Pharmacodynamics (PD) of the Beta-Lactamase Inhibitor Xeruborbactam When Administered as the Oral Prodrug in Combination with Ceftibuten

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Introduction

- There are limited oral treatment options for complicated UTIs due to ESBL- and particularly carbapenemase-producing Enterobacterales. The oral carbapenem tebipenem has recently been studied in cUTIs due to non-CRE, but showed reduced efficacy in infections due to ESBL-producing isolates compared to ertapenem, suggesting that oral agents may benefit from co-administration with a beta-lactamase inhibitor.
- Xeruborbactam (XERU) is an ultra broad-spectrum beta-lactamase inhibitor with inhibitory activity against Class A-D enzymes in Enterobacterales. Combinations of XERU with beta-lactam antibiotics, including oral agents, restores their activity against many strains of Enterobacterales producing serine and metallo beta-lactamases.
- The isobutyryloxymethyl prodrug of XERU has high oral bioavailability and produces high XERU concentrations in humans, with a long terminal plasma half-life that supports once-daily dosing.
- Results from a Phase 1 clinical trial (NCT03939429) of oral ceftibuten 800 mg once or twice daily showed these doses to be well-tolerated and produced plasma exposures that would have activity against strains with MICs up to 0.5 – 2 mg/L.
- The purpose of these studies was to determine the pharmacodynamic measure that best described the activity of XERU administered as its prodrug against Enterobacterales when administered in combination with a fixed dosage regimen of ceftibuten in the neutropenic mouse thigh infection model.

Methods

Mouse Pharmacokinetics

- Neutropenic, infected, female Swiss-Webster mice were administered single doses ranging from 5 to 50 mg/kg by the oral route. Additional studies assessed drug accumulation using a 30 mg/kg dose administered every 6 hours for 4 total doses.
- Blood samples (N = 3/timepoint) were collected at various timepoints over 24 hours.
- Plasma levels were determined using an LC-MS/MS method and the data were fit to a non-compartmental model (WinNonlin).

Methods (con't)

Mouse Thigh Infection Model

- Female Swiss-Webster mice were used.
- Mice were rendered temporarily neutropenic by the administration of 150 mg/kg of cyclophosphamide (Baxter, IL) on days −4 and −1 prior to infection.
- Infection was initiated (under isoflurane anesthesia) *via* an intramuscular injection of 0.1 mL of inoculum (~ 10^6 CFU/thigh).
- Treatment was initiated 2 h post-infection by the oral route.
- Controls were euthanized at the start of treatment while treated animals were euthanized 24 hours post-treatment using CO_2; thighs were removed aseptically, homogenized in 5 mL of saline, and plated on Mueller-Hinton Agar.

Pharmacodynamic Modeling

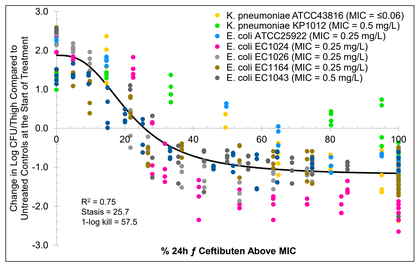
- The relationship between the PD indices and the change in log CFU compared to the start of treatment were fitted using the following inhibitory effect (Emax) model (Phoenix 64; Certara, Princeton, NJ):

$$Emax = E0 - (Imax \times X\gamma)/(X\gamma + IC50\gamma)$$

where E0 is the effect when X is equal to 0 (i.e., for the untreated control animals), Imax is the maximum reduction in the log number of CFU/lung, X is the PD index, IC50 is the PD parameter (X) corresponding to 50% of the maximum bacterial reduction, and γ is the steepness of the curve.

Results

Figure 1. Pharmacodynamics of Oral Ceftibuten Alone against Non-ESBL, non-CRE Enterobacterales in a Neutropenic Mouse Thigh Infection Model.



Results (con't)

Figure 2. Pharmacodynamic Measure that Best Describes the Activity of XERU Administered as the Oral Prodrug in Combination with Simulated Human Dosing of Ceftibuten 800 Once a Day against Eight Enterobacterales Isolates in the Neutropenic Mouse Thigh Infection Model

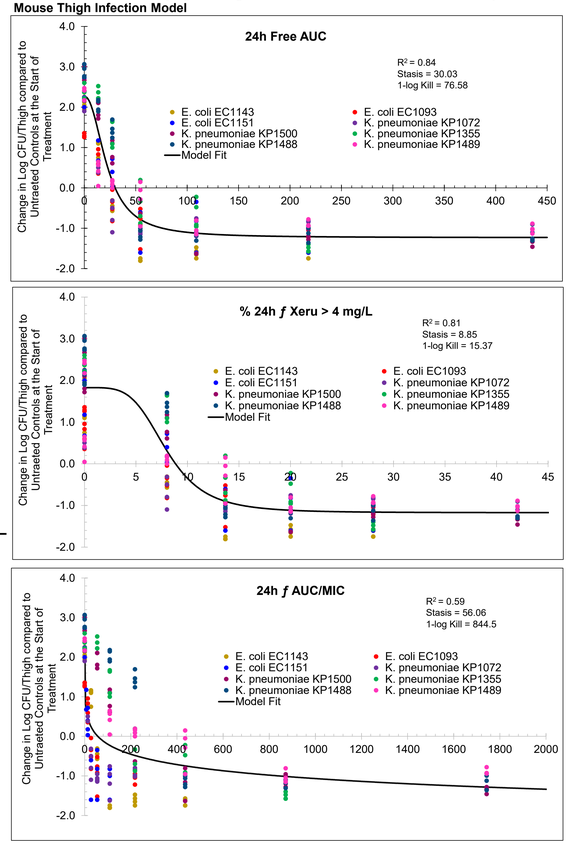


Table 1. Susceptibility Profile of Strains Used in PD Studies

Strains	β-lactamases Present	Ceftibuten MIC (mg/L)	
		Alone	w/ 4 mg/L Xeru
E. coli EC1143	CTX-M-15	> 64	0.5
E. coli EC1093	CMY-2	> 64	1
E. coli EC1151	SHV	> 64	2
K. pneumoniae KP1488	KPC-2; SHV-11; SHV-12	> 64	0.125
K. pneumoniae KP1489	KPC-3; TEM-1; SHV-11; CTX-M-15; OXA-1	> 64	0.125
K. pneumoniae KP1500	KPC-3; TEM-1; SHV-11; CTX-M-15; OXA-1; OXA-9	> 64	0.25
K. pneumoniae KP1355	KPC-2; TEM-1; SHV-11; SHV-12	> 64	0.25
K. pneumoniae KP1072	SHV; TEM	64	1

Table 2. Single Dose Pharmacokinetics of Ceftibuten and Xeruborbactam (Administered as the Oral Prodrug) in Mice

Compound	Dose (mg/kg)	AUC $_{0-\infty}$ (mg*hr/L)	CL/F (L/hr/kg)	Cmax (mg/L)	$T_{1/2}$ (h)
Ceftibuten	50	38.3	1.30	24.3	0.71
QPX7728 via QPX7831	5	8.7	0.57	3.7	2.56
QPX7728 via QPX7831	30	38.7	0.65	24.4	2.37
QPX7728 via QPX7831	50	99.7	0.50	109	3.30

Table 3. Comparison of Ceftibuten 24h free AUC and %24h ƒT>MIC in Mice and Humans.

Species	Dosage Regimen	% 24h ƒ Ceftibuten > MIC								24h Free AUC mg*h/L
		8	4	2	1	0.5	0.25	0.125	0.06	
Human	800 mg QD	22	30	42	54	65	77	87	100	63
Mouse	50 mg/kg q6h	27	36	44	51	58	65	72	79	138

Table 4. Pharmacodynamic Measures for Xeruborbactam Administered as the Oral Prodrug

Organism	24h ƒAUC			%24h ƒ T > 4			24h ƒAUC/MIC		
	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill
Enterobacterales (8 strains)	0.84	30.0	76.6	0.81	8.9	15.4	0.59	56.1	845

Summary

- The PK-PD index that best describes the bacterial killing of ceftibuten is the %24h ƒ ceftibuten Plasma concentrations exceed the MIC (T>MIC). A T>MIC of at least 58% is associated with 1-log of bacterial killing is 58% (Figure 1).
- The pharmacokinetic profile of xeruborbactam following oral administration as the isobutyryloxymethyl prodrug is, roughly, proportional to dose up to 50 mg/kg (Table 2).
- The XERU PK-PD measures that best described the bacterial killing in combination with a fixed oral dosage regimen of ceftibuten in the mouse thigh were 24h ƒ AUC, or %24h ƒ T > 4 mg/L. (Figure 2).
- One-log of bacterial killing in the thigh was associated with a 24h ƒ XERU AUC of 76.6 1/h or a %24h ƒ XERU > 4 mg/L of 15%. For stasis, 24h ƒ XERU AUC was 30 mg*h/Lor %24h ƒ XERU > 4 mg/L of 8.9%. (Table 4).
- Based on the microbiological surveillance, Phase 1 clinical data (IDWeek 2022, Abstract 218), and these PK-PD indices, an oral xeruborbactam dosage regimen of 800 mg/day in combination with 800 mg ceftibuten QD in humans would provide at least 1-log of bacterial killing for > 90% of ESBL producing and carbapenem-resistant Enterobacterales isolates.
- Continued development of xeruborbactam as the oral prodrug in combination with ceftibuten for the treatment of infections due to ESBL producing and carbapenem-resistant Enterobacterales isolates is warranted.

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