ENTASIS THERAPEUTICS

Innovative Antibacterials

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

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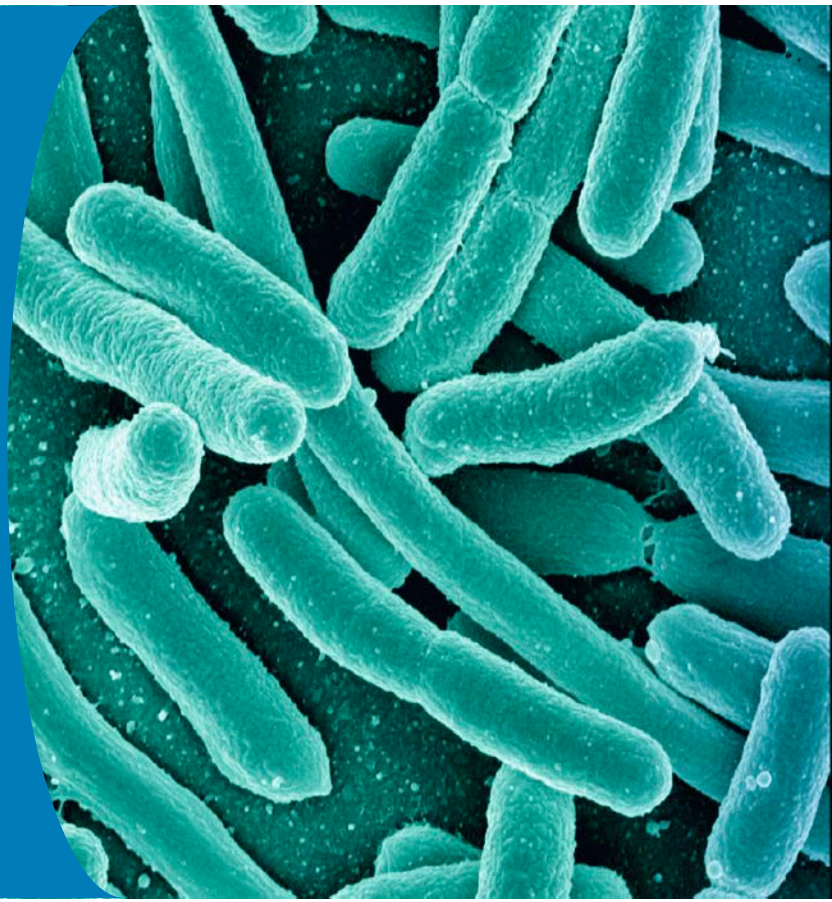
Disclosure: Full time employee of Entasis Therapeutics



Infections caused by *Acinetobacter baumannii* are a significant unmet medical need

- One of the six ESK**A**PE 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

Region	Number of Isolates	% Resistant to imipenem
Asia Pacific	398	**57.6%**
Europe	1229	**64.1%**
Latin America	299	**75.9%**
Middle East/Africa	189	**73.6%**
North America	235	**54.0%**
All Regions	**2350**	**64.2%**

ESKAPE – ***E****nterococcus faecium,* ***S****taphylococcus aureus,* ***K****lebsiella pneumoniae,* ***A****cinetobacter baumannii,* ***P****seudomonas aeruginosa,* ***E****nterobacter* species

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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 MIC_{90} = 64 mg/L
  - Sulbactam + ETX2514 MIC_{90} = 4 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

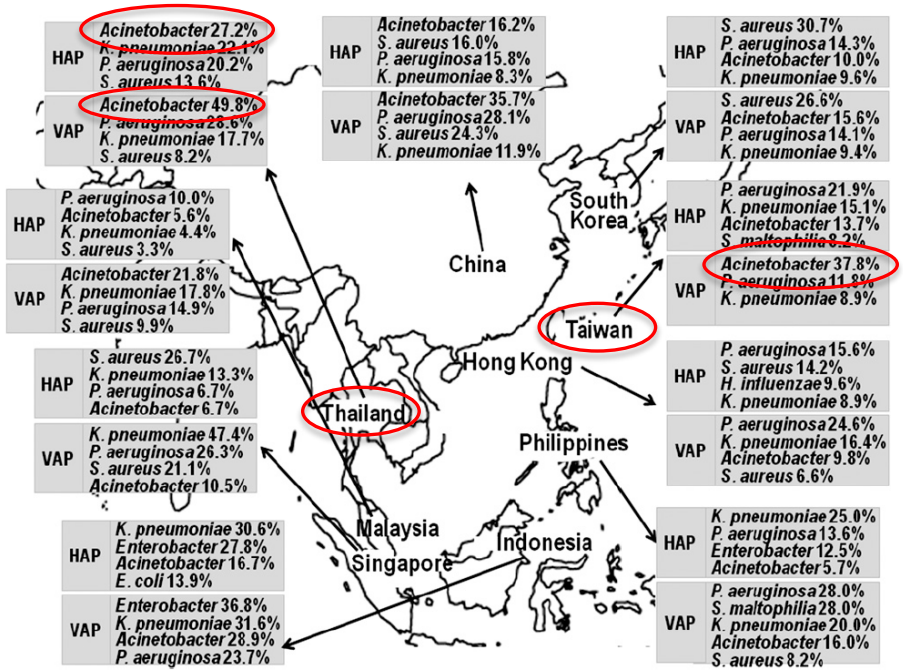

Figure 1. Comparison of major microorganisms isolated from hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in Asian countries.

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

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Enrollment of “sick” patients with significant co-morbitities
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!