Developing Antibacterial Drugs for Patients with Unmet Need: Experience and Recommendations

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FDA Workshop
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Disclosure: Full time employee of Achaogen
Achaogen’s Position

• Infeasible to conduct fully powered trials given low number of enrollable patients
• Studies conducted in patients with unmet need provide critical data for clinicians
• Smaller datasets provide highly descriptive information for prescribers and can support exposure/response analyses
• Imperative that data in the unmet need population, including outcomes, is integrated into the product label
## Standard Indications Do Not Address Unmet Need
* Differences in Patient Populations are Profound*

<table>
<thead>
<tr>
<th></th>
<th>Standard Study</th>
<th>Unmet Need Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmet Need</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td>Few co-morbidities, Low mortality, No need for organ support</td>
<td>Significant co-morbidities, High mortality, Need for organ support</td>
</tr>
<tr>
<td><strong>Duration of Therapy</strong></td>
<td>≤ 7 days</td>
<td>7 to 14 days</td>
</tr>
<tr>
<td><strong>Pathogens</strong></td>
<td>Usual resistance, ~20% ESBLs, Few CRE, Polymicrobial infections rare</td>
<td>All MDR, Some XDR or PDR, Polymicrobial infections common</td>
</tr>
<tr>
<td><strong>PK</strong></td>
<td>Similar to healthy volunteers, Mildly increased $V_d$</td>
<td>Less predictable, More variable, Significantly increased $V_d$</td>
</tr>
<tr>
<td><strong>Combination Rx</strong></td>
<td>Single agent data only</td>
<td>Adequate coverage may require use of combination therapy</td>
</tr>
</tbody>
</table>
Plazomicin is a New Aminoglycoside with Broad Enterobacteriaceae Activity Including CRE

In vitro Activity vs. Clinical Isolates of CRE

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class</th>
<th>N</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>983</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Aminoglycoside</td>
<td>978</td>
<td>4</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Aminoglycoside</td>
<td>983</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Fluoroquinolone</td>
<td>822</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Cephalosporin</td>
<td>498</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>Penicillin/Beta-</td>
<td>756</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td></td>
<td>lactamase inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Glycylcycline</td>
<td>804</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Colistin/polymyxin B</td>
<td>Polymyxin</td>
<td>877</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>


Susceptible

Non-Susceptible
EPIC (cUTI) Provides Basis for Registration, CARE Provides Critical Data in an Unmet Need Population

Achaogen’s plazomicin program is funded in part with Federal funds from the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHSO100201000046C.
Superiority in 28d ACM

Assumed 35% mortality in the Control Arm (Meta-Analysis) with 12% absolute reduction with plazomicin

70% Power

One-sided alpha of 0.05

286 pts with proven CRE → Total N of 360 (evaluability of 80%)

Bloodstream Infection, VABP or Ventilated HABP due to CRE

Stratification
- Infection Type
- Duration of Empiric Therapy
- APACHE II Score

Plazomicin + Meropenem or Tigecycline

Colistin + Meropenem or Tigecycline

1:1 (n = ~360)

1o Endpoint
28 day all-cause mortality

Originally Intended to be Registrational Phase 3 Study
### Feasibility Assessment Suggested 3 Years of Enrollment to Reach 360 Patients

<table>
<thead>
<tr>
<th>Country</th>
<th>No. sites recommended</th>
<th>CRO Projected Enrollment (pts/site/yr)</th>
<th>No. Pts per year</th>
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</thead>
<tbody>
<tr>
<td>Germany</td>
<td>5</td>
<td>1.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Greece</td>
<td>10</td>
<td>1.4</td>
<td>14.4</td>
</tr>
<tr>
<td>Israel</td>
<td>5</td>
<td>2.4</td>
<td>12.0</td>
</tr>
<tr>
<td>Poland</td>
<td>7</td>
<td>1.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Russia</td>
<td>11</td>
<td>1.8</td>
<td>19.8</td>
</tr>
<tr>
<td>Spain</td>
<td>7</td>
<td>1.8</td>
<td>12.6</td>
</tr>
<tr>
<td>Ukraine</td>
<td>6</td>
<td>0.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Brazil</td>
<td>12</td>
<td>2.4</td>
<td>28.8</td>
</tr>
<tr>
<td>USA</td>
<td>5</td>
<td>0.9</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>68</strong></td>
<td><strong>Avg: 1.32</strong></td>
<td><strong>115</strong></td>
</tr>
</tbody>
</table>
Enrollment Significantly Lower Than Projections

Early Metrics in CARE

659 Prescreened

14 Enrolled

Major Reasons for Prescreen Failure (~50%)
- Pathogen is not CRE
- >72 hrs empiric therapy

Additional Reasons
- Lack of consent
- Polymicrobial infection
- APACHE II Score <15
- Emerging colistin resistance
Enrollment Challenges
Experience from One Hospital in Greece

- 17 patients with CR-*Klebsiella* in 4 month period
- None from ICU
- 2 patients were enrolled
- Reasons for exclusion
  - 7 patients had APACHE II score < 15
  - 4 isolates were resistant to colistin
  - 2 refused consent
  - 1 patient terminal
  - 1 concomitant BSI with *A. baumannii*
Two Amendments Designed to Boost Enrollment While Maintaining Potential for Superiority

Cohort 1: BSI, HABP or VABP

Presumed or Documented CRE
Restricted Eligibility
• APACHE II < 15 ✗
• Known colistin resistance ✗
• Polymicrobial infection ✗
• Need prohibited antibiotics ✗

Plazomicin
+ Meropenem or Tigecycline

Colistin
+ Meropenem or Tigecycline

Primary Endpoint:
Mortality at D28 or Significant Disease-Related Complications

1:1 N~360

Cohort 2: BSI, HABP, VABP, cUTI or AP

Presumed or Documented CRE
Broader Eligibility
• cUTI or AP ✔
• APACHE II ≤ 30 ✔
• Known colistin resistance ✔
• Polymicrobial infection ✔

BSI/HABP/VABP: Plazomicin + any suppl. antibiotic (N~50)
cUTI/AP: Plazomicin monoRx. +/- oral switch (N~50)

Patients can only enroll in cohort 2 if they are not eligible for cohort 1
Despite Significant Site Engagement and Broadening Eligibility, Enrollment Potential Limited

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Lessons Learned from CARE
Real World Experience

- Site surveys overestimated potential enrollment
- Only a small subset of sites enrolled patients
- Superiority study only feasible if many countries have CRE incidence similar to Greece
- Barriers to enrollment evolve: resistance to comparator, study competition, etc
- Intensive site engagement critical to support enrollment
- Studies are expensive; BARDA support essential to the program
Critical to Include Data in the Label to Ensure Information is Available to Prescribers

- Efficacy data in unmet need population, including clinical outcomes of highly resistant infections
  - Provided in context of proven efficacy in “usual” population
  - Nature of dataset, including uncertainty, can be highlighted

- PK in different populations

- Unique microbiological data

- Safety information in different populations

- Combination therapy
Critical Data Generated in CARE to Guide Plazomicin Use in Unmet Need Population

Baseline renal function in CARE is distinct from EPIC and Population PK Model

- Continuous Renal Replacement Therapy
- Moderate Impairment
- Mild Impairment
- Normal
- Severe Impairment
- Hyperclearance

Broad Range of Renal Function

Difficult to Study in Phase 1 or cUTI Population

More Variable Drug Exposure Allows Exposure/Response Analyses

Implications for Dosing, Including Guidance for Dose Adjustment
CARE Provides Unique Microbiology to Inform Label and Support Breakpoint Assessment

<table>
<thead>
<tr>
<th>Organism</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CARE</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>✔️</td>
</tr>
<tr>
<td>Multi-drug resistant Enterobacteriaceae</td>
<td>✔️</td>
</tr>
<tr>
<td>Aminoglycoside resistant Enterobacteriaceae</td>
<td>✔️</td>
</tr>
<tr>
<td>CRE</td>
<td>✔️</td>
</tr>
<tr>
<td>Colistin-resistant CRE</td>
<td>✔️</td>
</tr>
<tr>
<td>Tigecycline-resistant CRE</td>
<td>✔️</td>
</tr>
</tbody>
</table>

- Pathogens from CARE provide data on higher MIC organisms, supporting clinically relevant breakpoint assessment
- Different bacterial species in CARE vs. EPIC
Conclusions

- Infeasible to conduct rigorous inferential trials given low number of enrollable patients
- Studies conducted in patients with unmet need provide critical data for clinicians
- Smaller datasets provide critical information for prescribers
- Imperative that data in the unmet need population, including outcomes, is integrated into the product label
- If the regulatory path is clear, studies in unmet need population are more likely to be undertaken and funded
Recommendations for Viable Study Designs
Small, Efficient Studies with Enrollment at Time of Empiric Therapy

Start with what’s feasible: 40-80 patient studies

More sensitive endpoints (e.g. clinical response in BSI, HABP/VABP)

Aim for nearly all or all patients to receive study drug

Consider external or shared controls (trial network)

Designs that allow empiric therapy (rapid diagnostics can help)

Combination regimens: polymicrobial infections, empiric therapy

Harmonization between FDA and EMA