Presentation # 1836

Safety and Pharmacokinetics (PK) in Humans of Intravenous ETX2514, a β-lactamase Inhibitor (BLI) which Broadly Inhibits Ambler Class A, C, and D β-lactamases.

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Abstract

Background: ETX2514 is a novel BLI with broad spectrum activity against Ambler class A, C and D β-lactamases. The addition of ETX2514 to sulbactam (SUL) *in vitro* restores SUL activity against *Acinetobacter baumannii;* SUL-ETX2514 (ETX2514SUL) MIC_{90} 4 mg/L (>1,800 globally diverse, recent clinical isolates). ETX2514SUL is under development for the treatment of *A. baumannii* infections.
Methods: A Phase 1, randomized, placebo-controlled trial in 4 parts (15 cohorts) was conducted in 124 healthy subjects to assess the plasma and urine PK of ETX2514 either alone or in combination with SUL and/or imipenem/cilastatin (IMP/CIL): Part A (Cohorts 1-8): ETX2514 single ascending dose (SAD) (0.25-8 g) including an elderly cohort (1 g); Part B (Cohorts 9-12): ETX2514 multiple ascending dose (MAD) (0.25-2 g); Part C (Cohorts 13-14):drug-drug interaction (DDI) between ETX2514 (1 g) with SUL (1 g) and/or IMP/CIL (0.5/0.5 g); Part D (Cohort 15): 11 days of ETX2514SUL (1/1 g) and IMP/CIL (0.5/0.5 g). ETX2514 and SUL were infused over 3 hours (except Cohort 2, 2 hours). Concentrations of ETX2514, SUL, and IMP/CIL were quantified by LC-MS/MS. Non-compartmental analysis was performed using Phoenix WinNonlin v6.4 to determine PK parameters.
Results: Results from Parts A, B, and C are complete (112 subjects; ETX2514:Placebo 84:28). ETX2514 was generally safe and well tolerated either alone or in combination with SUL and/or IMP/CIL; no significant changes in hematology, clinical chemistry, vital signs or ECGs were noted. In SAD, ETX2514 demonstrated linear dose proportional exposure across the dose range with renal excretion as a predominant clearance mechanism. ETX2514 demonstrated lower total clearance and renal clearance in the elderly cohort. In MAD, ETX2514 demonstrated linear dose proportional exposure across the dose range studied with minimal accumulation at Day 8. There was no DDI (either way) between ETX2514 and SUL and/or IMP/CIL.
Conclusions: ETX2514, either alone or in combination with SUL and/or IMP/CIL, was generally well tolerated at doses predicted to be clinically efficacious. ETX2514 PK is consistent with a therapeutic dose in the range 0.5-1 g IV q6hour in combination with SUL 1 g. Further evaluation of ETX2514SUL to treat *A. baumannii* infections is warranted.

Introduction

Acinetobacter baumannii is a nonfermenting Gram-negative bacteria that is increasingly being recognized as an important cause of severe infections with associated high mortality. It is a significant public health concern and is ranked as "critical" on the WHO Priority Pathogens List for R&D of New Antibiotics. In the US, ~ 63% of *A. baumannii* are multi-drug resistant. Production of β-lactamases is the most important resistance mechanism for β-lactam therapy; expression of Class D β-lactamase in *A. baumannii* is ubiquitous, but Class A and/or extended spectrum Class C co-expression is also common. Restoration of β-lactam activity against *A. baumannii* would require a β-lactamase inhibitor capable of broadly inhibiting Class A, C, and D β-lactamases. ETX2514 is a novel diazabicyclooctenone β-lactamase inhibitor with such a broad coverage. Sulbactam-ETX2514 (ETX2514SUL) is under development as an *A. baumannii*-specific antimicrobial agent. The addition of ETX2514 to sulbactam *in vitro* restores sulbactam's activity against *A. baumannii*; ETX2514SUL MIC_{90} 2 mg/L (>2,800 globally diverse recent clinical isolates).

Methods

A 4-part double-blind, placebo-controlled study (15 cohorts) of ETX2514 administered as an IV infusion
Healthy adult male and female subjects (age 18-55 years) with a single elderly cohort (age≥65 years)

Part A single ascending dose escalation (8 cohorts [6 active, 2 placebo])
- **Cohort 1, 2, 3, 5, 6, 7**: 0.25, 0.5, 1, 2, 4, or 8 g IV ETX2514/placebo infused over 3 hours
- **Cohort 4**: 1 g IV ETX2514/placebo infused over 2 hours
- **Cohort 8 (elderly subjects)**: 1 g IV ETX2514/placebo infused over 3 hours

Part B multiple ascending dose escalation (4 cohorts [6 active, 2 placebo])
- **Cohort 9, 10, 11, 12**: 0.25, 0.5, 1, or 2 g IV ETX2514/placebo infused over 3 hours every six hours for 29 doses

Part C cross-over drug-drug interaction (2 cohorts [6 active, 2 placebo])
- **Cohort 13:** 2-way single dose between ETX2514 (1 g) and sulbactam (1 g)
- **Cohort 14**: 2-way single dose between ETX2514 (1 g) and imipenem/cilastatin (0.5 g)

Part D repeat dosing of sulbactam-ETX2514 plus imipenem/cilastatin (1 cohort [10 active, 2 placebo])
- **Cohort 15**: 1 g IV ETX2514/placebo and 1 g IV sulbactam both infused over 3 hours and 0.5 g IV imipenem/cilastatin infused over 30 minutes every six hours for 41 doses

Parameters
- Plasma and urine samples for PK
- Safety monitoring including laboratory testing and ECG

Analysis of plasma concentrations
- ETX2514, sulbactam, imipenem and cilastatin determined by LC/MS/MS.
- Dynamic range: Plasma 5 to 5000 ng/mL; Urine (ETX2514) 50 to 50,000 ng/mL
- Data presented are based on preliminary non-compartmental analysis using non-QA'ed data

Clinical trial registration
- ClinicalTrials.gov Identifier: NCT02971423

Results

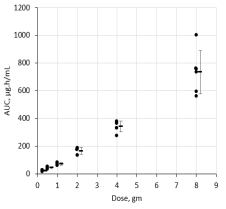
Part A: Single Ascending Dose Escalation

- Dose proportional exposure achieved across studied range
- PK consistent with predicted therapeutic dose range
- Renal excretion was a predominant clearance mechanism (~54% intact drug renally excreted)
  - ETX2514 demonstrated lower total and renal clearance in the elderly cohort (Cohort 8).

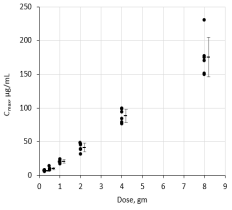
Cohort	Dose (g)	$T_{1/2}$ (hr)	C_{max} (µg/mL)	AUC (µg•h/mL)	CL (L/h)	Vd_{ss} (L)
1	0.25 (3h infusion)	1.48±0.13	6.94±0.96	25.0±3.8	10.2±1.6	16.9±3.7
2	0.5 (3h infusion)	2.05±0.40	9.92±2.02	46.6±6.8	11.0±1.8	26.3±2.8
3	1.0 (3h infusion)	1.94±0.28	20.6±2.8	74.2±10.4	13.7±1.9	26.0±5.0
4	1.0 (2h infusion)	2.22±0.23	31.4±7.0	92.8±19.2	11.2±2.3	24.6±3.2
5	2.0 (3h infusion)	2.14±0.16	41.4±6.4	168±24	12.2±1.9	24.4±3.3
6	4.0 (3h infusion)	2.50±0.45	88.4±10.2	345±41	11.8±1.6	23.8±3.3
7	8.0 (3h infusion)	2.67±0.40	175±29	736±156	11.3±2.3	25.6±8.6
8*	1.0 (3h infusion)	2.34±0.25	37.8±2.6	146±13	6.90±0.70	14.8±2.2

* PK data in elderly subjects > 65 years of age

Individual AUC (0.25 gm to 8.0 gm)



Individual C_{max} (0.25 gm to 8.0 gm)

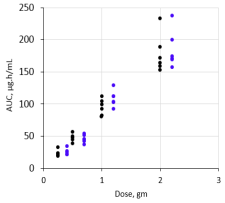


Part B: Multiple Ascending Dose Escalation

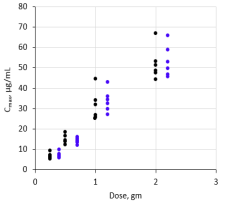
- Minimal accumulation with multiple dosing
- Steady state exposure consistent with half-life

Cohort	Dose	Day of Dosing	$T_{1/2}$ (hr)	C_{max} (µg/mL)	AUC (µg•h/mL)	CL (L/h)	Vd_{ss} (L)
9	0.25 g q6hours (3h infusion)	1	1.42±0.29	6.88±1.38	23.0±5.0	10.2±1.9	17.6±4.0
		8	1.74±0.35	7.30±1.52	27.6±6.2	9.3±1.7	17.4±2.7
10	0.5 g q6hours (3h infusion)	1	1.33±0.09	14.9±2.2	50.0±9.0	9.3±1.7	16.3±2.6
		8	2.28±0.57	14.3±1.6	53.8±6.6	9.3±1.2	20.4±1.0
11	1 g q6hours 3h infusion)	1	1.2±0.2	31.2±8.2	93.0±13.2	10.1±1.6	16.5±1.7
		8	2.9±0.4	33.4±6.0	108±14	8.5±1.1	14.9±1.9
12	2 g q6hours (3h infusion)	1	1.3±0.1	52.0±8.0	178±30	10.5±1.7	17.9±1.6
		8	3.6±0.4	53.4±7.8	185±29	9.7±1.6	20.1±2.0

Individual AUC 0.25 gm to 2.0 gm
Day 1 (black) vs. Day 8 (blue)



Individual C_{max} 0.25 gm to 2.0 gm
Day 1 (black) vs. Day 8 (blue)



Part C: ETX2514-Sulbactam Drug-Drug Interaction (Cohort 13)

- Co-administration of ETX2514 and sulbactam did not alter the PK of ETX2514
- Co-administration of ETX2514 and sulbactam did not alter the PK of sulbactam

	$T_{1/2}$ (hr)	C_{max} (µg/mL)	AUC (µg•h/mL)	CL (L/h)	Vd_{ss} (L)
ETX2514 PK					
ETX2514	2.0 ± 0.4	27.0 ± 3.6	102 ± 6	9.9 ± 0.6	17.8 ± 2.2
ETX2514 + Sulbactam	2.0 ± 0.4	28.2 ± 2.4	103 ± 6	9.8 ± 0.6	17.6 ± 1.7
Sulbactam PK					
Sulbactam	1.3 ± 0.1	20.8 ± 0.6	67.2 ± 4.6	14.9 ± 1.1	18.3 ± 1.6
Sulbactam + ETX2514	1.2 ± 0.1	22.0 ± 0.7	69.2 ± 7.6	14.6 ± 1.6	19.2 ± 3.5

Part C: ETX2514-Imipenem/Cilastatin Drug-Drug Interaction (Cohort 14)

- Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of ETX2514
- Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of imipenem/cilastatin

Drug Regimen	$T_{1/2}$ (hr)	C_{max} (µg/mL)	AUC (µg•h/mL)	CL (L/h)	Vd_{ss} (L)
ETX2514 PK					
ETX2514	1.8 ± 0.4	30.0 ± 9.2	104.0 ± 15.1	10.1 ± 2.1	16.1 ± 2.7
ETX2514 + Imipenem/cilastatin	1.6 ± 0.3	26.6 ± 5.2	101.2 ± 21.6	10.1 ± 1.9	15.7 ± 2.0
Imipenem PK					
Imipenem/cilastatin	1.2 ± 0.1	31.0 ± 8.0	41.6 ± 7.6	12.3 ± 1.9	17.0 ± 3.4
Imipenem/cilastatin + ETX2514	1.2 ± 0.1	30.4 ± 4.8	39.6 ± 5.0	12.8 ± 1.5	17.2 ± 2.3
Cilastatin PK					
Cilastatin/imipenem	1.2 ± 0.2	42.0 ± 11.0	47.0 ± 8.2	10.9 ± 1.8	12.2 ± 3.1
Cilastatin/imipenem + ETX2514	1.2 ± 0.2	41.6 ± 8.2	43.8 ± 6.4	11.7 ± 1.8	11.9 ± 2.0

ETX2514SUL maintains excellent *in vitro* activity versus *A. baumannii* over time

MIC distributions by year for globally diverse *A. baumannii* clinical strains*

MIC (mg/L)		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>64
2011 N=195	Cumulative %	1	3.1	13.8	41.5	65.6	89.7	96.9	97.9	99.5	100	100
2012 N=209	Cumulative %	0	0.5	2.9	20.1	46.9	79	98.6	100	100	100	100
2013 N=207	Cumulative %	0	0	4.3	15.9	43.4	73.8	96.5	97.5	99	99	100
2014 N=1131	Cumulative %	1	1.6	7.8	27.9	63.7	88.9	99.6	99.6	99.7	100	100
2015 N=202	Cumulative %	0	1.0	7.4	43.1	78.7	97.0	99.5	99.5	100	100	100

* Susceptibility testing performed by IHMA Inc.

Safety and Tolerability

- Safety review after each cohort by Safety Review Committee (SRC)
  - Upon each cohort review, SRC approved moving to next cohort
- ETX2514 has been generally safe and well tolerated
  - 124 (94 ETX2514; 30 placebo) subjects have received ≥1 dose of ETX2514
  - Most common (≥5% of subjects) treatment-emergent AEs
    - Headache (ETX2514 14%; Placebo 13%)
    - Catheter site phlebitis (ETX2514 9%; Placebo 3%)
  - Most common (≥3% of subjects) drug-related treatment-emergent AEs
    - Headache (ETX2514 11%; Placebo 10%)
    - Cather site phlebitis (ETX2514 5%; Placebo 0%)
  - Two discontinuations in 500 mg ETX2514 q6hour multi-dose cohort
    - Drug-related mild-moderate adverse experience
      - Somnolence (Graded: mild) and nausea (Graded: moderate)
    - Non-drug-related SAE
      - Anaphylactic reaction (Brazil nuts) in known nut allergy
  - One discontinuation in 1 g ETX2514 q6hour multi-dose cohort
    - Drug-related moderate adverse experience
      - Infusion site reaction (Graded: moderate)

Conclusions

Pharmacokinetics
Based on preliminary non-compartmental analysis:
- ETX2514, as single doses, demonstrates linear dose proportional exposure across the entire dose range studied (i.e. 0.25 g – 8 g).
- ETX2514, as multiple doses for 29 doses, demonstrates linear dose proportional exposure across the entire dose range studied (i.e. 0.25 g – 2 g infused over 3 hours every 6 hours) with minimal accumulation, consistent with half-life, indicated by Day 8.
- There is no significant drug-drug interaction (either way) between ETX2514 and sulbactam.
- There is no significant drug-drug interaction (either way) between ETX2514 and imipenem/cilastatin.

Safety
ETX2514 is generally safe and well tolerated as a single dose up to 8 g and in multiple doses up to 2 g infused over 3 hours every 6 hours.
- The general safety profile of ETX2514 is unchanged when co-administered, as a single dose, with sulbactam, with imipenem/cilastatin, and with sulbactam and imipenem/cilastatin.

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