Poster# 2245

Human PK and Dose Projection of ETX2514 / Sulbactam Combination for Use in the Treatment of Infections Caused by *Acinetobacter baumannii*

J. O'Donnell[1], A. Miller[1], H. Shankaran[2], D. Ferguson[2], J. Newman[2], R. Tommasi[1], and J. Mueller[1]

[1]Entasis Therapeutics and [2]AstraZeneca, Waltham, MA USA

Entasis Therapeutics
35 Gatehouse Drive
Waltham MA 02451
1-781-810-0118
john.odonnell@entasistx.com

Abstract

Background: ETX2514 is a novel diazabicyclooctenone β-lactamase inhibitor with broad spectrum activity against Ambler class A, C and D serine β-lactamases that successfully restores activity of sulbactam (SUL) against *Acinetobacter baumannii*. Preclinical pharmacokinetic/pharmacodynamic (PK/PD) investigations determined exposures required for SUL and ETX2514 for efficacy as a combination. In support of clinical dose projections, dog and rat PK of ETX2514 was used to predict human PK parameters.

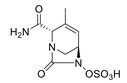
Methods: Human PK prediction of ETX2514 was completed using single species allometry for volume of distribution (Vd_{ss}) from dog PK and rat and dog allometry to predict non-renal clearance (CL_{metab}). Renal excretion of unchanged drug was found to be a significant route of elimination. Human renal clearance (CL_{renal}) was predicted using dog-human renal correlation. Half-life was calculated as $ln2*Vd_{ss}/CL_{total}$. Variance in Phase 1 PK data for avibactam was applied to the prediction of ETX2514 and combined with Phase 2 population PK modeling of existing SUL human PK in support of probability of target attainment (pTA) analysis to meet PK/PD exposure targets. MIC distribution of a contemporary panel of clinical *A. baumannii* isolates was used to determine cumulative fraction of response (CFR). A clinical dose regimen predicted to exceed >90% pTA and CFR was considered as criteria for success.

Results: Allometric scaling predicted human Vd_{ss} of 0.26 L/kg (range: 0.22-0.31) and CL_{Total} of 3.1 mL/min/kg (range 2.4-4.0) suggesting a half-life of 1.1 hr. Urinary excretion of >90% of unchanged drug was projected based upon dog-human renal correlation. These PK properties were consistent with those of SUL, enabling use of the combination in the same dose regimen. Accounting for projected PK variability of ETX2514 and SUL, the current clinical dose of SUL at 4 gm/day combined with 2 gm/day of ETX2514 is expected to deliver >90% CFR when administered as 3 hr infusions of 0.5 gm ETX2514/1.0 gm SUL q6hr.

Conclusions: Human PK predictions of ETX02514 suggested good compatibility for use in combination with SUL for the treatment of *A. baumannii* infections. A clinical regimen of 0.5 gm ETX2514/1.0 gm SUL q6h infused over 3 hr is anticipated to have >90% pTA and >90% CFR.

Introduction

The increasing incidence of extensively drug resistant resistant (XDR) *A. baumannii* has become a worldwide healthcare concern. More disturbingly, cases of XDR strains showing poor susceptibility to colistin, once considered the drug of last resort, are finding their way into hospitals. The novel diazabicyclooctenone β-lactamase inhibitor ETX2514 is active against a broad range of Class A, C and D serine β-lactamases and has been shown to effectively restore the antibacterial activity of sulbactam against resistant XDR *A. baumannii* isolates within *in vitro* and *in vivo* efficacy studies. PK/PD targets derived from these studies were used along with allometric predictions of human PK to estimate human dosing requirements of the combination. Use of available population PK data for sulbactam and projected inter-subject variability of the target patient population were considered with susceptibility data from n=1131 clinical *A. baumannii* isolates to determine probability of target attainment.



ETX2514

sulbactam

Methods

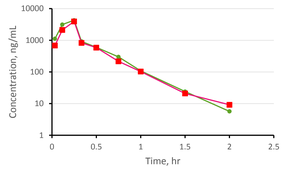
IV pharmacokinetics in rats and dogs: Single dose IV pharmacokinetics of ETX2514 were conducted in n=2 male Han-Wistar rats (200 gm) and n=3 male beagle dogs at 3 and 0.45 mg/kg respectively. Doses were dissolved in 5% dextrose and administered as 15 minute infusions. Serial blood samples were obtained via venipuncture to 12 h post-dose, prepared for plasma and assayed for drug concentrations by LC/MS/MS. Bile-duct cannulated rats (n=3) were administered a bolus 25 mg/kg IV dose with bile collected to 24 hpd. ETX2514 concentrations were assayed in bile, urine, and plasma to determine clearance mechanism.

Cryopreserved hepatocytes: *In vitro* incubations of ETX2514 in rat, dog and human hepatocytes were completed and the data scaled via standard procedures (1) at 3 µM. Serial samples taken over 4 hrs were assayed for ETX2514 concentration and the first order reduction in drug was used to estimate intrinsic clearance (CL_{int}). CL_{int} was scaled to determine metabolic clearance (CL_{metab}) associated with the liver in each species.

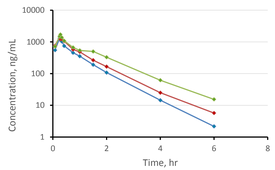
Non-compartment PK and population PK simulations: Rat and dog time vs. plasma concentration data was modelled using non-compartmental analysis (Phoenix WinNonLin 6.4). Pharmacokinetic parameters were scaled allometrically via cited methods (2,3) to predict human PK of ETX2514. Population PK simulations were performed using Phoenix Non-Linear Mixed Effects v1.3. Patient demographics including age, body weight, and creatinine clearance suggestive of the targeted patient population were obtained from Rubino et al.(4) and population PK (fixed true value, covariate and inter-individual variability) parameters for sulbactam were obtained from Soto et al. (5) Allometrically scaled PK predictions for ETX2514 were used as true value estimates with inter-individual variability and creatinine clearance covariate dependencies derived from avibactam clinical experience (8). Monte Carlo simulation of the combined model (n=1000 virtual patients) was performed with target attainment considered met when simulated exposures exceeded both PK/PD targets for ETX2514 and sulbactam.

Results: Rat and Dog IV PK

Rat IV Pharmacokinetics (n=2)



Dog IV Pharmacokinetics (n=3)



Parameter	Rat	Dog
Dose (mg/kg)	3	0.45
C_{max}, µg/mL	4.13 (3.95-4.30)	1.43±0.12
$AUC_{0-\infty}$, µg.h/mL	1.09 (0.98-1.19)	1.39±0.42
$T_{1/2}$, h	0.23	0.8±0.13
CL, mL/min/kg	46 (41-49)	5.10±1.50
Vd_{ss}, L/kg	0.51 (0.44-0.59)	0.28±0.03
Fraction excreted in urine	0.71	0.58
Protein binding, fraction unbound	0.88	>0.95

In Vitro and In Vivo Clearance Results:

Clearance	Rat	Dog	Human
Hepatocyte CL_{int}, µL/min/10^6 cells	6	0.5	<1.0
Predicted CL_{metab}, mL/min/kg	17.2	4.0	0.5
Observed Cl_{metab}, mL/min/kg	19	1.5	--
Cl_{renal}, mL/min/kg	27	3.6	--
$CL_{biliary}$, mL/min/kg	0.1	NT	--
CL_{Total}, mL/min/kg	46	5.1	--

Allometric Predictions of ETX2514 Human PK:

Human PK parameter	Prediction	Method
CL_{total} (ml/min/kg)	**3.1 (2.0-4.7)**	$CL_{total} = CL_{metabolic} + CL_{renal}$
$CL_{metabolic}$ (ml/min/kg)	**0.5**	$CL_{metabolic}$ = standard allometry (rat and dog non-renal CL)
Cl_{renal} (mL/min/kg)	***2.6***	CL_{renal} = Dog renal CL correlation method (2)
Vd_{ss} (L/kg)	**0.26 (0.19-0.35)**	Dog to human Vd_{ss} (3)
$t_{1/2}$ (h)	**1.1 (0.7-1.3)***	$Ln2*Vd_{ss}/CL_{total}$

Human Dose Projection of ETX2514 : Sulbactam Combination

Pop PK tigecycline CAP/HAP patients Rubino *et al.* 2010

Patient population demographics incorporated:
- Age,
- Weight,
- Creatinine Clearance

Pop PK sulbactam CAP patients Soto *et al.* 2014

Assumed ETX2514 CL-CrCL Relationship (8):

$CL \propto (CrCL/80)^{1.15}(Age/35)^{-0.15}$

ETX2514 Vd_{ss} scaled to body weight

CrCL is a covariate for CL of both compounds (70% correlated)

Sulbactam CL-CrCL Relationship:

$CL \propto (CrCL/71)^{0.701}$

Sulbactam Vd_{ss} scaled to body weight

Monte Carlo Simulation (n=1000 patients)
1.0 gm sulbactam:0.5 gm ETX2514 3hr inf. q6h

PK/PD Targets ref (6): sulbactam - 50% T>MIC of 4 mg/L
ETX2514 - 50% $T>C_T$ of 2.5 mg/L

Probability of target attainment (pTA) for meeting *BOTH* criteria

Patient Demographics Utilized:

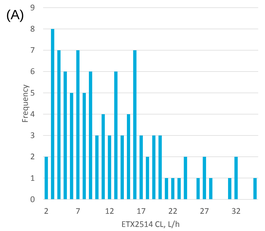
Continuous variables	Mean±SD
Age, yr	55.2±17.5
Body weight, kg	74.7±17.8
Creatinine CL, mL/min/1.73m^2	79.7±35.1

Population PK model parameters:

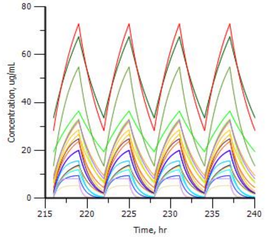
Parameter	ETX2514	Sulbactam
$tvCL_1$, L/hr	13.0	10.4
tvV_1, L	18.2	10.2
$tvCL_2$, L/hr	--	4.58
tvV_2, L	--	4.04
%CV CL_1	15	15
%CV V_1	20	--
%CV V_2	--	15

Predicted ETX2514 clearance (CL) distribution (A) (n=100 patients) and simulated steady state time vs. concentration profiles of a 3 hr infusion of 500 mg q6h (B) (n=20 patients)

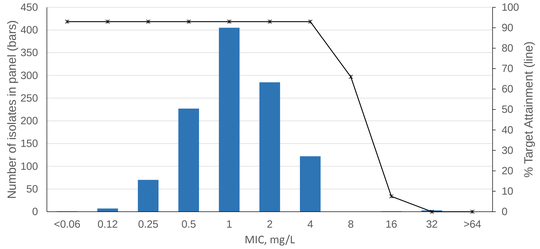
(A)



(B)



Results: Probability of Target Attainment



Predicted probability of target attainment for 1.0 gm sulbactam:0.5 gm ETX2514 3 hr infusion, q6h to treat strains with MICs of 4 mg/L or less (*n=1131 strains, 1000 patients*)

MIC_i (mg/L)	pTA (%)	F_i (fraction MIC=MIC_i)	CF_i (Cumulative fraction with MIC ≤MIC_i)	pTA X F_i
≤0.25	92.5%	88	88	81.4
0.5	92.5%	227	315	210
1	92.5%	405	720	375
2	92.5%	285	1005	264
4	92.5%	122	1127	113
8	66.6%	0	1127	0
16	7.5%	1	1128	0.075
≥32	0.0%	3	1131	0
		Totals:	1131	1043

Conclusions

- Rat and dog PK of ETX2514 were consistent with low to moderate clearance and low volume of distribution translating to a projected half life of 1.1 hr in humans.
- Excretion of unchanged drug was the predominant clearance mechanism with relatively low metabolism characterized *in vitro* and *in vivo*.
- Available population PK of sulbactam as well as demographics from HAP patients was used in conjunction with predicted PK parameters of ETX2514 to develop a population model simulation of the combination of the two compounds.
- Monte Carlo simulation of 1000 patients administered 1.0 gm of sulbactam:0.5 gm of ETX2514 via a 3 hr infusion q6h is predicted to have a probability of target attainment of 92.5% for PK/PD targets at MICs of 4 mg/L or less.
- With nearly 99.6% of all pathogens susceptible at an MIC of 4 mg/L or less, a dose of 1.0 gm sulbactam : 0.5 gm ETX2514 is expected to provide 92.2% cumulative fraction of response (1043/1131 strains).

References:

(1) Sohlenius-Sternbeck et al. (2012) *Xenobiotica* 42: 841-853
(2) Paine et al. *Drug Metab. Dispos*. 39(6): 1008-1013
(3) McGinnity et al. *Curr Drug Metab*. 8(5): 463-479.
(4) Rubino et al. (2010) *Antimicrob. Agents Chemother*. 54(12): 5180-5186
(5) Soto et al. (2014) *Br J Clin Pharmacol*. 77(3): 509-521
(6) O'Donnell et al. (2016) Microbe, Boston MA poster #LB-117
(7) Hackel et al. (2016) IDWeek, New Orleans LA poster #2243
(8) Merdjan et al. (2016) *J Clin Pharmacol*. doi:10.1002/jcph.793

Presented at IDweek™ New Orleans, LA October 2016