Sunday # 517

Plasma and Intrapulmonary Concentrations of ETX2514 and Sulbactam in Healthy Adult Subjects

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Abstract

Background: ETX2514 is a novel β-lactamase inhibitor with broad-spectrum Ambler class A, C and D activity. ETX2514 combined with sulbactam (SUL) *in vitro* restores SUL activity against *Acinetobacter baumannii*; SUL-ETX2514 (ETX2514SUL) MIC_{90} 2 mg/L (>2100 clinical isolates). ETX2514SUL is under development for the treatment of *A. baumannii* infections. Pulmonary epithelial lining fluid (ELF) and alveolar macrophages (AM) have been advocated as important sites of infection for extracellular and intracellular respiratory pathogens, respectively. The primary objective of this study was to determine and compare plasma, ELF, and AM concentrations following intravenous (IV) SUL and ETX2514. **Methods:** SUL and ETX2514 concentrations in plasma, ELF, and AM were measured by LC-MS/MS in 30 healthy adult subjects following repeated dosing (SUL [1 g] and ETX2514 [1 g] q6h, as a 3-hour IV infusion, for a total of 3 doses). A bronchoscopy and bronchoalveolar lavage (BAL) was performed once in each subject at 1, 2.5, 3.25, 4 or 6 h after the start of the last infusion. Noncompartmental PK parameters were determined from serial plasma samples collected over a 6-hour dosing interval. Penetration ratios were calculated from AUC_{0-6} values for total plasma, ELF, and AM using mean and median concentrations at the BAL sampling times. **Results:** Plasma concentrations and PK parameters for SUL and ETX2514 are in the table.

	C_{max} (μg/mL)	C_{min} (μg/mL)	$t_{1/2}$ (h)	V_{ss} (L)	CL (L/h)	AUC_{0-6} (μg•h/mL)	
						Mean	Median
SUL	23.10 ± 7.61	2.50 ± 1.09	1.12 ± 0.14	20.7 ± 4.3	15.56 ± 3.63	68.9	69.1
ETX2514	33.41 ± 8.89	5.79 ± 2.08	1.40 ± 0.18	16.7 ± 3.0	9.56 ± 1.92	107.8	108.7

CL = Clearance. V_{ss} = Volume of distribution.

Respective ELF AUC_{0-6}, based on mean and median concentrations, were 34.7 and 34.5 μg•h/mL for SUL, and 40.1 and 39.4 μg•h/mL for ETX2514. Respective penetration ratios of ELF to total plasma concentrations, based on mean and median AUC_{0-6}, of ETX2514 were 0.37 and 0.36, whereas these same ratio values were 0.50 for SUL. SUL and ETX2514 concentrations in AM were measurable and fairly constant throughout the dosing interval (median values of 1.31 and 1.01 μg/mL, respectively). ETX2514SUL was generally well tolerated. **Conclusions:** ETX2514 and SUL demonstrated a similar time course and magnitude of concentrations in plasma and ELF. The intrapulmonary penetration of SUL and ETX2514 were approximately 50% and 37%, respectively. These data support further study of ETX2514SUL for treatment of pneumonia caused by susceptible pathogens.

Introduction

Acinetobacter baumannii is a Gram-negative pathogen that causes serious infections which are associated with high morbidity and mortality. Sulbactam is a β-lactam agent which is a β-lactamase inhibitor but also has intrinsic activity against *A. baumannii*. Unfortunately, *A. baumannii* resistance to sulbactam, generally mediated by β-lactamases, is now widespread among resistant isolates; expression of Class D β-lactamase is nearly ubiquitous, but Class A and/or extended spectrum Class C co-expression is also common. Therefore, 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. Currently there are no β-lactamase inhibitors available which provide broad coverage of Class D β-lactamases.

ETX2514 is a potent, broad inhibitor of Ambler Class A, C, and D β-lactamases. ETX2514 has no significant intrinsic activity against *A. baumannii* . The addition of ETX2514 to sulbactam *in vitro* restores the activity of sulbactam such that minimum inhibitory concentration for 90% (MIC_{90}) from a collection of globally diverse contemporary *A. baumannii* clinical isolates (n=2,177) decreases from >32 μg/mL in the absence of ETX2514 to 2 μg/mL in the presence of ETX2514 (held constant at 4 μg/mL). The combination of ETX2514/sulbactam (ETX2514SUL) is being developed to treat infections caused by multidrug-resistant (MDR) *A. baumannii* infections. The U.S. Food and Drug Administration (FDA) has granted Qualified Infectious Disease Product (QIDP) designation and Fast Track status to ETX2514SUL for the treatment of hospital-acquired and ventilator-acquired bacterial pneumonia and bloodstream infections due to *A. baumannii*.

Study Objectives and Methods

Objectives of this study:

- Determine and compare plasma, epithelial lining fluid (ELF) and alveolar macrophage (AM) concentrations of ETX2514 and sulbactam after ETX2514 1 g was given concurrently with sulbactam 1 g every 6 hours (q6h) infused intravenously (IV) over 3 hours for a total of three consecutive doses;
- Characterize the plasma pharmacokinetics of ETX2514 and sulbactam with the third IV infusion; and
- Assess the safety and tolerability of concurrently administration of ETX2514 1.0 g and sulbactam 1.0 g for three consecutive IV doses in healthy adult subjects

Study design

- Phase 1, multiple-dose, open-label pharmacokinetic study in healthy adult male and female subjects
- Each subject had undergone one standardized bronchoscopy with BAL in the outpatient bronchoscopy suite at one of the five bronchoscopy timepoints at 1.0, 2.5, 3.25, 4.0 or 6.0 hours after start of the infusion of the third doses of ETX2514 and sulbactam (6 subjects per BAL sampling time point)
- Blood and BAL samples for determining drug and urea concentrations were obtained at each BAL sampling time

.Parameters

- Plasma, ELF, and AM concentrations for determining pharmacokinetics
- Safety monitoring including laboratory testing and ECG

Analysis of concentrations

- ETX2514, sulbactam and urea concentrations determined by LC/MS/MS
- Plasma concentrations of ETX2514 and sulbactam assayed at Covance
- ELF and AM concentrations of ETX2514 and sulbactam assayed at Keystone Bioanalytical
- Plasma and BAL urea concentrations assayed at Keystone Bioanalytical
- Data presented are based on noncompartmental pharmacokinetic analysis

Clinical trial registration

- ClinicalTrials.gov Identifier: NCT03303924

Results

Subjects

Characteristics of 30 healthy adult subjects enrolled into the study[a]

Sampling Time (h)	Sex of patients	Age (yr)	Height (cm)	Weight (kg)	eCL_{CR} (mL/min)	Total Cell Count in BAL Fluid (cells/mm^3)	Macrophages (%)
All	18 M, 12 F	42 ± 11	173 ± 9	79.7 ± 11.8	110 ± 22	145 ± 159	81 ± 10
1-hour[b]	3 M, 3 F	46 ± 12	168 ± 5	71.6 ± 7.0	93 ± 23	114 ± 61	82 ± 6
2.5-hour[b]	3 M, 3 F	45 ± 6	174 ± 8	82.2 ± 10.0	115 ± 15	137 ± 87	82 ± 17
3.25-hour[b]	5 M, 1 F	33 ± 10	176 ± 8	84.3 ± 11.8	111 ± 15	141 ± 57	86 ± 6
4-hour[b]	3 M, 3 F	46 ± 13	170 ± 12	76.6 ± 14.7	103 ± 17	267 ± 368[c]	78 ± 10
6-hour[b]	4 M, 2 F	37 ± 12	176 ± 8	80.0 ± 12.6	122 ± 31	72 ± 54	75 ± 10

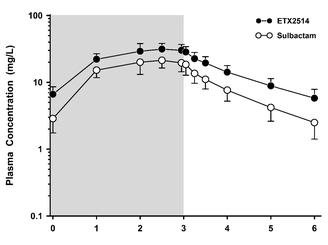
[a] Data are expressed as mean ± SD except for the data on sex
[b] 6 subjects per sampling period
[c] One subject at this sampling time had an extremely high total cell count of 900 cells/mm^3
Abbreviations: M = males; F = females; eCL_{CR} = estimated creatinine clearance based on Cockcroft-Gault equation

Safety and Tolerability

- ETX2514SUL was generally well tolerated and no serious adverse events were reported
- Four (4) subjects (13.3%) experienced a total of five (5) treatment-emergent adverse events (TEAEs)
- The observed (number) TEAEs included constipation (n=1), IV infusion site pain (n=2), eye contusion (n=1), and hepatic enzyme elevation (n=1). All TEAEs were considered mild (n=3) or moderate (n=2) in severity
- One TEAE (infusion site pain) was considered related to the study drug administration. All TEAEs resolved during the study

Plasma Concentrations and Pharmacokinetic Parameters

Mean (± SD) plasma concentration-versus-time profile of ETX2514 (filled circles) and sulbactam (open circles) with the third dose of ETX2514SUL (1 g ETX2514/1 g sulbactam) administered as a 3-h IV infusion q6h. Shaded region represents the 3-h infusion period.



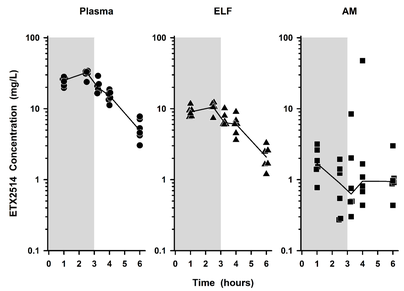
Pharmacokinetic parameters of ETX2514 and sulbactam in plasma following the third IV dose of ETX2514SUL[a]

Drug	C_{max} (μg/mL)	C_{min} (μg/mL)	AUC_{0-6} (μg•h/mL)	$t_{½}$ (h)	V_{ss} (L)	CL (L/h)
ETX2514	33.41 ± 8.89	5.79 ± 2.08	109.05 ± 23.44	1.40 ± 0.18	16.7 ± 3.0	9.56 ± 1.92
Sulbactam	23.10 ± 7.61	2.50 ± 1.09	67.89 ± 16.69	1.12 ± 0.14	20.7 ± 4.3	15.56 ± 3.63

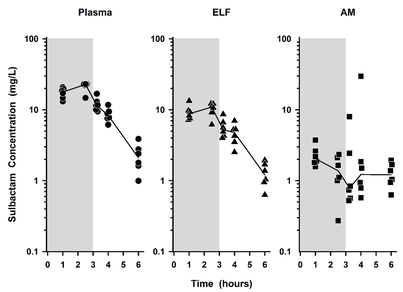
[a] Data are expressed as mean ± SD and from 30 subjects per parameter estimate

Plasma, Epithelial Lining, and Alveolar Macrophage Concentrations at BAL Sampling Times

Individual concentrations of ETX2514 in plasma, epithelial lining fluid (ELF), and alveolar macrophages (AM) at 1, 2.5, 3.25, 4, and 6 hours after the third dose of ETX2514SUL (1 g ETX2514 / 1 g sulbactam) administered as a 3-h IV infusion q6h. Line represents the median concentrations. Shaded region represents the 3-h infusion period.



Individual concentrations of sulbactam in plasma, epithelial lining fluid (ELF), and alveolar macrophages (AM) at 1, 2.5, 3.25, 4, and 6 hours after the third dose of ETX2514SUL (1 g ETX2514/1 g sulbactam) administered as a 3-h IV infusion q6h. Line represents the median concentrations. Shaded region represents the 3-h infusion period.



ETX2514 concentrations and ratios of ELF or AM to unbound plasma concentration[a]

Sampling Time (h)	ETX2514 concentrations (μg/mL) in:			Ratios of ETX2514 in:	
	Plasma (total)	ELF	AM	ELF-to-Plasma (unbound)[d]	AM-to-Plasma (unbound)[d]
1-hour[b]	12.16 ± 1.68	9.14 ± 1.51	1.89 ± 0.87	0.42 ± 0.04	0.09 ± 0.04
2.5-hour[b]	15.62 ± 1.90	10.47 ± 1.70	0.95 ± 0.68	0.37 ± 0.02	0.04 ± 0.03
3.25-hour[b]	10.39 ± 2.27	7.14 ± 1.66	2.09 ± 3.18	0.38 ± 0.04	0.12 ± 0.21
4-hour[b]	7.55 ± 1.33	6.03 ± 1.88	0.94 ± 0.47[c]	0.45 ± 0.11	0.07 ± 0.03[c]
6-hour[b]	2.67 ± 0.90	2.15 ± 0.78	1.21 ± 0.91	0.46 ± 0.11	0.32 ± 0.38

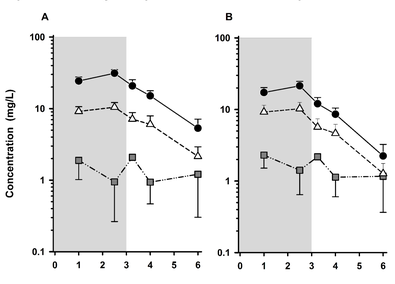
[a] Data are expressed as mean ± SD
[b] 6 subjects per sampling period
[c] Value reflects the mean ± SD of 5 samples
[d] The unbound fraction of ETX2514 in plasma = 0.90

Sulbactam concentrations and ratios of ELF or AM to unbound plasma concentration[a]

Sampling Time (h)	Sulbactam concentrations (μg/mL) in:			Ratios of sulbactam in:	
	Plasma (total)	ELF	AM	ELF-to-Plasma (unbound)[d]	AM-to-Plasma (unbound)[d]
1-hour[b]	17.28 ± 2.97	9.22 ± 2.25	2.30 ± 0.79	0.81 ± 0.14	0.21 ± 0.09
2.5-hour[b]	21.42 ± 3.31	10.25 ± 2.29	1.41 ± 0.77	0.73 ± 0.16	0.11 ± 0.07
3.25-hour[b]	12.03 ± 2.66	5.67 ± 1.74	2.18 ± 2.94	0.72 ± 0.14	0.26 ± 0.34
4-hour[b]	8.58 ± 1.90	4.64 ± 1.56	1.31 ± 0.53[c]	0.83 ± 0.25	0.21 ± 0.11[c]
6-hour[b]	2.24 ± 1.01	1.27 ± 0.49	1.16 ± 0.80	0.94 ± 0.42	1.22 ± 1.63

[a] Data are expressed as mean ± SD
[b] 6 subjects per sampling period
[c] Value reflects the mean ± SD of 5 samples
[d] The unbound fraction of sulbactam in plasma = 0.62

Mean (± SD) plasma (filled circles), epithelial lining fluid (ELF) (open triangles), and alveolar macrophages (AM) (gray squares) concentrations of ETX2514 and sulbactam after the third dose of ETX2514SUL (1 g ETX2514/1 g sulbactam) administered as a 3-h IV infusion q6h. Shaded region represents the 3-h infusion period.



AUC_{0-6} based on mean and median ELF concentrations at the BAL sampling times and ELF-to-plasma (total and unbound) ratios based AUC_{0-6} values

Drug	Mean ELF AUC_{0-6} (μg•h/mL)	ELF-to-Plasma Ratios (Total/Unbound)	Median ELF AUC_{0-6} (μg•h/mL)	ELF-to-Plasma Ratios (Total/Unbound)
ETX2514	40.1	0.37 / 0.41	39.4	0.36 / 0.40
Sulbactam	34.7	0.50 / 0.81	34.5	0.50 / 0.80

Conclusions

- ETX2514SUL was generally safe and well tolerated at a dosing regimen of ETX2514 1 g and sulbactam 1 g administered q6h as a 3-hour IV infusion for a total of three doses.
- The penetration ratios of ELF to unbound plasma concentrations based on the respective mean and median AUC_{0-6} values were 0.41 and 0.40 for ETX2514 and 0.81 and 0.80 for sulbactam, and were consistent with ratios observed at each sampling time.
- Intrapulmonary concentrations of ETX2514 and sulbactam were also detected in AM and median values remained fairly constant (~1 to 2 μg/mL) throughout the 6-hour dosing interval.
- The results from this study support further considerations of ETX2514SUL as a potential agent for the treatment of lower respiratory tract bacterial infections caused by MDR *A. baumannii*.

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