G E P O T I D A C I N (GSK1440944)  
A Pharmacokinetic-Pharmacodynamic Evaluation  

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Brian VanScoy  
Institute for Clinical Pharmacodynamics, Inc.  
Schenectady, New York
Urinary Tract Infections
Activity limited to Staphylococci and Escherichia coli but not other Gram-negative urine pathogens

Gonorrhea
Active against ciprofloxacin-resistant isolates and may be useful in this area of unmet medical need

Gepotidacin
A first-in-class triazaacenaphthylene antibiotic that inhibits DNA replication

Three Important Questions

PK-PD Index
Identify the PK-PD index associated with efficacy

PK-PD Target
Determine non-clinical PK-PD targets associated with efficacy

Resistance
Determine the exposure necessary to prevent resistance amplification
To this end, we utilized two different \textit{in vitro} PK-PD infection models, the first of which was...
One-Compartment Model

![Diagram of a one-compartment model](image-url)
Methods

One-Compartment
Dose-fractionation and-range design, 24 hour experiment

Challenge Isolate
E. coli 13441, ST-131
MIC = 2 mg/L
Initial inoculum: 1 X 10⁶ CFU/mL

Healthy Human PK
Simulated within the model,
T₁/₂ = 7 hours

PK Sampling
Samples collected at 1, 2, 4, 6, 11, 14 and 24 hours

Mutation Frequency
1 resistant CFU in every
2.8 x 10⁻⁹ CFU/mL at
4 x the gepotidacin MIC

CFU Sampling
Samples collected at 0, 2, 4, 8, 12 and 24 hours
Dose-Fractionation Study Results

The PK-PD indices that best describe gepotidacin efficacy are AUC:MIC and Cmax:MIC ratio.

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<table>
<thead>
<tr>
<th>PK-PD index</th>
<th>$r^2$</th>
<th>Stasis</th>
<th>1-log$_{10}$ CFU decline</th>
<th>2-log$_{10}$ CFU decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{24h}$:MIC ratio</td>
<td>0.93</td>
<td>35.0</td>
<td>42.7</td>
<td>52.2</td>
</tr>
<tr>
<td>Cmax:MIC ratio</td>
<td>0.87</td>
<td>2.4</td>
<td>2.9</td>
<td>3.5</td>
</tr>
</tbody>
</table>
Multiple Isolate Dose-Range Study Results

Across isolates, relationship between gepotidacin exposure and response was well described by AUC:MIC ratio.
Resistance

Within the one-compartment infection model, we detected the amplification of a resistant bacterial subpopulations.

The relationship between drug exposure and response took the functional form of an inverted U.
To further explore the relationship between gepotidacin exposure, resistance amplification, and therapy duration, we employed...
Hollow Fiber Model
Methods...

**Hollow Fiber Model**
Dose-range design, 10 day experiment

**Challenge Isolate**
*E. coli* 13441, ST-131
MIC = 2 mg/L
Initial inoculum: $1 \times 10^8$ CFU/mL

**Mutation Frequency**
1 resistant CFU in every $2.8 \times 10^{-9}$ CFU/mL at 4 x MIC

**Healthy Human PK**
Simulated within the model, $T_{1/2} = 7$ hours

**PK Sampling**
Samples collected at 2, 4, 6, 9, 11, 14, 23, 26, 28, 30, 33, 35, 38 and 47 hours

**CFU Sampling**
Samples collected on days 1, 2, 3, 4, 6, 8, and 10
After 24 hours of therapy, resistance amplification was prevented with AUC values of approximately 140.
Between-Model Concordance

After 24 hours of therapy, similar drug exposures are needed to suppress drug-resistant subpopulations in the hollow-fiber and one-compartment models.
Hollow-Fiber Model

As expected, the AUC needed to suppress resistance amplification increased with duration of therapy.
So what did we learn about gepotidacin from these studies?
PK-PD Index
The PK-PD indices that best describe gepotidacin efficacy are AUC:MIC and $C_{\text{max}}$:MIC ratio.

Magnitude of PK-PD Target
In the one-compartment model, the AUC:MIC ratio associated with a $2\log_{10}$ CFU/mL reduction at 24 hours was 50.

Similar results were found using the hollow-fiber model, where the AUC:MIC ratio for a $2\log_{10}$ at 24 hours was 59.
Key Learnings

Resistance

Mechanism of resistance was determined to be overexpression of efflux pump

- MIC decreased with addition of a broad-spectrum efflux pump inhibitor

The longer the duration of gepotidacin exposure, the greater the exposure required to suppress resistance

AUC:MIC ratios of:

- 50-60 necessary to suppress resistance for 24 hours
- 250-300 necessary to suppress resistance for 10 days
This study was supported by GSK and funded through OTA HHSO100201300011C with HHS/BARDA
Thank you for your attention.
• For the four isolates examined in the one-compartment model the gepotidacin micro-broth MICs ranged from 1 to 4 mg/L
  - The range of gepotidacin MIC values represent the MIC$_{50}$ to MIC$_{90}$ value for E. coli [1]

Pharmacokinetic Profiles

- Gepotidacin health volunteer profiles simulated within the in vitro systems simulating observed free drug plasma concentrations, following oral administration.
### Healthy Volunteer PK

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Visit</th>
<th>h</th>
<th>AUC(0-∞) (µg·h/mL)</th>
<th>AUC(0-τ) (µg·h/mL)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK2140944</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg BID</td>
<td>6</td>
<td>Day 1</td>
<td>6</td>
<td>2.94 (19.6)</td>
<td>2.22 (23.3)</td>
</tr>
<tr>
<td>(fed)</td>
<td></td>
<td>Day 16</td>
<td>6</td>
<td>NA</td>
<td>3.00 (43.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>12</td>
<td>8.20 (37.0)</td>
<td>6.60 (40.5)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg BID</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(fed)</td>
<td></td>
<td>Day 1</td>
<td>12</td>
<td>20.1 (21.5)</td>
<td>17.3 (23.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 16</td>
<td>12</td>
<td>NA</td>
<td>22.4 (29.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>12</td>
<td>20.1 (21.5)</td>
<td>17.3 (23.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 16</td>
<td>12</td>
<td>NA</td>
<td>22.4 (29.6)</td>
</tr>
</tbody>
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