Pharmacokinetic Interaction Between HCV Protease Inhibitor Boceprevir and Methadone or Buprenorphine/Naloxone in Subjects on Stable Maintenance Therapy

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Background

- Boceprevir is a potent, orally administered ketoamide inhibitor targeting the active site of the HCV NS3 protease\textsuperscript{1-3}
- Intravenous drug use is one of the most common routes of HCV infection, and treatment frequently requires maintenance therapy with methadone or buprenorphine/naloxone
- Treatment of HCV in active drug users is generally considered acceptable, providing they have been on stable substitution therapy for at least 6-12 months\textsuperscript{4}

HCV, hepatitis C virus; NS3, nonstructural protein 3.
Metabolic Interactions

- Boceprevir is a strong cytochrome P450 (CYP) 3A4 inhibitor

- Methadone metabolism occurs primarily in the liver and intestine by multiple members of the cytochrome P450 family, including CYP3A4

- Buprenorphine is metabolized via CYP3A4 to form norbuprenorphine, an active metabolite, in addition to other pathways
  - Norbuprenorphine has an estimated 2% the analgesic potency of buprenorphine, and is generally not considered of significant clinical importance in the treatment of opioid dependence\(^1\)

- Naloxone, co-formulated with buprenorphine, is primarily metabolized by conjugation with glucuronic acid, but also has been reported to be metabolized by CYP3A4 \textit{in vitro}

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Aims

● Primary
  – To determine the effect of steady-state boceprevir on the pharmacokinetic profile of methadone and buprenorphine/naloxone

● Secondary
  – To evaluate the safety and tolerability of coadministration of methadone or buprenorphine/naloxone with boceprevir
  – To determine the effect of steady-state boceprevir on the pharmacokinetic profile of naloxone
  – To evaluate the effect of steady-state methadone and buprenorphine/naloxone on the pharmacokinetic profile of boceprevir
Methods: Study Design

- A two-center, open-label, fixed-sequence, drug-drug interaction study in 21 adult volunteers on maintenance therapy
  - Cohort A: Methadone 20-150 mg, as tablets, liquid, or diskets QD
  - Cohort B: Buprenorphine/naloxone 8/2-24/6 mg tablets QD

Boceprevir 800 mg TID, days 2-7

PK, pharmacokinetic; QD, once daily; TID, three times daily.

aPharmacokinetic samples were taken pre-dose and for 24 hours post-dose on days 1 and 7.
bDay 7 samples also used for assessment of boceprevir pharmacokinetics.
Methods: Subjects

- Adult male and female subjects between 18 and 65 years old.
- Reliable participation in:
  - Methadone or buprenorphine maintenance or buprenorphine/naloxone maintenance program for at least 2 months.
  - Stable dosing of methadone or buprenorphine for at least 4 weeks, and with stable dosing of buprenorphine/naloxone for at least 2 weeks.
- On adequate birth control.
- No clinically significant disease.
- Negative for hepatitis B surface antigen, hepatitis C antibodies, and HIV.
- Provided written informed consent.
- Subjects with positive screen for drugs with high abuse potential were excluded.

HIV, human immunodeficiency virus.
## Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir + Methadone (n = 10)</th>
<th>Boceprevir + Buprenorphine / Naloxone (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (20)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (80)</td>
<td>9 (82)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (90)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>1 (10)</td>
<td>1 (9)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>4 (40)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Non-Hispanic/Latino</td>
<td>6 (60)</td>
<td>9 (82)</td>
</tr>
<tr>
<td><strong>Mean age, years (SD)</strong></td>
<td>34.2 (10.2)</td>
<td>33.2 (10.5)</td>
</tr>
<tr>
<td><strong>Mean BMI, kg/m^2 (SD)</strong></td>
<td>28.3 (7.1)</td>
<td>26.5 (3.9)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation.
Effect of Boceprevir on Methadone Pharmacokinetics

- Ten subjects were enrolled and completed the study.
- Boceprevir (800 mg TID) added to stable methadone therapy reduced the $\text{AUC}_\tau$ and $C_{\text{max}}$ of R-methadone (active enantiomer) by 15% and 22%, respectively, and of S-methadone by 22% and 17%, respectively.

Arithmetic Mean Dose-Normalized Plasma Concentration-Time Profiles of R- and S-Methadone (inset = semi-log scale)

$\text{AUC}_\tau$, area under the concentration-time curve during a dosing interval $\tau$; $C_{\text{max}}$, maximum observed plasma (or blood) concentration; TID, three times daily.
Effect of Boceprevir on Buprenorphine and Naloxone Pharmacokinetics

- Eleven subjects were enrolled and completed the study
  - Two subjects discontinued early (noncompliance, n = 1; personal reasons, n = 1)
- Boceprevir (800 TID) added to stable buprenorphine/naloxone therapy increased the AUC$_\tau$ and $C_{\text{max}}$ of buprenorphine by 19% and 18%, respectively, and of naloxone by 33% and 9%, respectively

Arithmetic Mean Dose-Normalized Plasma Concentration-Time Profiles for Buprenorphine and Naloxone (inset = semi-log scale)

AUC$_\tau$, area under the concentration-time curve during a dosing interval $\tau$; $C_{\text{max}}$, maximum observed plasma (or blood) concentration; TID, three times daily.
### Effect of Boceprevir on Buprenorphine and Naloxone Pharmacokinetics (cont)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Geometric Mean&lt;sup&gt;a&lt;/sup&gt;</th>
<th>GMR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>90% CI for GMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;t&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP/NAL + BOC (n = 9)</td>
<td>1896</td>
<td>0.55</td>
<td>0.36, 0.86</td>
</tr>
<tr>
<td>BUP/NAL alone (n = 11)</td>
<td>3422</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP/NAL + BOC (n = 10)</td>
<td>129.4</td>
<td>0.54</td>
<td>0.36, 0.83</td>
</tr>
<tr>
<td>BUP/NAL alone (n = 11)</td>
<td>237.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;min&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP/NAL + BOC (n = 10)</td>
<td>53.5</td>
<td>0.68</td>
<td>0.41, 1.11</td>
</tr>
<tr>
<td>BUP/NAL alone (n = 11)</td>
<td>78.8</td>
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</table>

- The observed 19% increase in buprenorphine exposure and 45% decrease in norbuprenorphine exposure are consistent with inhibition of buprenorphine metabolism via the CYP3A pathway upon boceprevir coadministration.
- The difference in effect suggests that some of the buprenorphine blocked at CYP3A4 is being shunted through a separate metabolic system — likely UGT1A1.
- As norbuprenorphine has an estimated 2% of the analgesic potency of buprenorphine, the ~2-fold reduction in norbuprenorphine levels is not considered to be clinically significant.

AUC<sub>t</sub>, area under the concentration-time curve during the dosing interval τ; BOC, boceprevir; BUP, buprenorphine; CI, confidence interval; C<sub>max</sub>, maximum observed concentration; C<sub>min</sub>, minimum observed concentration; GMR, geometric mean ratio; MSE, mean squared error; NAL, naloxone.

<sup>a</sup>Back-transformed least squares means and CIs from mixed effect model performed on natural log-transformed values.

<sup>b</sup>Comparison of BUP/NAL + BOC versus BUP/NAL alone.

<sup>c</sup>Square root of conditional mean squared error (residual error) from the linear mixed effect model.
Boceprevir Exposure Was Not Clinically Significantly Different From Historical Controls

<table>
<thead>
<tr>
<th>Methadone study</th>
<th>Treatmenta</th>
<th>Geometric meanb</th>
<th>GMC 90% CI for GMR</th>
<th>rMSEd</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCτ (ng·h/mL/mg)</td>
<td>BOC + Methadone</td>
<td>4261</td>
<td>0.80</td>
<td>0.69, 0.93</td>
</tr>
<tr>
<td></td>
<td>BOC (historical)d</td>
<td>5307</td>
<td>0.89</td>
<td>0.80, 0.99</td>
</tr>
<tr>
<td>Cmax (ng/mL/mg)</td>
<td>BOC + Methadone</td>
<td>1042</td>
<td>0.62</td>
<td>0.53, 0.72</td>
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<tr>
<td></td>
<td>BOC (historical)d</td>
<td>1695</td>
<td>0.55</td>
<td>0.48, 0.64</td>
</tr>
<tr>
<td>Cmin (ng/mL/mg)</td>
<td>BOC + Methadone</td>
<td>99.4</td>
<td>1.03</td>
<td>0.75, 1.42</td>
</tr>
<tr>
<td></td>
<td>BOC (historical)d</td>
<td>96.4</td>
<td>1.02</td>
<td>0.75, 1.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine / naloxone study</th>
<th>Treatmenta</th>
<th>Geometric meanb</th>
<th>GMC 90% CI for GMR</th>
<th>rMSEd</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCτ (ng·h/mL/mg)</td>
<td>BOC + BUP/NALe</td>
<td>4708</td>
<td>0.88</td>
<td>0.76, 1.02</td>
</tr>
<tr>
<td></td>
<td>BOC (historical)d</td>
<td>5346</td>
<td>0.88</td>
<td>0.76, 1.02</td>
</tr>
<tr>
<td>Cmax (ng/mL/mg)</td>
<td>BOC + BUP/NAL</td>
<td>1390</td>
<td>0.82</td>
<td>0.71, 0.94</td>
</tr>
<tr>
<td></td>
<td>BOC (historical)d</td>
<td>1694</td>
<td>0.75</td>
<td>0.68, 0.84</td>
</tr>
<tr>
<td>Cmin (ng/mL/mg)</td>
<td>BOC + BUP/NAL</td>
<td>93.1</td>
<td>0.95</td>
<td>0.70, 1.28</td>
</tr>
<tr>
<td></td>
<td>BOC (historical)d</td>
<td>98.3</td>
<td>1.04</td>
<td>0.81, 1.36</td>
</tr>
</tbody>
</table>

AUCτ, area under the concentration-time curve during the dosing interval τ; BOC, boceprevir; BUP, buprenorphine; CI, confidence interval; Cmax, maximum observed concentration; Cmin, minimum observed concentration; GMR, geometric mean ratio; MSE, mean squared error; NAL, naloxone.
a n = 10 for all groups unless otherwise indicated.
bBack-transformed least squares means and CIs from mixed effect model performed on natural log-transformed values.
cComparison of BOC + maintenance therapy versus maintenance therapy alone.
dSquare root of conditional mean squared error (residual error) from the linear mixed effect model.
e n = 80–92 obtained from historical control group treated with the same dose/regimen/formulation.
f n = 9.
Safety

- No deaths, serious AEs, or treatment discontinuations due to an AE
- No clinically relevant changes in BP, pulse rate, ECG, or laboratory values
- No changes in opioid withdrawal or opioid excess
- Methadone
  - All 10 subjects reported AEs — all mild intensity
  - Most frequent AEs were nausea, headache, and somnolence (n = 3 each)
  - 9 subjects reported treatment-related AEs, most commonly nausea (n = 3) and somnolence (n = 3)
- Buprenorphine/naloxone
  - 9 subjects reported AEs
    - 2 subjects reported moderate-intensity AEs (abnormal taste/dry mouth/pollakiuria and thrombophlebitis)
    - Most frequent AEs were dysgeusia (n = 5) and headache (n = 3)
    - 8 subjects reported treatment-related AEs, most commonly dysgeusia (n = 5)

AE, adverse event; BP, blood pressure; ECG, electrocardiogram.
Conclusions

- There was no clinically meaningful impact of boceprevir on the pharmacokinetics of methadone
  - Boceprevir added to stable methadone therapy reduced the AUC$_\tau$ and C$_{max}$ of R-methadone by 15% and 22%, respectively, and of S-methadone by 22% and 17%, respectively
  - The observed reductions in exposure to both R- and S-methadone cannot be explained solely on the basis of CYP3A4 inhibition by boceprevir
- There was no clinically meaningful impact of boceprevir on the pharmacokinetics of buprenorphine/naloxone
  - The observed 19% increase in buprenorphine exposure and 45% decrease in norbuprenorphine exposure are consistent with inhibition of buprenorphine metabolism via the CYP3A pathway upon boceprevir coadministration. The difference in effect suggests that some of the buprenorphine blocked at CYP3A4 is being shunted through a separate metabolic system — likely UGT1A1
  - Consistent with the known metabolic pathways of naloxone being CYP2C18 and CYP2C19, the addition of boceprevir did not meaningfully affect the exposure to steady-state naloxone
- Steady-state boceprevir exposure in the presence of methadone or buprenorphine/naloxone was not clinically significantly different from historical controls

AUC$_\tau$, area under the concentration-time curve during the dosing interval $\tau$; C$_{max}$, maximum observed concentration; TID, three times daily.
Conclusions (cont)

- These data suggest that no dose adjustment of methadone or buprenorphine is needed upon coadministration of methadone or buprenorphine/naloxone with boceprevir.
- Coadministration of boceprevir with methadone or buprenorphine/naloxone is well tolerated.
- Individual patients may require additional titration of their methadone dosage when boceprevir is started or stopped to ensure clinical effect of methadone.
Disclosures

- RD Bruce and LR Webster have had a financial relationship within the last 12 months relevant to these data with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA
- H-P Feng, F Xuan, WH Lin, E O'Mara, JA Wagner, and JR Butterton are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA
- E Hulskotte is an employee of Merck Sharp & Dohme, The Netherlands
- This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ
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