ETX2514SUL (sulbactam/ETX2514) for the treatment of *Acinetobacter baumannii* infections

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Multi-drug resistant Acinetobacter infections
High mortality rates and growing prevalence of resistance

• Estimated *Acinetobacter* incidence
  – U.S.\(^1\): 60,000 to 100,000 per year
  – EU5\(^1\): 90,000 to 120,000 per year

• Infections generally in critically ill patients
  – Pulmonary, bloodstream, and wound infections

• Carbapenems are an important treatment option

• US carbapenem-resistance \(~50\%\)^2
  – Mortality rates close to \(~50\%\)^3

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\(^1\) Decision Resources.
\(^2\) IntechOpen, DOI: 10.5772/30379.
\(^4\) CDDEP Antibiotic Resistance Map (resistancemap.cddep.org).
β-lactam resistance in *A. baumannii* is mediated by Class A, C and D β-lactamases(1)

**β-lactamase content in MDR Acinetobacter**(2)

Inhibition of β-lactamase classes A, C and D required for restoration of β-lactam activity in *A. baumannii*

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ETX2514SUL is a novel bactericidal β-lactam/β-lactamase inhibitor combination
Under development as a fixed dose combination for intravenous treatment of *Acinetobacter* infections

Sulbactam

- Activity as a β-lactamase inhibitor
- Also a β-lactam with intrinsic activity against *A. baumannii*
- Extensively use to treat *A. baumannii*
- β-lactamase-mediated resistance now common with MIC$_{90} >$32 mg/L

ETX2514

- Novel β-lactamase inhibitor
- Potent broad-spectrum inhibitor of Class D β-lactamases
- Also potent broad-spectrum inhibitor of Class A and C β-lactamases
ETX2514 restores sulbactam’s activity against *A. baumannii calcoaceticus* complex
Frequency of spontaneous resistance to ETX2514SUL is low (2.8 x 10^-8 at 4X MIC and undetectable at 8X MIC)
**In vitro** activity against *Acinetobacter baumannii*
Activity unchanged in carbapenem-resistant, colistin-resistant and multidrug resistant strains

<table>
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<th>Year</th>
<th>N</th>
<th>MIC (mg/L)</th>
<th>0.06</th>
<th>0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
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<tr>
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<td>4.3</td>
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<td>78.7</td>
<td>97.0</td>
<td>99.5</td>
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<td>80.1</td>
<td>94.8</td>
<td>98.8</td>
<td>99.3</td>
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<td>86.8</td>
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<td>97.9</td>
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<td>99.8</td>
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<tr>
<td>All</td>
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<td>99.1</td>
<td>99.3</td>
<td>99.7</td>
<td>100</td>
</tr>
</tbody>
</table>

1 Combined with 4 mg/L of ETX2514.
2 2015 study performed at JMI; other years performed at IHMA.
In vivo activity of ETX2514SUL in murine thigh and lung infection models
Bacterial load suppression of XDR Acinetobacter infections

(1) ETX2514, sulbactam, and colistin were dosed subcutaneously. Colistin injected to maximum tolerated dose.
(2) Extensively drug resistant (XDR) A. baumannii ARC3486 (OXA-72, OXA-66, TEM-1, AmpC): MIC(sulbactam) ≥ 32 mg/L, MIC(sulbactam/ETX2514) = 0.5 mg/L.
ETX2514SUL PK/PD

- Key PK drivers identified by PK/PD evaluations *in vitro* and *in vivo*
- Exposure targets for sulbactam and for ETX2514 established
  - Sulbactam: 50% Time>MIC
  - ETX2514: $\frac{AUC_{0-24h}}{\text{MIC}} = 10$
- Dosing regimen for Phase 2/3
  - Sulbactam 1 g plus ETX2514 1 g
  - 3-hour infusion
  - Dosed every 6 hours
  - Probability of target attainment for MIC ≤ 4 mg/L is ≥99%

*Relationship between ETX02514 AUC$_{0-24h}$/$\tau$ in the *in vitro* chemostat model*$(1)$

$(1)$ *A. baumannii* ARC5081 (OXA-23; OXA-94): MIC (sulbactam) = 16 mg/L, MIC (sulbactam/ETX2514) = 2.9 mg/L.
ETX2514SUL has completed Phase 1 and Phase 2 evaluation
Generally safe and well tolerated in 3 Phase 1 and a Phase 2 clinical study

- 139 healthy subjects and 79 patients have received ≥1 dose of ETX2514
- No dose-related systemic adverse events
  - Up to 8 g single dose or 2 g q6h
- Sulbactam 1 g plus ETX2514 1 g with imipenem/cilastatin 0.5 g
  - Generally well tolerated for up to 11 days
- ETX2514 demonstrated well behaved PK
  - Dose proportional exposure up to 8 g
  - No drug-drug interaction (2-way) with sulbactam and/or imipenem/cilastatin
  - Good pulmonary exposure in healthy subjects
  - PK in patients with renal impairment pending

Mean ETX2514 Concentration in Plasma and Epithelial Lining Fluid (ELF) (n=30)(1)

(1) Phase 1 study in 30 healthy subjects receiving sulbactam 1 g and ETX2514 1g infused over 3 hours q6h for 3 doses.
ETX2514SUL Phase 2

Generally safe and well tolerated in patients with PK comparable to healthy subjects

80 patients Complicated UTIs

53 patients ETX2514SUL + IMI

27 patients Placebo + IMI

Analysis

1°Endpoint: Safety

2°Endpoint: Efficacy at TOC

Exploratory: Efficacy in carbapenem non-susceptible infections

• Key objectives
  – Evaluate safety profile on ETX2514SUL in patients
  – PK profile in patients

• Exploratory objective
  – Efficacy in carbapenem-resistant isolates

• Overall microbiological success rates similar
  – 80% (36/45) for ETX2514SUL versus 81% (17/21) for comparator
  – ETX2514SUL plus IMI eradicated imipenem non-susceptible isolates
    ▪ 100% (3/3) for ETX2514SUL versus 60% (3/5) for comparator

IMI = imipenem/cilastatin.

Population PK from Phase 2 study
**ETX2514SUL Phase 3 study design**

Phase 3 study planned to start in 1Q2019

- Dose selection based on robust PK/PD
- Single Phase 3 non-inferiority study
  - ETX2514SUL + IMI versus Colistin + IMI
  - Primary efficacy endpoint 28-day all-cause mortality in patients with carbapenem-resistant *Acinetobacter*
  - Non-inferiority margin = 19%
    - Justified by detailed literature review

### 28-day mortality rate with *A. baumannii*

<table>
<thead>
<tr>
<th></th>
<th>Estimate of Mortality</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Colistin-based therapy</td>
<td>41%</td>
<td>36%, 47%</td>
</tr>
<tr>
<td>Untreated or delayed treatment</td>
<td>76%</td>
<td>66%, 86%</td>
</tr>
</tbody>
</table>

BSI = Blood stream infections. HABP = Hospital acquired bacterial pneumonia. IMI = imipenem/cilastatin. VABP = Ventilator acquired bacterial pneumonia.
ETX2514SUL Summary

- There is an urgent need for new agents to treat multi-drug resistant *Acinetobacter baumannii* infections
- ETX2514SUL is a bactericidal $\beta$-lactam/$\beta$-lactamase inhibitor combination with *in vitro* activity against *Acinetobacter*
  - MIC$_{90}$ 2 mg/L (3,611 contemporary global isolates)
- ETX2514SUL has demonstrated *in vivo* activity in murine thigh and lung infection models of *Acinetobacter* infection
- ETX2514SUL is generally safe and well tolerated in Phase 1 and 2 clinical studies
- ETX2514SUL has well behaved PK including good pulmonary exposure
- A fixed-dose combination of sulbactam 1 g and ETX2514 1 g infused over 3 hours q6h has a very high (>99%) probability of target attainment for *A. baumannii* with MICs ≤4 mg/L
- Phase 3 is planned to initiate in 1Q2019
Questions