A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous Sulbactam-ETX2514 in the Treatment of Hospitalized Adults with Complicated Urinary Tract Infections, Including Acute Pyelonephritis

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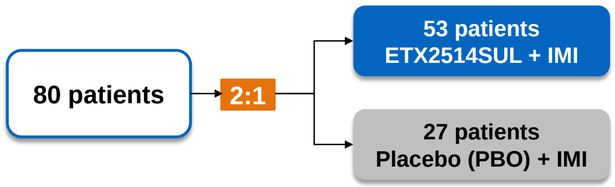
Introduction

- *Acinetobacter baumannii-calcoaceticus complex* (ABC) causes serious Gram-negative infections which are associated with high morbidity and mortality
- ETX2514 is a novel, broad spectrum inhibitor of Class A, C and D β-lactamases that restores sulbactam (SUL) intrinsic activity against ABC
- The combination of sulbactam-ETX2514 (ETX2514SUL) is being developed to treat serious and resistant ABC infections

Study Design and Objectives



Key Objectives	
Primary	Evaluate Safety
Secondary	Compare Efficacy at Test of Cure (TOC)
Exploratory	Evaluate Efficacy in Imipenem non-susceptible Infections Descriptive PK

Study Treatment

- ETX2514SUL (1g/1g 3h infusion) or PBO q6h each with Imipenem/cilastatin (IMI) (500mg 30min infusion) q6h (background therapy)
- Duration: 7d, extended up to 14d if bacteremic

Patient Eligibility

- Male and female patients 18-90 yrs of age and hospitalized for cUTI/AP were eligible
- Patients with confounding renal disorders, creatinine clearance <70mL/min or had other concurrent infections were excluded

Results

Patient Disposition

78/80 (97.5%) completed treatment; 2 on ETX2514SUL discontinued treatment due to adverse events (AEs).

Table 1. Baseline Characteristics

Demographics/ Characteristic	ETX2514SUL (N=53)	PBO (N=27)
Age (years), mean (SD)	51.4 (17.55)	54.9 (15.92)
Gender, n (%)		
Male	26 (49.1)	16 (59.3)
Female	27 (50.9)	11 (40.7)
Race, n (%)		
White	53 (100.0)	27 (100.0)
BMI (kg/m^2), mean (SD)	28.09 (6.661)	28.63 (5.856)
Creatinine clearance (mL/min), mean (SD)	94.3 (23.76)	91.7 (18.19)
Infection type, n (%)		
cUTI	31 (66.0)	16 (76.2)
AP	16 (34.0)	5 (23.8)

BMI = body mass index; cUTI = complicated urinary tract infection; AP = acute pyelonephritis; SD = standard deviation

Table 2. Baseline Pathogens (m-MITT population)

Baseline Pathogen	ETX2514SUL (N=47) n (%)	PBO (N=21) n (%)
Escherichia coli	23 (48.9)	7 (33.3)
Klebsiella pneumoniae	10 (21.3)	7 (33.3)
Enterococcus faecalis	8 (17.0)	3 (14.3)
Pseudomonas aeruginosa	3 (6.4)	2 (9.5)
Citrobacter freundii	3 (6.4)	0 (0.0)
Enterobacter cloacae	0 (0.0)	3 (14.3)
Other pathogens	6 (12.8)	0 (0.0)

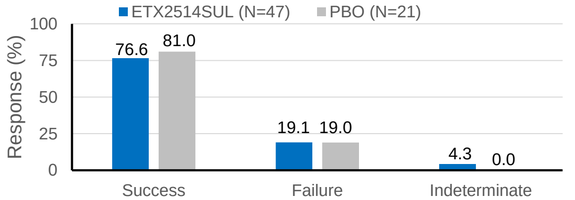
Table 3. Pharmacokinetics in hospitalized patients were comparable to healthy volunteers[1]

Compound	Cmax µg/mL	AUC0-tau µg*h/mL	CLss L/h	Vss L	Half-life h
ETX2514	39.9	124	10.3	31.6	2.2
(SD)	(38.2)	(86)	(4.0)	(13.1)	(1.6)
Sulbactam	39.1	108	13.4	36.0	1.6
(SD)	(38.6)	(83)	(8.4)	(23.4)	(1.1)

Efficacy

Fig.1. Overall Response (Microbiologic Eradication+ Clinical Cure) Rates at TOC*

Microbiologically Modified Intent-to-Treat (m-MITT) Population



*Microbiologically Evaluable (ME) population rates were 80% and 81%, respectively, for ETX2514SUL and PBO.

Table 4. Overall Response in AP and cUTI (m-MITT)

Response	ETX2514SUL	PBO
AP	N=16	N=5
Success, n (%)	15 (93.8)	3 (60.0)
Failure, n (%)	1 (6.3)	2 (40.0)
cUTI	N=31	N=16
Success, n (%)	21 (67.7)	14 (87.5)
Failure, n (%)	8 (25.8)	2 (12.5)
Indeterminate, n (%)	2 (6.5)	0 (0)

Fig. 2. Relative Rates of Microbiological Eradication of Common Uropathogens (m-MITT)

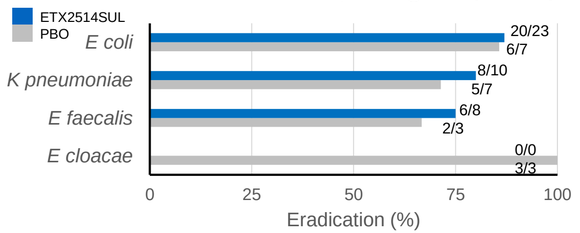


Table 5. Response in IMI non-susceptible Infections

Baseline Pathogen	ETX2514SUL (N=3) n/N (%)	PBO (N=4) n/N (%)
Klebsiella pneumoniae	0/0 (0.0)	1/2 (50.0)
Proteus mirabilis	1/1* (100.0)	0/0 (0.0)
Pseudomonas aeruginosa	2/2 (100.0)	2/2 (100.0)

*Blood and Urine Culture – *P. mirabilis*, IMI MIC=2mg/L

Safety

Adverse events

- ETX2514SUL was generally safe and well tolerated. No SAEs were reported.
- Treatment-emergent AEs (TEAE): ETX2514SUL 37.7% vs. PBO 29.6%. Most were mild to moderate in severity; ETX2514SUL, 1 severe TEAE (nausea). Headache, phlebitis and nausea were the most commonly reported TEAEs on ETX2514SUL. No safety signals emerged from the review of vital signs, ECGs and laboratory safety data.

Table 6. Drug-Related (DR) TEAEs

	ETX2514SUL (N=53) n (%)	PBO (N=27) n (%)
Patients with any DR-TEAE	12 (22.6)	4 (14.8)
Gastrointestinal disorders	4 (7.5)	2 (7.4)
Nausea	2 (3.8)	1 (3.7)
Diarrhea	2 (3.8)	0 (0.0)
Nervous system disorders	3 (5.7)	1 (3.7)
Headache	3 (5.7)	1 (3.7)
Vascular disorders	2 (3.8)	0 (0.0)
Vascular pain	2 (3.8)	0 (0.0)

TEAE = treatment-emergent adverse event

Conclusions

- Overall, ETX2514SUL+IMI was generally safe and well tolerated in moderately ill, hospitalized adults with cUTIs, including AP.
- The majority of TEAEs in the ETX2514SUL+IMI group were mild or moderate in severity, with no SAEs reported.
- The majority of patients had an overall response of success, experienced a sustained clinical cure, and had a microbiological response of eradication, as would be expected with background IMI therapy.

Reference: 1. Rodvold KA et al. AAC 2018;62:e01089-18.

Author Disclosures: 1-4-None, 5-FTE Entasis Therapeutics.

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