**RESULTS AND DISCUSSION**

In vitro studies

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>FEP-ZID</th>
<th>ZID</th>
<th>MEC</th>
<th>FEP</th>
<th>ZID</th>
<th>MEC</th>
<th>FEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC (µg/mL)</td>
<td>1.74</td>
<td>0.15</td>
<td>3.2</td>
<td>0.06</td>
<td>0.12</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>MIC50 (µg/mL)</td>
<td>1.2</td>
<td>0.13</td>
<td>2.7</td>
<td>0.06</td>
<td>0.12</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>MIC90 (µg/mL)</td>
<td>2.7</td>
<td>0.15</td>
<td>5.6</td>
<td>0.06</td>
<td>0.12</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>Time &gt;MIC (%)(h)</td>
<td>60</td>
<td>45</td>
<td>32</td>
<td>18</td>
<td>25</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>Drug combination</td>
<td>FEP-ZID</td>
<td>ZID</td>
<td>MEC</td>
<td>FEP</td>
<td>ZID</td>
<td>MEC</td>
<td>FEP</td>
</tr>
<tr>
<td>Effect against</td>
<td>3.2</td>
<td>0.15</td>
<td>3.2</td>
<td>0.06</td>
<td>0.12</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>Drug effect</td>
<td>1.2</td>
<td>0.13</td>
<td>2.7</td>
<td>0.06</td>
<td>0.12</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>Drug combination</td>
<td>FEP-ZID</td>
<td>ZID</td>
<td>MEC</td>
<td>FEP</td>
<td>ZID</td>
<td>MEC</td>
<td>FEP</td>
</tr>
<tr>
<td>Effect against</td>
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<td>5.6</td>
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<td>Drug effect</td>
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<td>0.13</td>
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<td>0.12</td>
<td>0.08</td>
<td>0.25</td>
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</table>

**Conclusions**

- In the presence of ZID, FEP's requirement for ZID to cause a 1 and 2-log kill is drastically lower thereby enhancing WCK 5222 therapeutic scope for the coverage of high MIC PA strains.
- In the presence of ZID, FEP with a wide range of HIC EC and PA isolates and provided sufficient cidal action for uncomplicated urinary tract infections (UTIs).
- Studies showed here demonstrated that FEP's enhanced dual target action (PD gain) against high MIC PA strains.
- In vivo studies demonstrated that WCK 5222 and ZID were efficacious in murine lung infection studies.

**References**

1. **In vitro** studies of FEP-ZID combination against MBL expressing PA are limited
2. **In vivo** studies using FEP-ZID were conducted in neutropenic mice (cyclophosphamide-150 mg/kg intraperitoneal injection) (4 days before treatment initiation).
3. **In vitro** studies were performed using a 96-well microtiter plate, with WCK 5222 MIC of 32 µg/mL (Year 2015 surveillance study: WCK 5222 PA MIC was 8 µg/mL).
4. **In vivo** studies were conducted in neutropenic mice (cyclophosphamide-150 mg/kg intraperitoneal injection) (4 days before treatment initiation).
5. **In vitro** studies were performed using a 96-well microtiter plate, with WCK 5222 MIC of 32 µg/mL (Year 2015 surveillance study: WCK 5222 PA MIC was 8 µg/mL).
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**Tables**

- Table 1: FEP and ZID susceptibility of human PS based on Phase I studies
- Table 2: FEP-ZID combination against MBL expressing PA
- Table 3: FEP-ZID combination against MBL expressing PS

**Figures**

- Figure 1: Time-kill studies of FEP-ZID and ZID against EC and PA
- Figure 2: Time-kill studies of FEP-ZID and ZID against KP
- Figure 3: Time-kill studies of FEP-ZID and ZID against PA
- Figure 4: Time-kill studies of FEP-ZID and ZID against EC and PA
- Figure 5: Time-kill studies of FEP-ZID and ZID against KP
- Figure 6: Time-kill studies of FEP-ZID and ZID against PA

**Abbreviations**

- MBL: Metallo-β-lactamase
- PA: Pseudomonas aeruginosa
- EC: Escherichia coli
- KP: Klebsiella pneumoniae
- PS: Pseudomonas species
- MEC: Meropenem
- FEP: E. coli (K)
- ZID: Zolidronate
- PD: Pharmacodynamic
- MEC: Meropenem
- FEP: E. coli (K)
- ZID: Zolidronate
- PD: Pharmacodynamic

**Keywords**

- β-lactamase
- Metallo-β-lactamase
- FEP-ZID combination
- In vitro pharmacodynamic
- Mouse lung infection model
- PD gain

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**Authors' Contributions**

- B. Moya: Conceptualization, Writing - Original Draft, Formal Analysis
- A. Barcelo: Investigation, Data Curation
- B. Bhagwat: Methodology, Project Administration
- M. Patel: Validation
- G. Booth: Supervision
- O. Oliver: Funding Acquisition

**Competing Interests**

The authors declare that they have no competing interests.

**Ethical Approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Consent to Participate**

The consent to participate was obtained from all individual participants included in the study.

**Consent for Publication**

The consent for publication was obtained from all individual participants included in the study.

**Data Availability**

The data that support the findings of this study are available on request from the corresponding author.

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