Challenges with Clinical Trial Design for a Drug Targeting a Single Species of Bacteria: *Acinetobacter baumannii*

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Disclosure: Full time employee of Entasis Therapeutics
Infections caused by *Acinetobacter baumannii* are a significant unmet medical need

- One of the six ESKAPE pathogens
- 60 – 100,000 infections in the U.S. and ~130,000 in EU5 per year
- Common infection sites:
  - Blood stream, lung, urinary tract, and skin
- Causes infections among critically ill patients
  - Mortality rate ~40% with current therapies
- ~60% of *A. baumannii* isolates are multi-drug resistant

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Isolates</th>
<th>% Resistant to imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>398</td>
<td>57.6%</td>
</tr>
<tr>
<td>Europe</td>
<td>1229</td>
<td>64.1%</td>
</tr>
<tr>
<td>Latin America</td>
<td>299</td>
<td>75.9%</td>
</tr>
<tr>
<td>Middle East/Africa</td>
<td>189</td>
<td>73.6%</td>
</tr>
<tr>
<td>North America</td>
<td>235</td>
<td>54.0%</td>
</tr>
<tr>
<td>All Regions</td>
<td>2350</td>
<td>64.2%</td>
</tr>
</tbody>
</table>
Sulbactam-ETX2514 (ETX2514SUL) is in clinical development as a pathogen-specific drug to treat *Acinetobacter baumannii* infections

- **Sulbactam**
  - A β-lactam that is widely used as a β-lactamase inhibitor in the combination product Unasyn™
  - Has intrinsic antimicrobial activity against *A. baumannii*
- **ETX2514**
  - A novel, non-β-lactam, β-lactamase inhibitor
    - Broad potent inhibitor of Class A, Class C, and Class D β-lactamases
- **ETX2514 restores the *in vitro* and *in vivo* activity of sulbactam against contemporary multi-drug resistant *A. baumannii***
  - Sulbactam \( \text{MIC}_{90} = 64 \, \text{mg/L} \)
  - Sulbactam + ETX2514 \( \text{MIC}_{90} = 4 \, \text{mg/L} \)
    - >99% of 2014 isolates (n=1,131) had MIC ≤ 4 mg/L
Sulbactam-ETX2514 is under development as a pathogen-specific drug

The challenges:

- Identification of patients with *A. baumannii* infections
  - Represent ~2% of hospitalized Gram-negative infections
- Patients are “sick”
  - Usually hospitalized
  - Generally compromised health
  - Often in ICUs
  - Generally receiving broad spectrum coverage
  - Patients may have renal impairment
- ~40-50% of patients have pulmonary infections

How do we translate this into a development program?
Identification of patients with *A. baumannii* infections

How can we enrich for what is important?

- What is the target of a new therapy
  - The unmet need = multi-drug resistant pathogens
- Although *A. baumannii* infections are relatively uncommon
  - Multi-drug resistance is very common
  - Routine microbiology can identify *A. baumannii* within 48-hours
    - We can “enrich” for multi-drug resistance by allowing ≤48-hours of prior therapy
- Prior knowledge of *A. baumannii* is critical before enrollment
  - BUT prior knowledge of susceptibility is not
    - ~60% will be multi-drug resistant
- A rapid “bed-side” diagnostic to enrich enrollment and minimize prior antimicrobial therapy would be helpful but is not essential
Identification of patients with *A. baumannii* infections

Where to find the patients?

- Focus on infections where *A. baumannii* is more common
  - Hospital acquired/ventilator acquired bacterial pneumonia
    - ~5-10% of cases in US
- Focus on geographies where *A. baumannii* is more common

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1 Chung DR *et al*. Am J Crit Care Med 2011, 184:1409

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![Figure 1. Comparison of major microorganisms isolated from hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in Asian countries.](image-url)
Enrollment of “sick” patients with significant co-morbidities
Understand pulmonary penetration and renal dose adjustment early

- Patients with *A. baumannii* infections have complex medical issues
- Need substantive preclinical efficacy data prior to clinical studies
  - Establish PK targets likely predictive of efficacy
  - Establish clinical dose using robust modelling of Phase 1 PK and preclinical PD targets
- While establishing Phase 3 readiness
  - Generate a limited amount of safety data in “relatively” healthy patients
  - Provides a baseline to review safety data in much sicker population
How do you establish efficacy?

• An event-driven study based on multidrug resistant pathogens
• Enrolling patients with proven *A. baumannii* infections
• Focusing on most common infections; i.e. lung and/or bloodstream
  – Allow patients with other infections into a parallel non-comparative arm to collect supportive data
• In a non-inferiority comparison against a standard-of-care regimen
  – Test superiority if non-inferiority met
• Utilizing a hard endpoint; e.g., 28-day mortality
  – Comparator regimen ~40% mortality
  – No treatment ~80% mortality
  – Proposed non-inferiority margin 20%

➢ Require ~200 patients to provide 118 patients with multi-drug resistant infections
  – 80% power with a two-sided 95% CI assuming 40% mortality in the comparator group and 35% mortality in the experimental group
What might a NDA package look like?

Proposed key elements

• A strong microbiology package
• Strong evidence of *in vivo* efficacy in relevant animal models
• Robust demonstration of PK/PD parameters based on *in vitro* hollow fiber and *in vivo* animal models
• Establish dose for Phase 2 and Phase 3 based on high probability of target attainment using robust modelling of preclinical and clinical data
• A safety data base of ~300-400 patients/subjects
  – Consistent with FDA guidance documents
• Demonstrate efficacy compared to standard-of-care in a Phase 3 non-inferiority study
  – Comprehensive justification of non-inferiority margin from published literature

➤ It’s not easy but it is potentially achievable!