concentration weighted, least-squares regression algorithm was used to quantify unknown samples containing the boceprevir stereoisomers. The second plate was analyzed for the boceprevir metabolites via HPLC with MS/MS detection using positive ion electrospray with a linear range of 2.50–2500 ng/mL for each stereoisomer of boceprevir metabolite (SCH783007, SCH783005, SCH783006, and SCH783004). The chromatographic separation of boceprevir metabolites and the internal standard was accomplished on a Waters Sunfire C18  $2.1 \times 100\text{-mm}$  column with a 3.5  $\mu\text{m}$  particle size. The mobile phase consisted of ammonium acetate in water (10 mM) and acetonitrile. A quadratic, 1 per square concentration weighted, least-squares regression algorithm was used to quantify unknown samples containing the boceprevir metabolite stereoisomers. The coefficients of determination ( $r^2$ ) for all the standard curves of all analytes were  $\geq 0.9950$ . Inter- and intraday accuracy and precision were within +20% at the lower limit of quantification and  $\pm 15\%$  at other concentrations for all analytes.

### Etravirine in Plasma

Etravirine in plasma was analyzed by the Colorado Antiviral Pharmacology Laboratory (Aurora, CO). Blood for determination of etravirine was processed by centrifugation and plasma stored ( $-70^{\circ}\text{C}$ ) within 30 minutes of collection. Etravirine plasma concentrations were determined using a validated HPLC ultraviolet (UV) method. Briefly, after addition of internal standard (6,7-dimethyl-2,3-di(2-pyridyl)quinoxaline), a liquid–liquid extraction procedure with *t*-butylmethylether at basic pH was used to prepare the samples. The chromatographic separation of etravirine and the internal standard was accomplished on a Phenomenex Kinetex  $50 \times 4.6\text{-mm}$  C8 column with a 2.6  $\mu\text{m}$  particle size. The mobile phase consisted of 50% 20 mM acetate buffer/50% acetonitrile, pH 4.88, with

an isocratic flow rate of 1.5 mL/min. Detection and quantification of the drug was performed at 305 nm. The assay used 0.2 mL of EDTA plasma and linear weighting (1 per square concentration) within the reportable range of 20 ng/mL (LLOQ)–5000 ng/mL upper limit of quantification. Proficiency samples for external validation passed. The standard curves generated had coefficients of determination ( $r^2$ )  $> 0.9988$ . Inter- and intraday accuracy and precision were within  $\pm 20\%$  at the LLOQ and  $\pm 15\%$  at all other concentrations.

### Pharmacokinetic Analysis

Boceprevir and etravirine pharmacokinetics were determined by noncompartmental methods (WinNonLin, v5.3; Pharsight Corporation, Mountain View, CA).  $C_{\text{max}}$ , time to  $C_{\text{max}}$  ( $T_{\text{max}}$ ),  $C_8$ , and  $C_{\text{min}}$  were determined visually.  $\text{AUC}_{0,\tau}$  was determined using the linear-log trapezoidal rule. Total apparent oral clearance (CL/F) was determined as dose divided by  $\text{AUC}_{0,\tau}$ . The apparent volume of distribution (V/F) was estimated using the following equation:  $V_z = \text{dose}/(\lambda_z \times \text{AUC}_{0,\tau})$ . Half-lives were calculated using the following equation:  $t_{1/2} = \ln 2/K_e$ , where  $K_e$  is the elimination rate.

### Safety and Tolerability Assessments

Clinical adverse effects were verbally assessed by study investigators and graded as mild (does not interfere with normal activities), moderate (interferes with normal activities to some extent), serious (persistent or significant disability/incapacity), or life threatening (requiring hospitalization). Laboratory tests were performed at baseline and at all 3 intensive pharmacokinetic study visits. Clinical and laboratory adverse events were graded by study investigators using the 2004 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences.<sup>20</sup>

### Statistical Analysis

The primary endpoints for this study were boceprevir and etravirine  $\text{AUC}_{0,\tau}$ ,  $C_{\text{max}}$ ,  $C_8$  (boceprevir), and  $C_{\text{min}}$  (etravirine) bioequivalence when given in combination versus alone. The study was powered based on the assumption that 15, 19, and 22 subjects would provide 90% power to determine boceprevir  $\text{AUC}_{0,\tau}$ ,  $C_{\text{max}}$ , and  $C_8$  bioequivalence [Geometric mean ratio (GMR) 90% CI: 0.8 to 1.25], respectively, with versus without etravirine given a boceprevir  $\text{AUC}_{0,\tau}$  mean ( $\pm\text{SD}$ ) of 4302 ng·h/mL (1436),  $C_{\text{max}}$  mean ( $\pm\text{SD}$ ) of 1002 (383) ng/mL,  $C_8$  mean ( $\pm\text{SD}$ ) of 213 (89) ng/mL and within subject correlation of 0.7 (Merck; data on file). Similarly, 13, 12, and 15 subjects would provide 90% power to determine etravirine  $\text{AUC}_{0,\tau}$ ,  $C_{\text{max}}$ , and  $C_{\text{min}}$  bioequivalence, respectively, with versus without boceprevir assuming an etravirine  $\text{AUC}_{0,\tau}$  mean ( $\pm\text{SD}$ ) of 8195 ng·h/mL (2428),  $C_{\text{max}}$  mean ( $\pm\text{SD}$ ) of 959 (278) ng/mL,  $C_{\text{min}}$  mean ( $\pm\text{SD}$ ) of 530 (173) ng/mL, and within subject correlation of 0.7.<sup>21</sup>

GMRs and 90% CI for the combination sequence versus alone were evaluated using 2 one-sided *t* tests.<sup>22</sup> The hypothesis of equivalence was rejected if the lower confidence limit was  $< 0.8$  or the upper confidence limit was  $> 1.25$ . Other pharmacokinetic parameters were compared using paired *t* tests. No adjustments were made for multiple

**TABLE 1.** Summary of Demographic Information for Study Subjects

	Enrolled Patients, N = 26	Evaluable Patients, N = 20
Age (yrs): median, (range)	32.4 (18.7–59.0)	36.7 (18.7–59.0)
Weight (kgs): median, (range)	70.2 (56–102.9)	73.0 (56.0–91.0)
Females	14	10
Males	12	10
Whites, n (%)	17 (65)	14 (70)
African Americans, n (%)	4 (15)	3 (15)
Hispanics, n (%)	4 (15)	3 (15)
Asians, n (%)	1 (4)	—

comparisons. SAS version 9.3 (SAS Institute, Cary, NC) was used for data analyses.

## RESULTS

### Subjects

Thirty-four subjects consented to participate, 26 subjects enrolled, and 20 subjects completed all 3 sequences. Of the 8 subjects who were not enrolled in the study, 3 failed screening because of laboratory abnormalities, and 5 subjects decided not to participate for various personal reasons before starting study medications. All 6 subjects who were not included in the pharmacokinetic analyses were discontinued because of an adverse event related to study medication. A summary of demographic information is presented in Table 1.

### Etravirine Pharmacokinetics

The results of the pharmacokinetic analyses comparing etravirine given alone with etravirine in combination with boceprevir are shown in Table 2. Etravirine  $AUC_{0,\tau}$ ,  $C_{max}$ , and  $C_{min}$  were decreased 23%, 24%, and 29% (Fig. 1), respectively, in the presence of boceprevir; whereas, CL/F and V/F increased from a mean (CV%) of 26 L/h (30%) to 34 L/h (79%) and from 416 L (44%) to 554 L (37%), respectively, in the presence of boceprevir. The lower bound of the 90% confidence intervals (CIs) for the GMRs for  $AUC_{0,\tau}$ ,  $C_{max}$ , and  $C_{min}$  were all below the lower

bioequivalence limit of 80% indicating that etravirine pharmacokinetics when given in combination with boceprevir are not bioequivalent to etravirine pharmacokinetics when administered alone.

### Boceprevir Pharmacokinetics

The results of the pharmacokinetic analyses comparing boceprevir given alone with boceprevir in combination with etravirine are shown in Table 3. The  $AUC_{0,\tau}$  and  $C_{max}$  were increased by 10% in the presence of etravirine (Fig. 2); whereas, the  $C_8$  was decreased by 12% in the presence of etravirine. The CL/F and V/F mean (CV%) decreased from 174 L/h (30%) to 159 L/h (23%) and from 310 L (47%) to 263 L (65%), respectively, in the presence of etravirine. The upper bound of the 90% CIs for the GMRs for  $AUC_{0,\tau}$  and  $C_{max}$  were above the upper bioequivalence limit of 125% and the lower bound of the 90% CI for the GMR for  $C_8$  was below the lower bioequivalence limit of 80%. Thus, boceprevir pharmacokinetics when given in combination with etravirine is not bioequivalent to boceprevir pharmacokinetics when administered alone. Similar pharmacokinetic results were seen with the keto-reduced boceprevir metabolites (SCH629144) in the presence of etravirine. The  $AUC_{0,\tau}$  and  $C_{max}$  were increased for SCH629144, whereas  $C_8$ , CL/F, and V/F were decreased in the presence of etravirine (data not shown).

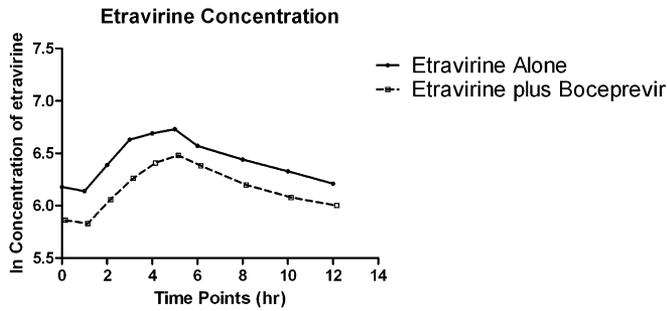
### Safety and Tolerability

All clinical and laboratory adverse events observed in the study were graded as mild or moderate (n = 112). The most common adverse event was altered taste, a common side-effect of boceprevir administration, reported by 18 (86%) of 21 subjects during the boceprevir alone sequence and 16 (64%) of 25 subjects during the combination sequence. Other adverse events observed at a frequency of greater than 10% included headache reported in 4 (19%) of 21 subjects, 5 (22.7%) of 22 subjects, and 4 (16%) of 25 subjects receiving boceprevir alone, etravirine alone, and the combination, respectively; fatigue reported in 3 (14.3%) of 21, 1 (4.5%) of 22, and 3 (12%) of 25 subjects receiving boceprevir alone, etravirine alone, and the combination, respectively; nausea reported in 4 (19%) of 21 and 3 (12%) of 25 receiving boceprevir alone and the combination, respectively;

**TABLE 2.** Etravirine Pharmacokinetics (n = 20)

	Geometric Mean (CV %)					Median (IQR)	
	$AUC_{0,\tau}$ (ng h/mL)	$C_{max}$ (ng/mL)	$C_{min}$ (ng/mL)	CL/F (L/h)	V/F (L)	Half-Life (h)	$T_{max}$ (h)
ETV alone	7698 (33%)	900 (29%)	439 (46%)	26 (30%)	416 (44%)	10 (9–15)	4.51 (3.0–5.0)
ETV + BOC	5957 (54%)	686 (45%)	313 (69%)	34 (79%)	554 (37%)	12 (8–15)	4.51 (3.53–5.0)
GMR (90% CI) ETV + BOC versus ETV alone	0.77 (0.66 to 0.91)	0.76 (0.68 to 0.85)	0.71 (0.54 to 0.95)	—	—	—	—
<i>P</i> *	—	—	—	0.112	0.0315	0.7388	0.7916

\*Based on paired *t* tests. No adjustments were made for multiple comparisons. BOC, boceprevir; ETV, etravirine.



**FIGURE 1.** Linear-natural log representation of mean etravirine concentrations, administered alone versus in combination with boceprevir, measured in nanograms per milliliter over the dosing interval measured in hours.

hypokalemia ( $\leq 2.9$  mmol/L) observed in 4 (19%) of 21 on boceprevir alone and 2 (8%) of 25 on the combination; and rash which was mild in one subject each on etravirine alone and the combination and moderate in 1 subject on etravirine alone and in 3 subjects receiving the combination. Six subjects discontinued study; 4 due to grade 2 rash (3 on combination, 1 on etravirine only); 1 due to increased energy, anxiety, nervousness, and insomnia while on the combination; and 1 due to presumed viral illness while on the combination, causing her to miss 3 consecutive days of study medications.

**DISCUSSION**

The results of this study were not predicted based on the known pharmacology of these drugs; boceprevir concentrations were expected to be reduced by etravirine, via induction of CYP3A, and etravirine concentrations were expected to increase via inhibition of CYP3A. However, this was not the case. Etravirine  $AUC_{0,\tau}$ ,  $C_{max}$ , and  $C_{min}$  were reduced 23%, 24%, and 29%, respectively, by boceprevir. Boceprevir  $AUC_{0,\tau}$  and  $C_{max}$  were slightly increased (~10%) and  $C_8$  was reduced by an average of 12% in the presence of etravirine. For boceprevir, the 10% increase in both  $AUC_{0,\tau}$  and  $C_{max}$ , along with the 12% decrease in  $C_8$  are within the suggested clinical equivalence range for boceprevir of 0.5–2.0.<sup>23</sup> Thus, it is unlikely that these observed small changes in boceprevir concentrations would have clinical relevance.

The mechanism for boceprevir causing decreased etravirine concentrations is unclear; however, boceprevir has also been shown to decrease the exposure of ritonavir-boosted HIV protease inhibitors.<sup>24</sup> Several mechanisms can be hypothesized to explain this interaction, including a reduction in bioavailability, protein binding displacement, and hepatic enzyme induction.

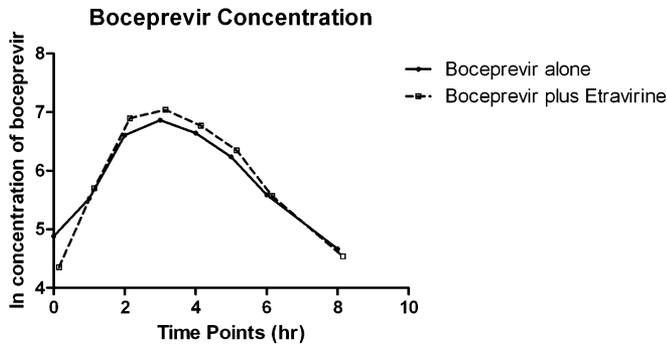
Etravirine CL/F and V/F were increased to a similar extent, suggesting boceprevir may decrease etravirine’s bioavailability (F). There are 2 factors contributing to bioavailability: absorption and first-pass hepatic uptake. Etravirine absorption could be decreased by reduced etravirine solubility. Etravirine is very insoluble, lending merit to this hypothesis.<sup>25</sup> However, there is a lack of literature supporting solubility interactions with either etravirine or boceprevir. Furthermore, etravirine is not affected by coadministration of oral ranitidine or omeprazole.<sup>17</sup> Influx and efflux transporters at the gut influence absorption as well. However, etravirine is not a substrate for P-gp, multidrug resistance proteins or breast cancer resistance protein.<sup>26</sup> Alternatively, induction of hepatic uptake transporters (eg, organic anion-transporting polypeptide) would increase the amount of etravirine taken up by the liver and decrease etravirine plasma concentrations. There are no data to support boceprevir as an inducer of transporters. In fact, boceprevir is a breast cancer resistance protein and organic anion-transporting polypeptide 1B1 inhibitor.<sup>27,28</sup>

Drug displacement from plasma proteins may account for decreased drug levels of etravirine. Etravirine is 99.9% bound to plasma proteins, primarily to albumin (99.6%) and alpha 1-acid glycoprotein (97.66%–99.02%).<sup>17</sup> If boceprevir displaces etravirine from its plasma protein binding site, the fraction of unbound etravirine would remain the same but total concentrations would be reduced. There are no data on ability of boceprevir to cause drug displacement interactions. However, when telaprevir, an HCV protease inhibitor like boceprevir, was administered with methadone, the total  $C_{min}$ ,  $C_{max}$ , and  $AUC_{0,\tau}$  for R-methadone (active form) was reduced 31%, 29%, and 29%, respectively, compared with telaprevir alone, but the unbound fraction was unchanged.<sup>29</sup> Telaprevir is 59%–76% protein bound, whereas methadone is 85%–90% protein bound.<sup>30,31</sup> Although it is difficult to compare boceprevir with telaprevir regarding etravirine interaction potential, etravirine combined with telaprevir resulted in no changes in pharmacokinetics of etravirine and only a slight 16% decrease in AUC of telaprevir.<sup>32</sup>

**TABLE 3.** Boceprevir Pharmacokinetics (n = 20)

	Geometric Mean (CV%)					Median (IQR)	
	$AUC_{0,\tau}$ (ng h/mL)	$C_{max}$ (ng/mL)	$C_8$ (ng/mL)	CL/F (L/h)	V/F (L)	Half-Life (h)	$T_{max}$ (h)
BOC	4601 (47%)	1423 (43%)	106 (64%)	174 (30%)	310 (47%)	1 (1–1.5)	3.0 (2.0–4.0)
BOC + ETV	5047 (30%)	1565 (28%)	94 (98%)	159 (23%)	263 (65%)	1. (0.9–1.3)	2.5 (2.0–3.02)
GMR (90% CI) ETV + BOC vs. BOC	1.10 (0.94 to 1.28)	1.10 (0.94 to 1.29)	0.88 (0.66 to 1.17)	—	—	—	—
<i>P</i> *	—	—	—	0.316	0.327	0.6771	0.1519

\*Based on paired *t* tests. No adjustments were made for multiple comparisons. BOC, boceprevir; ETV, etravirine.



**FIGURE 2.** Linear-natural log representation of mean boceprevir concentrations, administered alone versus in combination with etravirine, measured in nanograms per milliliter over the dosing interval measured in hours.

The last potential mechanism to consider is enzyme induction by boceprevir. Etravirine is primarily metabolized by CYP3A, 2C9, and 2C19.<sup>17</sup> Escitalopram and ethinyl estradiol, known substrates for these enzymes, have shown reduced AUCs in the presence of boceprevir.<sup>19,33</sup> In addition, mean  $t_{1/2}$  of escitalopram decreased from 31 to 22 hours.<sup>33</sup> However, the major active metabolite (desmethylcitalopram) seemed to have similar pharmacokinetics with and without boceprevir coadministration.<sup>33</sup> Furthermore, there is no in vitro data supporting boceprevir as an enzyme inducer.<sup>34</sup> Additionally, Figure 1 shows little change in the apparent etravirine  $t_{1/2}$  with the addition of boceprevir over the 12-hour interval in which subjects were sampled.

Regardless of the mechanism,  $AUC_{0,\tau}$ ,  $C_{max}$ , and  $C_{min}$  of etravirine were reduced 23%, 24%, and 29%, respectively, when coadministered with boceprevir. The suggested clinical equivalence limit for etravirine exposure is 0.5–2.0.<sup>35</sup> Thus, in isolation, reductions of this magnitude may not put patients at risk for HIV treatment failure. However, combinations of antiretroviral drugs are used to treat HIV. In the presence of tenofovir, etravirine exposures are decreased 19%, and etravirine is reduced more than 30% when coadministered with the ritonavir-boosted protease inhibitors, lopinavir, saquinavir, and darunavir.<sup>36,37</sup> Thus, in combination with the aforementioned antiretrovirals, patients on boceprevir may have clinically relevant decreases in etravirine exposure. Conversely, drug exposures may be higher in those with HCV-induced liver disease, which may provide protection against a reduction in drug exposures because of an interaction, but this requires study for etravirine.<sup>38</sup>

There are limitations to our study. Although a healthy volunteer study eliminates many confounding factors, responses in a clinical setting may differ. Multiple bidirectional interactions are possible in coinfecting individuals. Thus, the clinical implications of the interaction can only be fully realized in the patient population that will receive this combination. A second limitation relates to pharmacokinetic sampling. An interaction at the level of enzyme induction is difficult to rule out since we sampled etravirine over 12 hours while  $t_{1/2}$  of etravirine is 41 hours per the product label.<sup>17</sup> Thus, the determination of  $t_{1/2}$  may not be sufficiently accurate because of the short sampling time relative to the long  $t_{1/2}$ , and any change in  $K_e$  may not have

been detected. However, our sampling strategy mimicked the dosing strategy.

In conclusion, when boceprevir was combined with etravirine, no clinically relevant changes in boceprevir pharmacokinetics were observed, so dose adjustments of boceprevir are not required. However, coadministration of etravirine with boceprevir decreased  $AUC_{0,\tau}$  23%,  $C_{max}$  24%, and  $C_{min}$  29% of etravirine. Future research on the potential mechanism for the interaction and multiple combinations of antiretrovirals with etravirine in the presence of boceprevir is needed to optimize clinicians' confidence in using this combination.

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