Bioequivalence and Safety of HTX-019 (Surfactant-Free Aprepitant IV) and Fosaprepitant in Healthy Subjects

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Presented by Robert B. Geller
## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
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<tr>
<td>Heron Therapeutics</td>
<td>No</td>
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X Yes, please specify:

No, nothing to disclose
Chemotherapy-Induced Nausea and Vomiting (CINV)

- Consensus guideline—recommended treatment regimen for CINV following highly (HEC) and, frequently, for moderately emetogenic chemotherapy (MEC) comprises a 3-drug regimen:
  - 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist (RA)
  - dexamethasone
  - neurokinin 1 (NK-1) RA¹-⁴

- Aprepitant, an NK-1 RA, is available only in an oral formulation (EMEND PO),⁵ while fosaprepitant, an aprepitant prodrug,⁶ was developed to provide an IV route of administration
  - Fosaprepitant IV is associated with hypersensitivity and infusion-site reactions, primarily attributed to its surfactant, polysorbate 80⁷
    - Hypersensitivity reactions include flushing, erythema, and dyspnea
    - Infusion-site reactions include pain, erythema, swelling, induration, and thrombophlebitis⁸

References:
Rationale and Objectives

• Rationale for HTX-019 development
  − HTX-019 is a polysorbate 80–free IV formulation of aprepitant
    • May provide a safer IV NK-1 RA option with a lower risk of hypersensitivity and infusion-site reactions
    • Improve patient adherence versus an oral regimen

• Study objectives
  − Primary: To determine the bioequivalence (BE) of HTX-019 to fosaprepitant IV in healthy subjects
  − Secondary: To evaluate safety and tolerability of HTX-019 and fosaprepitant IV in healthy subjects
• Phase 1, open-label, randomized, 2-way crossover BE and safety evaluation of HTX-019 and fosaprepitant, each agent administered as a single IV dose to healthy subjects

• Observation period: 72 hours for each treatment period
  
  Note: Confinement lasted from morning of day -1 through day 4 of each treatment period (through the pharmacokinetic collection at 72 h on day 4), for a total of approximately 5 days per treatment period.

• Eligibility: Healthy men or women aged 18-55 years, ≥ 50 kg body weight (BMI 18-35 kg/m²), and not pregnant or breastfeeding
Methods

• Blood samples were collected before infusion start and 0.5-72 hours
  – All time points were analyzed for aprepitant
  – 0.5-1.5 hours were also analyzed for fosaprepitant

• Bioequivalence evaluation was based on aprepitant AUC\textsubscript{0-t}, AUC\textsubscript{0-inf}, and postequilibrium plasma aprepitant concentrations (C\textsubscript{12h})

• Bioequivalence was declared if 90% CI was within 80%-125%

• Safety evaluation included treatment-emergent adverse events (TEAEs) and serious AEs

AUC\textsubscript{0-t} = area under the time-concentration curve from zero to time t; AUC\textsubscript{0-inf} = area under the time-concentration curve from time zero extrapolated to infinity; C\textsubscript{12h} = plasma concentration at 12 hours.
Results

- 100 subjects enrolled
  - 97 of 100 completed the study and were included in BE analysis
  - All subjects were included in the safety analysis

- Demographics and baseline characteristics were comparable between the two treatment sequences

<table>
<thead>
<tr>
<th>Demographics and Baseline Clinical Characteristics (Safety Population)</th>
<th>Sequence I: AB N = 50</th>
<th>Sequence 2: BA N = 50</th>
<th>Overall N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>38 (10)</td>
<td>33 (9)</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>27 (3)</td>
<td>27 (4)</td>
<td>27 (4)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (36)</td>
<td>18 (36)</td>
<td>36 (36)</td>
</tr>
<tr>
<td>Male</td>
<td>32 (64)</td>
<td>32 (64)</td>
<td>64 (64)</td>
</tr>
<tr>
<td>Race, white, n (%)</td>
<td>30 (60)</td>
<td>25 (50)</td>
<td>55 (55)</td>
</tr>
</tbody>
</table>

Note: treatment A, HTX-019 130 mg IV; treatment B, fosaprepitant 150 mg IV. SD = standard deviation.
• 90% CIs for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\text{inf}}$, and $C_{12h}$ were well within bioequivalence bounds, consistent with comparable exposure.

• As expected, aprepitant mean $C_{\text{max}}$ was slightly higher for HTX-019 than for fosaprepitant IV due to ongoing conversion of fosaprepitant to aprepitant.

• Plasma aprepitant concentrations were essentially identical 15 minutes post-infusion through 72 hours.

$C_{\text{max}} =$ maximum concentration.
Results: Safety

- During the entire study period, fewer subjects had ≥1 TEAE with HTX-019 versus fosaprepitant IV (21% vs 28%); fewer HTX-019 subjects had a related TEAE (15% vs 28%)
- There was a lower incidence of TEAEs within 1 hour (1% vs 20%) and within 30 minutes (0% vs 17%) with HTX-019 versus fosaprepitant IV
- Most of the TEAEs occurred within the first 30 minutes

<table>
<thead>
<tr>
<th>Overall Summary of Treatment-Emergent Adverse Events (Safety Population)</th>
<th>HTX-019 130 mg N = 99</th>
<th>Fosaprepitant 150 mg N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 TEAE, n (%)</td>
<td>21 (21)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Subjects with related TEAE, n (%)</td>
<td>15 (15)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Subjects with TEAE leading to study discontinuation, n (%)</td>
<td>0</td>
<td>2 (2)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Events Within 1 Hour or 30 Minutes of Infusion Start (Safety Population)</th>
<th>HTX-019 130 mg N = 99</th>
<th>Fosaprepitant 150 mg N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 TEAE, n (%) Within 1 hour of infusion start</td>
<td>1 (1)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Subjects with ≥1 TEAE, n (%) Within 30 minutes of infusion start</td>
<td>0</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Number of TEAEs within 1 hour of infusion start</td>
<td>1</td>
<td>32</td>
</tr>
</tbody>
</table>

*2 subjects discontinued study drug because of moderate dyspnea.
Results: Safety

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Events in ≥ 3% patients in the Overall Study period (Safety Population)</th>
<th>HTX-019 130 mg N = 99</th>
<th>Fosaprepitant 150 mg N = 100</th>
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</thead>
<tbody>
<tr>
<td>Headache, n (%)</td>
<td>5 (5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Infusion-site pain, n (%)</td>
<td>1 (1)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>1 (1)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Vessel puncture site pain, n (%)</td>
<td>5 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness, n (%)</td>
<td>1 (1)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Pain in extremity, n (%)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Somnolence, n (%)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
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</table>

- A negative binomial analysis of TEAEs found the estimated event rate per subject-day for HTX-019 was approximately half the rate observed for fosaprepitant IV
  - 0.03 vs 0.06 TEAEs per subject-day; \( P = 0.0274 \)
- No severe TEAEs, serious TEAEs, or deaths occurred
- All TEAEs resolved by study end
Conclusions

• HTX-019 was bioequivalent to fosaprepitant IV
• HTX-019 was generally well tolerated, without the infusion-site reactions associated with fosaprepitant IV
  − The single case of dyspnea seen in the HTX-019 treatment group was not treatment-related and did not lead to discontinuation
  − 2 of 3 cases of dyspnea with fosaprepitant IV were treatment-related and led to study discontinuation
• Fewer subjects receiving HTX-019 versus fosaprepitant IV reported TEAEs within 1 hour of infusion start
  − The majority of TEAEs occurred within the first 30 minutes
• HTX-019 may provide a safer alternative to fosaprepitant IV for patients with CINV