A Phase 1 Study of the Single-Dose Safety, Tolerability, and Pharmacokinetics of the Beta-lactamase Inhibitor Xeruborbactam Administered as the Isobutyryloxymethyl Oral Prodrug to Healthy Adult Subjects

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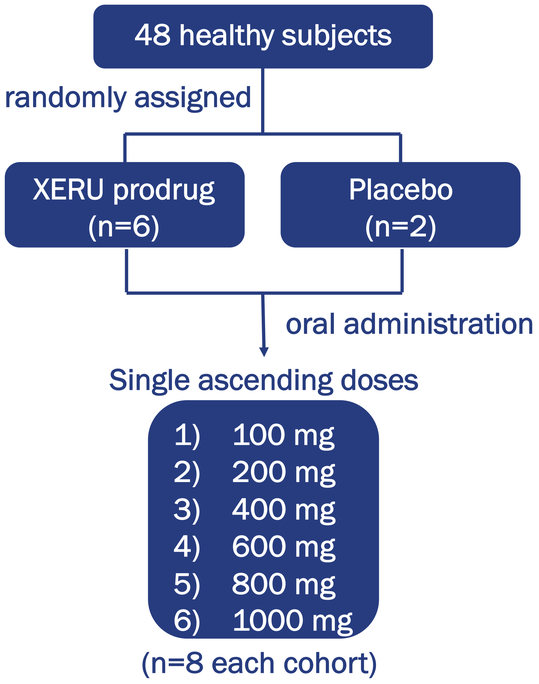
Introduction

Xeruborbactam (XERU) is a member of a new class of cyclic boronic acid β-lactamase inhibitors with inhibitory activity against major members of Class A, B, C, and D beta-lactamases.

This report describes the first safety and pharmacokinetic data following oral administration of XERU as the isobutyryloxymethyl prodrug form in humans.

Methods



Intensive plasma (total drug) and ultrafiltrate (free drug) sampling was obtained after dosing and assayed for QPX7831 and XERU content using validated HPLC-MS methods.

Data were fit using non-compartmental analysis.

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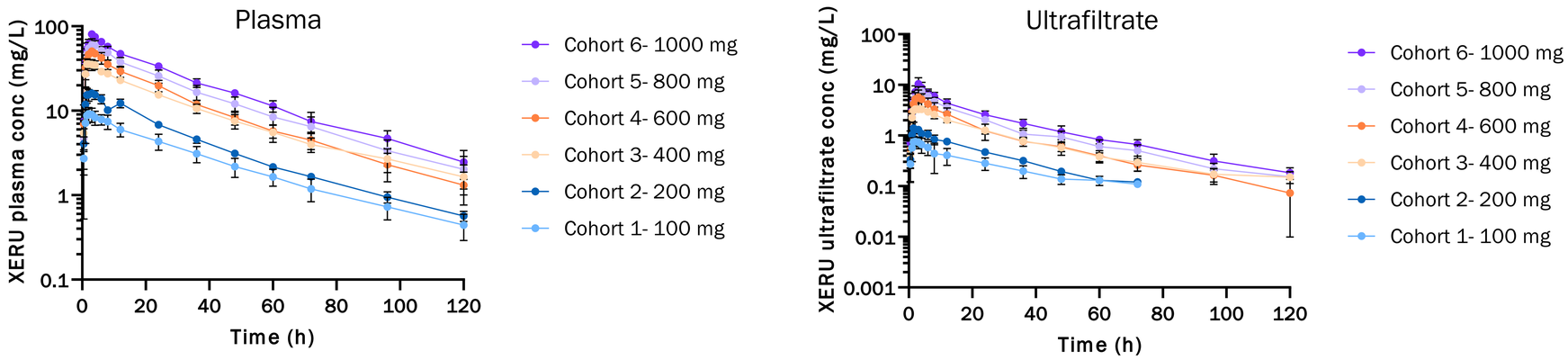
Results

- ✓ All AEs were mild in severity.
- ✓ No subjects discontinued due to AEs and no SAEs were observed.
- ✓ No evidence of increasing numbers or severity of AEs with increasing dose.

Adverse Events	Blinded n (%) Subjects with Events and Number of Events						
	100 mg (n=7)	200 mg (n=8)	400 mg (n=8)	600 mg (n=8)	800 mg (n=8)	1000 mg (n=7)	Overall (n=46)
Subjects with AEs	3 (42.9) 4	2 (25.0) 2	1 (12.5) 1	2 (25.0) 2	1 (12..5) 5	4 (57.1) 9	13 (28) 23
Headache	1 (14.3) 1	0	0	1 (12.5) 1	0	3 (42.9) 5	5 (10.9) 7
Nausea	0	0	0	0	1 (12.5) 2	1 (14.3) 1	2 (4.3) 3
Diarrhoea	0	0	0	0	1 (12.5) 1	1 (14.3) 1	2 (4.3) 3
Vascular Access Site Complication	2 (28.6) 2	0	0	0	0	0	2 (4.3) 2

Compared to IV XERU doses (data not shown), XERU is 90–100% orally bioavailable.



PK Parameter	100 mg (n=5)	200 mg (n=6)	400 mg (n=6)	600 mg (n=6)	800 mg (n=6)	1000 mg (n=5)
Cmax (mg/L)	9.3 ± 1.7	17.0 ± 1.9	37.8 ± 3.7	52.53 ± 2.8	62.0 ± 9.7	82.7 ± 5.0
Tmax (h)	2.3 ± 0.7	2.4 ± 1.1	2.3 ± 0.8	3.7 ± 1.4	3.3 ± 0.8	3.4 ± 0.6
$AUC_{0\text{-}INF}$ (mg·h/L)	324.0 ± 65.9	507.0 ± 36.8	1157.5 ± 153.4	1371.5 ± 150.3	1838.1 ± 302.6	2332.2 ± 197.1
Free $AUC_{0\text{-}INF}$ (mg·h/L)	20.8 ± 5.6	32.4 ± 2.8	93.1 ± 13.4	107.3 ± 25.5	155.8 ± 24.2	204.5 ± 40.0
Free $AUC_{0\text{-}24}$ (mg·h/L)	10.5 ± 3.4	18.8 ± 2.3	51.1 ± 5.4	68.1 ± 19.4	92.8 ± 15.3	115.6 ± 23.7
CL/F (L/h)	0.32 ± 0.06	0.40 ± 0.03	0.35 ± 0.05	0.44 ± 0.05	0.45 ± 0.07	0.43 ± 0.04
Vz/F (L)	15.4 ± 2.9	17.4 ± 1.3	15.0 ± 2.6	16.8 ± 3.0	17.61 ± 1.9	16.3 ± 1.3
Half-Life (h)	33.5 ± 2.1	30.5 ± 2.0	30.0 ± 5.3	26.4 ± 4.5	27.7 ± 2.4	26.4 ± 3.9

Conclusions

- XERU administered orally as a prodrug:
  - Was safe and well tolerated at all doses tested.
  - Has plasma PK properties that support once-daily administration.
- Plasma XERU AUC and Cmax increased with increasing dose.
- XERU exposures (free AUC0-24) with once-daily administration with ceftibuten exceed the predicted PK/PD index for stasis with once-daily doses of ≥ 400 mg, and exceed the PK/PD index for 1-log of bacterial killing with once-daily doses of ≥ 800 mg.