Dose-Escalation Study to Evaluate the Pharmacokinetics and Safety of Single and Repeat Doses of Ceftibuten in Healthy Participants

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Background

- Ceftibuten (CTB; Cedax®) is a broad-spectrum, third-generation, highly bioavailable oral cephalosporin antibiotic active against multiple Gram-positive and -negative pathogens.
- The 400mg daily dose was approved by the US FDA in 1995 for the treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial otitis media, pharyngitis and tonsillitis (1) but was discontinued due to a lack of a commercial market.
- The increasing global incidence of antibiotic resistance has created an unmet medical need for new oral agents to treat serious infections caused by Enterobacterales resistant to antibiotics including those producing ESBLs and serine carbapenemases (2,3).
- Approximately 10% of CTB is trans-CTB isomer, which has about one-eighth the antimicrobial potency of the cis-CTB isomer (1).
- CTB is the a β-lactam partner of choice for ledaborbactam etzadroxil (VNRX-7145), the prodrug of the active β-lactamase inhibitor ledaborbactam; the combination is being studied for the treatment of complicated urinary tract infections including pyelonephritis.
- This Phase 1 study evaluated the safety and pharmacokinetics of CTB at the range of doses and dose regimens above the approved 400 mg once daily dose that were likely to be studied in combination with ledaborbactam etzadroxil.

Methods

- This was a phase 1, two-period, randomized, double-blind, placebo-controlled, sequential-group, ascending dose study of CTB in healthy adults.
- Eligible participants were randomized at a 3:1 ratio to receive CTB or placebo into 1 of 3 cohorts; each cohort comprised 12 participants.
- Within each cohort, a single dose was administered on Day 1 (single dose period), followed by a 1-day washout period, and 10 days of repeated oral doses (Days 3–12; multiple dose period).

Cohort	Single Dose Period	Multiple Dose Period
1 – 400 mg	400 mg or placebo	400 mg or placebo q24h
2 – 800 mg	800 mg or placebo	400 mg or placebo q12h
3 – 1200 mg	1200 mg or placebo	400 mg or placebo q8h

- Healthy men and nonpregnant women, 18 to 55 years of age, with body mass index between ≥18.5 and ≤30.0 kg/m^2 and normal baseline vital signs, hematology, and clinical chemistry values were eligible to enroll.
- For determination of cis-CTB and trans-CTB plasma PK, serial blood samples were collected through 24 hours in the single dose period and on Day 3 and Day 12 in the single dose period. Trough samples were also collected on Days 4, 6, 8 and 10 during the multiple dose period.
- All urine was collected for 24 hours after the Day 1 dose (Cohort 3 only) for assessment of cis-CTB and trans-CTB urine PK.
- Plasma and urine PK samples were assayed for cis-CTB and trans-CTB using validated bioanalytical methods.
- Plasma and urine PK parameters were calculated using noncompartmental analysis of the plasma and urine concentration-time data for cis-CTB and trans-CTB (Certara WinNonlin; Radnor, PA).
- Dose proportionality based on Cmax and AUC were compared across dose levels on Days 1 and 12.
- Adverse events and other safety parameters were assessed through the follow-up visit and summarized using descriptive statistics for all participants who received at least 1 dose of study drug in the single or multiple dose periods.

Results – Disposition and Demographics

- All 36 subjects (27 ceftibuten; 9 placebo) were included in the safety analysis set and all ceftibuten subjects were in the PK analysis set.
- 39% were males and 61% were females; age range 19 to 48 years; BMI range 20.4 to 29.6 kg/m^2. The majority were white (75%) and non-Hispanic (97%).

Results – Safety and PK

Safety

- A summary of treatment-emergent adverse events (TEAEs) is shown in **Table 1** by dose group. TEAEs reported by Body System are summarized across ceftibuten cohorts in **Table 2**.
- All TEAEs were of mild severity, except for 1 moderate TEAE of headache reported by a placebo subject.
- No differences in the number of subjects reporting these TEAEs were noted between placebo subjects and subjects who received ceftibuten, or across multiple dose regimens of ceftibuten.
- There were no deaths or serious AEs reported. One TEAE of COVID-19 resulted in treatment and study discontinuation. There were no clinically relevant findings or trends with respect to clinical laboratory, ECGs, vital signs, or physical examination.

PK

- Mean cis- and trans-ceftibuten concentration-time profiles following single dose administration of ceftibuten are shown in the **Figure.** Geometric mean (%geoCV) single-dose and multiple-dose PK parameters are shown in **Table 3**.
- Cis-ceftibuten AUC_{inf} increased proportionally and cis-ceftibuten Cmax increased less than proportionally with increasing ceftibuten single doses.
- Following multiple-dose administration, accumulation of cis-ceftibuten (Rac, AUC_{tau} Day 12/Day 3) was modest and was highest for the 400 mg q8h ceftibuten cohort (1.24).
- During the 24-hour period after a single dose on Day 1 in the 400mg q8h cohort, 53% of the dose was recovered in urine (Fe): mean Fe of cis-CTB 47.0%; mean Fe of trans-CTB 6%.

Table 1: Summary of treatment-emergent adverse events in the Single Dose and Multiple Dose Periods

	Placebo	Ceftibuten Dose			
Single Dose Period	**(n=9)**	**400 mg (n=9)**	**800 mg (n=9)**	**1200 mg (n=9)**	**Total (n=27)**
All TEAEs	4 (44)	3 (33)	3 (33)	7 (78)	13 (48)
Related to study drug	1 (11)	1 (11)	2 (22)	2 (22)	5 (19)
Multiple Dose Period		**400 mg QD**	**400 mg q12h**	**400 mg q8h**	**Total**
All TEAEs	5 (56)	3 (33)	6 (67)	4 (44)	13 (48)
Related to study drug	4 (44)	3 (33)	5 (56)	2 (22)	10 (37)

Data are n (%). For each category, participants were counted only once, even if they experienced multiple events in that category.
TEAE: treatment emergent adverse events

Table 2: Summary of treatment-emergent adverse events across the Single Dose and Multiple Dose Periods

	Pooled Ceftibuten (n=27)	Pooled Placebo (n=9)
Participants with any TEAE	18 (67)	7 (78)
TEAEs occurring in ≥3 participants in the ceftibuten or placebo arms		
General disorders and administration site conditions	9 (33)	6 (67)
Fatigue	4 (15)	1 (11)
Gastrointestinal disorders	9 (33)	3 (33)
Nausea	6 (22)	1 (11)
Diarrhea	3 (11)	2 (22)
Abdominal pain	3 (11)	0
Nervous system disorders	4 (15)	3 (33)
Headache	4 (15)	3 (33)
Musculoskeletal and connective tissue disorders	3 (11)	1 (11)
Myalgia	2 (7)	0

Data are n (%). For each category, participants were counted only once, even if they experienced multiple events in that category.
TEAE: treatment emergent adverse events

Figure: Mean cis-CTB (solid lines) and trans-CTB (dashed-lines) plasma concentrations versus time (linear scale) following single doses of CTB

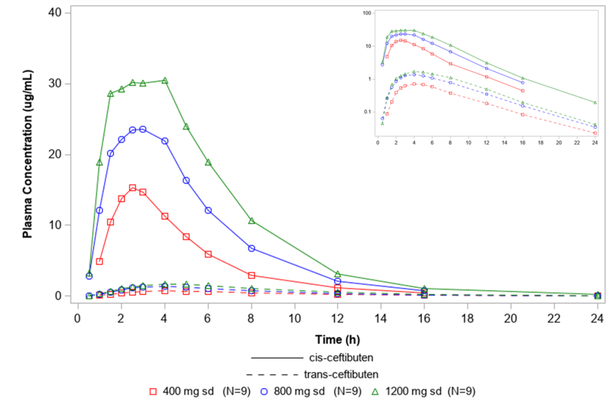

Table 3: Geometric mean (%GeoCV) cis-CTB and trans-CTB pharmacokinetic parameters following single and multiple dose oral administration of CTB

Single dose PK	**Parameter**	**400 mg N=9**	**800 mg N=9**	**1200 mg N=9**
Cis-CTB	AUC_{inf}(h*µg/mL)	75.5 (21.0)	143 (21.1)	203 (22.0)
	C_{max} (µg/mL)	16.9 (14.5)	27.5 (18.4)	35.8 (16.3)
	$t_{1/2}$ (h)	2.89 (22.0)	2.78 (23.5)	2.65 (22.7)
Trans-CTB	AUC_{inf} (h*µg/mL)	5.64 (22.4)	11.0 (26.5)	14.2 (26.9)
	C_{max} (µg/mL)	0.753 (18.7)	1.45 (26.1)	1.75 (18.9)
	$t_{1/2}$ (h)	3.52 (21.1)	3.46 (15.6)	3.30 (11.5)
Multiple dose PK		**400 mg QD N=9**	**400 mg Q12H N=9**	**400 mg Q8H N=9**
Cis-CTB	AUC_{tau} (h*µg/mL)	82.4 (19.3)	85.9 (21.0)	105 (16.3)
	C_{max} (µg/mL)	18.2 (19.1)	19.1 (15.6)	24.7 (15.5)
	$t_{1/2}$ (h)	2.68 (14.2)	2.52 (18.0)	2.80 (26.7)
Trans-CTB	AUC_{tau} (h*µg/mL)	5.80 (23.2)	6.25 (23.4)	7.27 (28.8)
	C_{max} (µg/mL)	0.756 (21.1)	0.970 (20.7)	1.28 (27.4)
	$t_{1/2}$ (h)	3.57 (13.1)	3.44 (13.3)	3.61 (12.9)

AUCinf, area under the concentration-time curve from time 0 to infinity; AUCtau, area under the concentration-time curve from time of administered dose through dosing interval; Cmax, maximum observed concentration; CTB, ceftibuten; %GeoCV, geometric coefficient of variation; QD, once daily; Q8h, every 8 hours; Q12h, every 12 hours; $t_{1/2}$, elimination half-life

Conclusions

- Single doses of ceftibuten up to 1200 mg and multiple doses up to 400 mg q8h for 10 days were safe and well tolerated. The adverse event profile were consistent with the CEDAX package insert.
- Dose proportionality was observed for AUC following single doses.
- Total urinary recovery was ~53% of total ceftibuten dose and trans isomer exposure was ~6%, consistent with the CEDAX package insert.
- Our results support the continued evaluation of CTB in combination with ledaborbactam etzadroxil as an oral treatment for infections due to multi-drug-resistant Enterobacterales.

References:
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