Evaluation of Single and Multiple Dose Safety and Pharmacokinetics of Ledaborbactam Etzadroxil and Ceftibuten-Ledaborbactam Etzadroxil in Healthy Volunteers

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Background

Complicated urinary tract infections (cUTI), including acute pyelonephritis, are common infections with limited oral therapeutic options due to resistance and safety issues (e.g., FQs, TMP-SMX). Ledaborbactam etzadroxil (LED-E), a novel oral prodrug that converts to the active β-lactamase inhibitor ledaborbactam (LED), is being developed in combination with ceftibuten (CTB) to address the urgent need for new oral (PO) treatments against drug-resistant Enterobacterales infections. Ceftibuten-ledaborbactam has demonstrated potent in vitro activity against drug-resistant Enterobacterales producing serine β-lactamases, including extended-spectrum β-lactamases (ESBLs), and serine carbapenemases, including KPC and OXA-48 producing strains (1).

Methods

- Study 101 (NCT04243863) was a randomized, double-blind, placebo-controlled, dose-escalation trial assessing the safety and pharmacokinetics of single ascending doses (SAD; 100 mg to 1000 mg) and multiple ascending doses (MAD; 75 mg to 500 mg every 8 hours for 10 days) of ledaborbactam etzadroxil (LED-E) or matching placebo (PBO) in 48 healthy adults.
- Study 102 (NCT04877379) was a three-part randomized study evaluating the safety and pharmacokinetics of LED-E and ceftibuten (CTB) in healthy adults.
  - In Part 1 of Study 102, participants received single doses of LED-E 500 mg, CTB 400 mg, or the combination of LED-E 500 mg + CTB 400 mg, using an open-label, cross-over design.
  - In Part 2, participants were administered multiple doses of LED-E 500 mg or PBO every 8 hours for 10 days.
  - Part 3 was a double-blind, parallel-group study where participants received either LED-E 300 mg + CTB 400 mg, LED-E 500 mg + CTB 400 mg, or PBO every 8 hours for 10 days.
- Serial blood and urine samples were collected to evaluate single-dose and steady-state pharmacokinetics (PK) of LED-E, CTB, and the active compound ledaborbactam (LED). parameters such as Cmax, Tmax, and AUC were determined from plasma drug concentrations and renal clearance was determined from plasma and urine drug concentrations.
- Safety assessments included the monitoring of adverse events (AEs), changes in clinical lab values, vital signs, and ECGs. Demography and safety data were summarized by considering the groups of participants who received LED-E with or without (+/-) CTB and participants who received a placebo (PBO).

Results

Disposition and participant demographics

- 136 participants were enrolled and received at least one dose of the study drug. 109 participants received LED-E +/- CTB, and 27 participants received PBO.
- The participants' mean age was 31.0 years (SD 8.5), ranging from 18 to 53 years. The gender distribution was 56.6% female and 43.4% male. Most participants were White (70.6%), followed by Black or African American (17.6%). 40.4% of participants were Hispanic or Latino. The mean BMI was 25.5 kg/m² (SD 3.2), ranging from 18.9 to 31.9.

Safety

The number of participants with treatment-emergent AEs (TEAE) was similar in the LED-E +/- CTB (81.7%) and PBO (77.8%) groups. Headache and fatigue were the most frequently preferred terms (PTs) reported as TEAEs in LED-E-dosed participants (Table 1). Most events were mild. One participant in Study 101, Part 2, discontinued the study due to a TEAE of noncardiac chest pain. No serious adverse events or deaths occurred. No clinically relevant changes were noted in clinical labs, ECGs, or vital signs.

Table 1: Summary of treatment-emergent adverse

	Ledaborbactam-etzadroxil +/- Ceftibuten	Placebo	Total
Preferred Term	N=109	N=27	N=136
Total PTs with TEAEs	89 (81.7%)	21 (77.8%)	110 (80.9%)
Headache	22 (20.2%)	2 (7.4%)	24 (17.6%)
Fatigue	10 (9.2%)	1 (3.7%)	11 (8.1%)
Nausea	9 (8.3%)	(0%)	9 (6.6%)
Abdominal pain	9 (8.3%)	2 (7.4%)	11 (8.1%)
Frequent bowel movements	7 (6.4%)	(0%)	7 (5.1%)
Dizziness	5 (4.6%)	1 (3.7%)	6 (4.4%)
Somnolence	4 (3.7%)	(0%)	4 (2.9%)
Constipation	4 (3.7%)	(0%)	4 (2.9%)

PK

AUC of LED-E was ≤ 2% of exposures of LED across the dose range tested, suggesting extensive conversion of the prodrug to the active drug. LED exposures generally increased dose-proportional across single LED-E doses from 100mg to 1000mg and multiple doses from 75mg to 500mg q8h. The terminal half-life of LED in plasma is approximately 11-12 h (Table 2), with 30-35% accumulation of LED following q8h dosing of LED-E. Excretion in the urine of LED-E-derived material was 84.4% over the 8-hour dosing interval at a steady state. No clinically relevant changes in the pharmacokinetics of CTB, LED, or LED-E occurred when CTB and LED-E were co-administered compared to each administered alone (Table 3).

Table 2: Plasma pharmacokinetic exposure parameters for ledaborbactam and amount of drug recovered in urine (Ae) following single ascending doses of ledaborbactam etzadroxil and on dosing Day 10 following multiple ascending doses of ledaborbactam etzadroxil

	Single Doses						Multiple Doses			
Parameter[a]	LE 100 mg (n=6)	LE 200 mg (n=6)	LE 300 mg (n=6)	LE 500 mg (n=6)	LE 800 mg (n=6)	LE 1000 mg (n=6)	LE 75 mg q8h (n=9)	LE 150 mg q8h (n=8)	LE 300 mg q8h (n=8)	LE 500 mg q8h (n=8)
AUCinf, h•ng/mL	15,400 (30.5)	26,200 (16.7)	33,100 (25.6)	69,300 (15.2)	125,000 (22.6)	114,000 (8.82)	13,900 (16.8)	20,800 (15.6)	40,900 (13.7)	69,988 (26.4)
Cmax, ng/mL	4010 (25.6)	5970 (11.8)	7570 (29.3)	16,800 (8.43)	24,000 (14.2)	26,500 (7.92)	3690 (25.5)	5870 (11.4)	11,600 (31.9)	15,788 (29.9)
Tmax, h	1.25 (0.50–2.00)	1.50 (1.00–3.00)	1.25 (0.50–2.00)	1.26 (1.00–3.00)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	1.00 (0.50–1.75)	0.75 (0.75–1.75)	1.13 (0.75–1.75)	1.5 (0.75-3.00)
t1/2, h	5.53 (18.7)	6.10 (27.4)	7.48 (32.4)	11.3 (34.5)	8.59 (42.9)	11.3 (19.1)	9.27 (8.48)	11.4 (25.0)	11.3 (10.4)	12.5 (6.5)
Total Ae_{0-8} [b],mg			131 (20.3)	220 (12.2)	438 (3.30)	515 (16.9)	51.6 (7.80)	86.6 (11.1)	166 (27.8)	

Ae = estimated amount of drug excreted in urine; AUCinf = area under the concentration-time curve from time zero to infinity; Cmax = maximum concentration; Tmax = time to maximum observed concentration; t1/2 = terminal elimination half-life in plasma
a All parameters presented as Geometric Mean (%GCV), except Tmax which is presented as Median (range)
b Ae parameter based on collection interval 0-48-h post dose

Table 3: Summary of Statistical Analysis of Potential Drug-Drug Interactions

		Geometric LSmeans		Ratio of Test/Reference		
					90% CI	
Analyte	PK Parameter (Unit)[c]	Test	Reference	Estimate	Lower	Upper
Cis-Ceftibuten[a]	C_{max} (µg/mL)	15,405	17,562	0.88	0.79	0.97
	AUC_{0-inf} (h•µg/mL)	79,027	90,092	0.88	0.81	0.95
Ledaborbactam[b]	C_{max} (µg/mL)	13,162	13,737	0.96	0.89	1.03
	AUC_{0-inf} (h•µg/mL)	65,362	66,302	0.99	0.95	1.03

AUC 0-inf=area under the concentration-time curve from time zero to infinity; CI=confidence interval; Cmax=maximum concentration; LSmeans=least-squares means; PK=pharmacokinetics
a For ceftibuten: Test= ledaborbactam etzadroxil (500 mg) sd + ceftibuten (400 mg); Reference=ceftibuten (400 mg)
b For ledaborbactam: Test=ledaborbactam etzadroxil (500 mg) sd + ceftibuten (400 mg); Reference= ledaborbactam etzadroxil (500 mg) sd
c Units for geometric LSmeans but are not applicable for the ratios and corresponding 90% CIs.

The analysis of variance model includes fixed effects for treatment, period, and sequence, and a random effect for participant within sequence.

Figure: Arithmetic Mean Plasma Ledaborbactam Concentrations After Single Ascending Doses of Ledaborbactam etzadroxil (SAD)

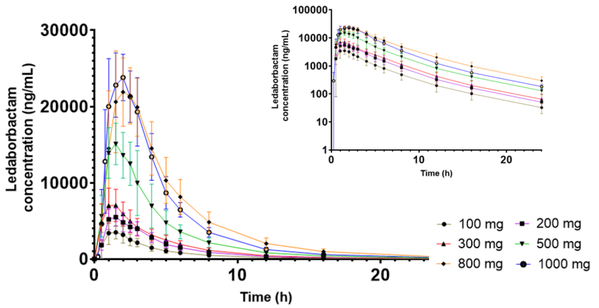
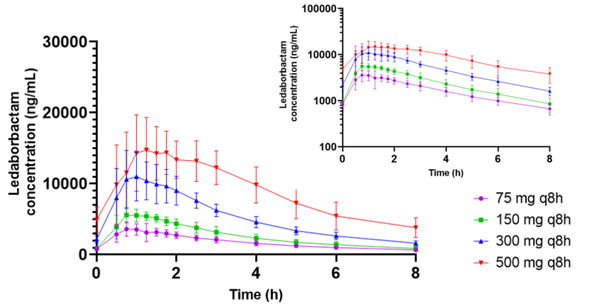


Figure: Arithmetic Mean Plasma Ledaborbactam Concentrations After Multiple Ascending Doses of Ledaborbactam etzadroxil (MAD)



Conclusions

LED exposure increased in a dose-proportional manner. No clinically relevant drug-drug interaction was observed between LED and CTB When LED-E and CTB are co-administered. LED-E was safe and well tolerated, when given with or without CTB, at multiple doses up to 1500mg daily for 10 days.

References:
1. Chatwin CL, Hamrick JC, Trout REL, Myers CL, Cusick SM, Weiss WJ, Pulse ME, Xerri L, Burns CJ, Moeck G, Daigle DM, John K, Uehara T, Pevear DC. 2021. Microbiological Characterization of VNRX-5236, a Broad-Spectrum beta-Lactamase Inhibitor for Rescue of the Orally Bioavailable Cephalosporin Ceftibuten as a Carbapenem-Sparing Agent against Strains of Enterobacterales Expressing Extended-Spectrum beta-Lactamases and Serine Carbapenemases. Antimicrob Agents Chemother 65:e0055221.

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