Ceftibuten-ledaborbactam etzadroxil

Addressing the need for an oral antibiotic to treat drug-resistant Enterobacterales

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Disclosures, Acknowledgments, and Thank You

- **Employee of Venatorx**

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- **Clinical Investigators**
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  - **Our Employees for discovering and developing ledaborbactam**

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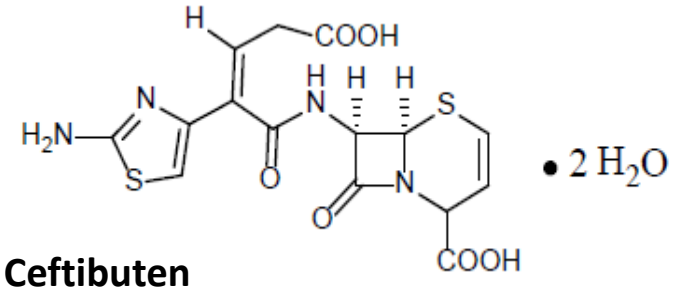
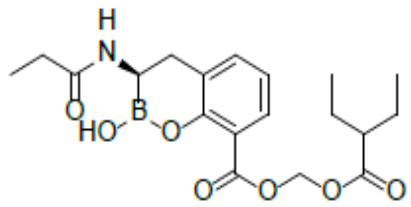
Ceftibuten, Ledaborbactam-etzadroxil, and Ledaborbactam

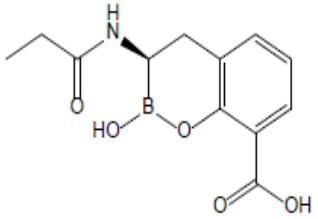
- Ceftibuten is a 3rd generation semi-synthetic oral cephalosporin
- Ceftibuten chosen as the β-lactam partner due to potency against Enterobacterales, PK, and protein binding
- EUCAST Enterobacterales breakpoint S≤1, R>1 μg/mL for infections originating from the urinary tract



Ceftibuten



Ledaborbactam etzadroxil (VNRX-7145)



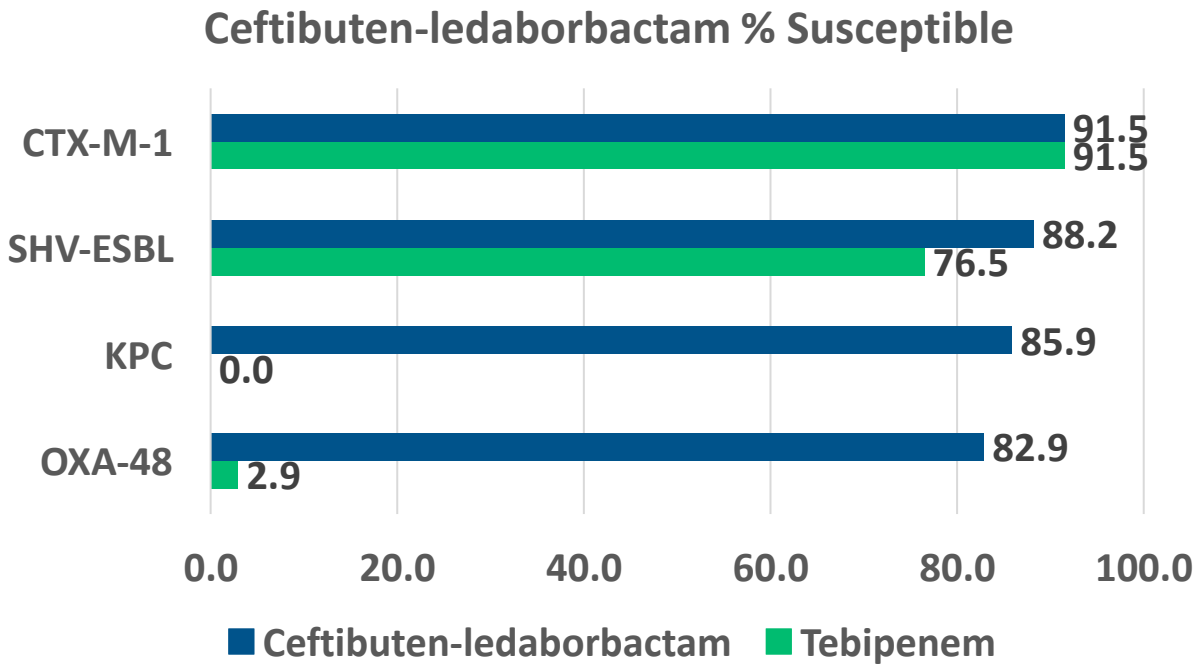
Ledaborbactam (VNRX-5236)

- Ledaborbactam has:
  1. No off target enzymatic or binding activity
  2. No CV, respiratory, or CNS effects
  3. No metabolites; no inhibition or induction of P450
  4. No inhibition of transporters; substrate of OCT1 and OAT3
  5. No mutagenicity, genotoxicity, or cytotoxicity
- Ledaborbactam etzadroxil substrate and inhibitor of P-gp and BCRP

Symbol: ^, has the potential to concentrate in the urine

Ledaborbactam Activity and Ceftibuten-Ledaborbactam Susceptibility Against Enterobacterales Carrying β-lactamases

		IC 50 (μM)	
Ambler Class	β-Lactamase	Ledaborbactam	Avibactam
A	CTM-M-15	0.02	0.003
	KPC-2	0.08	0.06
C	P99AmpC	0.01	0.02
	CMY-2	0.01	0.007
D	OXA-1	0.07	0.04
	OXA-48	0.32	0.55



- Ledaborbactam inhibits Ambler Class A, B, and D enzymes (Table)
- No intrinsic ant-bacterial activity
- PK-PD index: ($fAUC_{0-24}$) / ledaborbactam potentiated ceftibuten MIC
- Frequency of spontaneous mutations 10^{-10} – 10^{-11}

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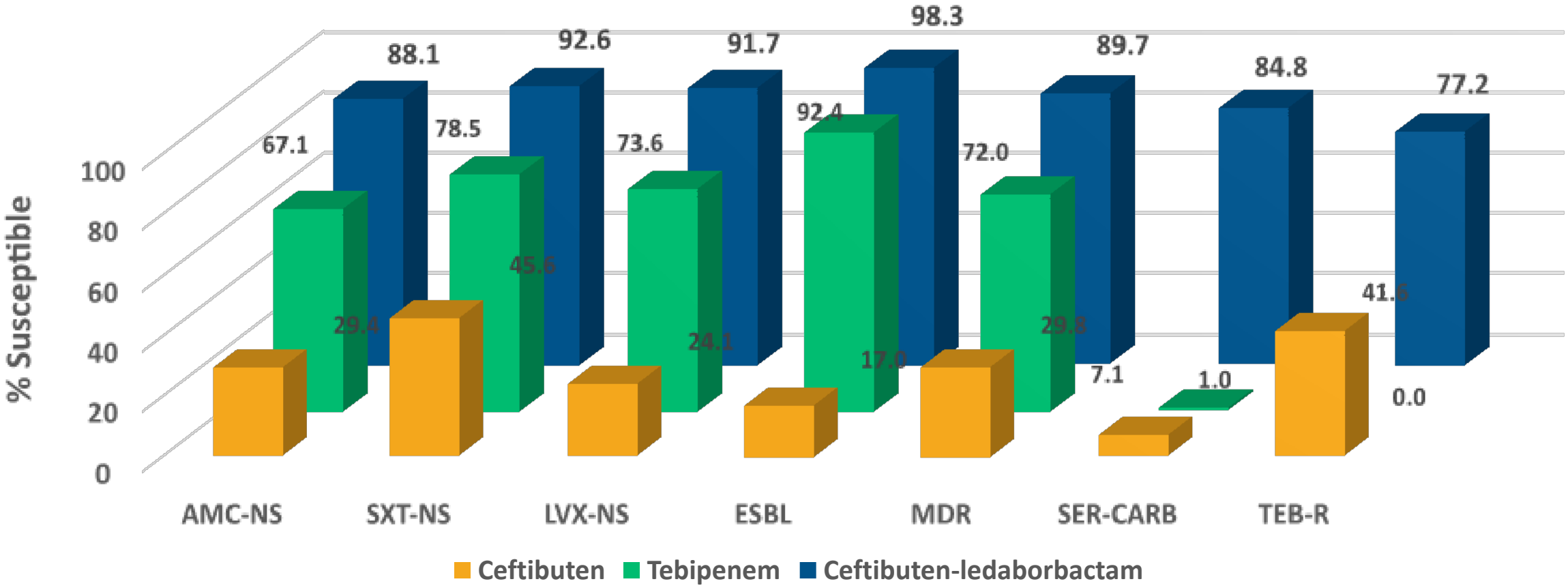
Trout et al, J Med Chem 2021; Chatwin Antimicrob Agents Chemother 2021, Karlowsky et al, AAC 2022

Ceftibuten-ledaborbactam Comparative In-Vitro Activity
Global Surveillance 2018-2020, N=3,389

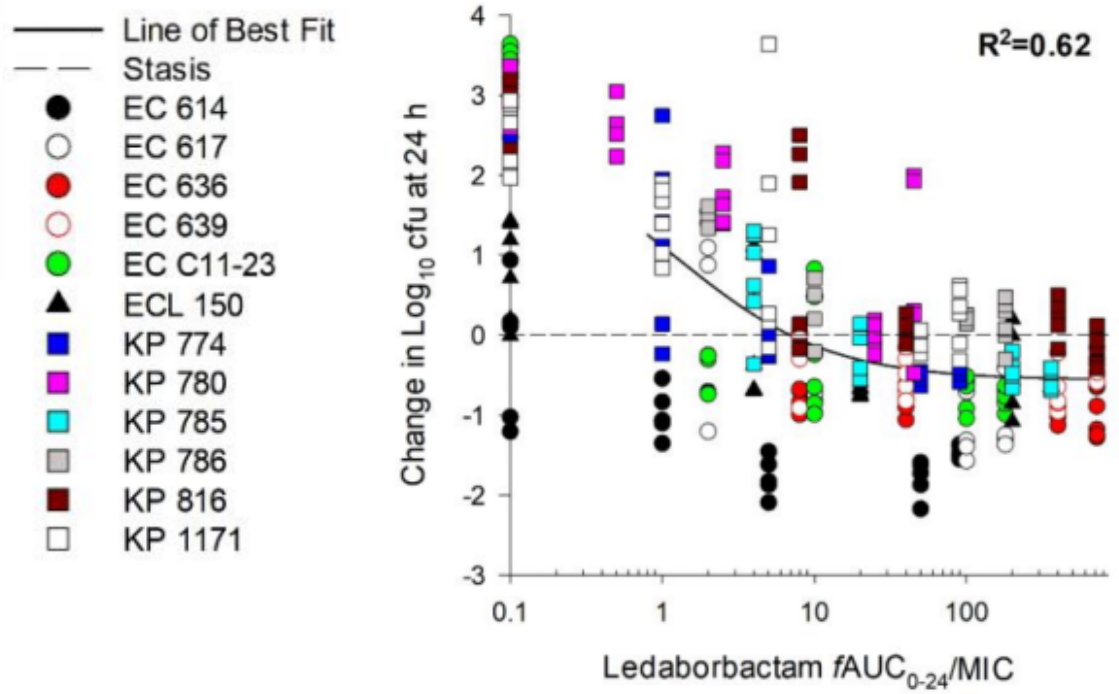


% Susceptible, % of isolates inhibited at EUCAST breakpoint of ≤1 µg/mL (ceftibuten) or provisional breakpoints of ≤1 µg/mL (ceftibuten-ledaborbactam) or ≤0.12 µg/mL (tebipenem); SER-CARB, serine carbapenemases include KPC and OXA-48; AMC, amoxicillin-clavulanate; SXT, trimethoprim-sulfamethoxazole; ESBL, extended-spectrum b-lactamase; LVX, levofloxacin; TEB, Tebipenem; NS, non-susceptible; MDR, multidrug resistant

Karlowsky et al, AAC 2022

Ceftibuten-ledaborbactam etzadroxil Murine Model of Infection

In vivo activity of a range of ledaborbactam plasma exposures, with fixed humanized ceftibuten regimen, against ceftibuten-resistant, β-lactamase-producing KP, EC, and E. cloacae (ECL) isolates



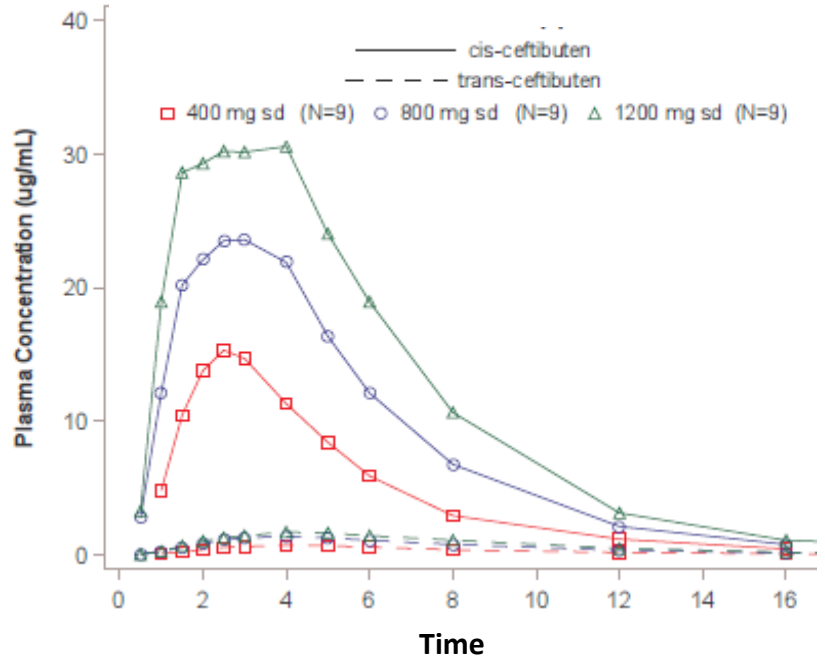
- Ceftibuten-ledaborbactam combination are efficacious in neutropenic murine thigh infection models

Lasko MJ, Asempa TE, Nicolau DP. *Antibiotics*. 2021; 10(2):201.
Fratoni et al. *J Antimicrob Chemother.* 2023; 78: 93–100.

HSR: Human-simulated regimen

Clinical Pharmacology Profile of Ceftibuten (Phase 1 Study)

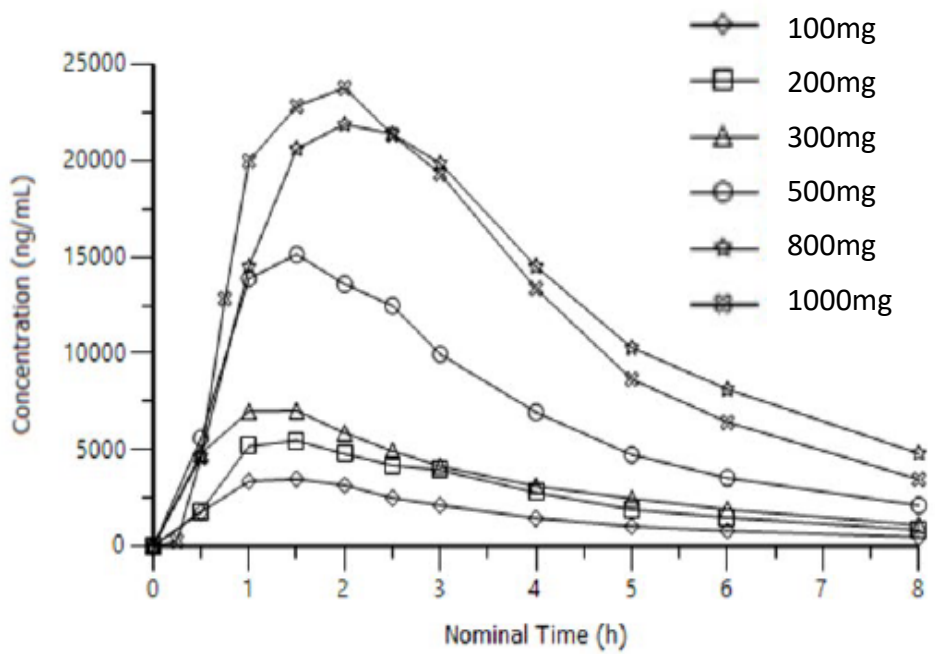
- Single doses of 400mg, 800mg, 1200mg; Multiple doses (10 days) of 400mg q24h, q12h, or q8h



Geometric Mean (%GeoCV)	
	400mg q8h N=8
C_{max} (µg/mL)	24.7 (15.5)
t_{max} (h)[a]	3.00 (2.00 - 4.00)
$AUC_{0\text{-}tau}$ (h·µg/mL)	105 (16.3)
$t_{1/2}$ (h)	2.80 (26.7)
Rac ($AUC_{0\text{-}tau}$ Day10/Day 1)	1.24 (14.4)
[a]Median (minimum-maximum) is presented	

- **Protein binding 60%, not concentration dependent**
- **Following a 1200mg single dose, 47% of cis-ceftibuten recovered in urine over 24 hours**
- **Concentration-QT model, an effect on ΔΔQTcF exceeding 10 ms can be excluded up to ~44 µg/mL for cis-ceftibuten**
- **Ceftibuten was safe and well-tolerated at all single and multiple dose levels**
  - **Most frequently reported TEAEs (3 or more patients): headache (15%), fatigue (15%), nausea (22%), diarrhea (11%), and abdominal pain (11%)**

Clinical Pharmacology Profile of Ledaborbactam-Etzadroxil



Geometric Mean (%GeoCV)	
	300mg q8h N=8
C_{max} (µg/mL)	11.6 (31.9)
t_{max} (h)[a]	1.13 (0.750-1.75)
$AUC_{0\text{-}tau}$ (h·µg/mL)	40.9 (13.7)
$t_{1/2}$ (h)	11.3 (1.2)
Rac ($AUC_{0\text{-}tau}$ Day10/Day 1)	1.30 (7.54)
[a]Median (minimum-maximum) is presented	

- Ledaborbactam etzadroxil rapidly absorbed and converted; plasma exposure of pro-drug is <2%
- Bioavailability is minimally 70% (>70% molar equivalent recovered in urine); <1% was pro-drug)
- Protein binding 65-80%, not concentration dependent
- No DDI between components $AUC_{0\text{-}inf}$ Ratio (90% CI) - cis-ceftibuten 0.88 (0.81 to 0.95) and ledaborbactam 0.99 (0.95 to 1.3)
- Concentration-QT model, an effect on ΔΔQTcF exceeding 10 ms can be excluded up to ~30 µg/mL for ledaborbactam
- Ceftibuten-ledaborbactam etzadroxil was safe and well-tolerated at all single and multiple dose levels
  - Most frequently reported TEAEs (3 or more patients): headache (30%), fatigue (20%), frequent bowel movements (35%), nausea (15%), and abdominal pain (15%)

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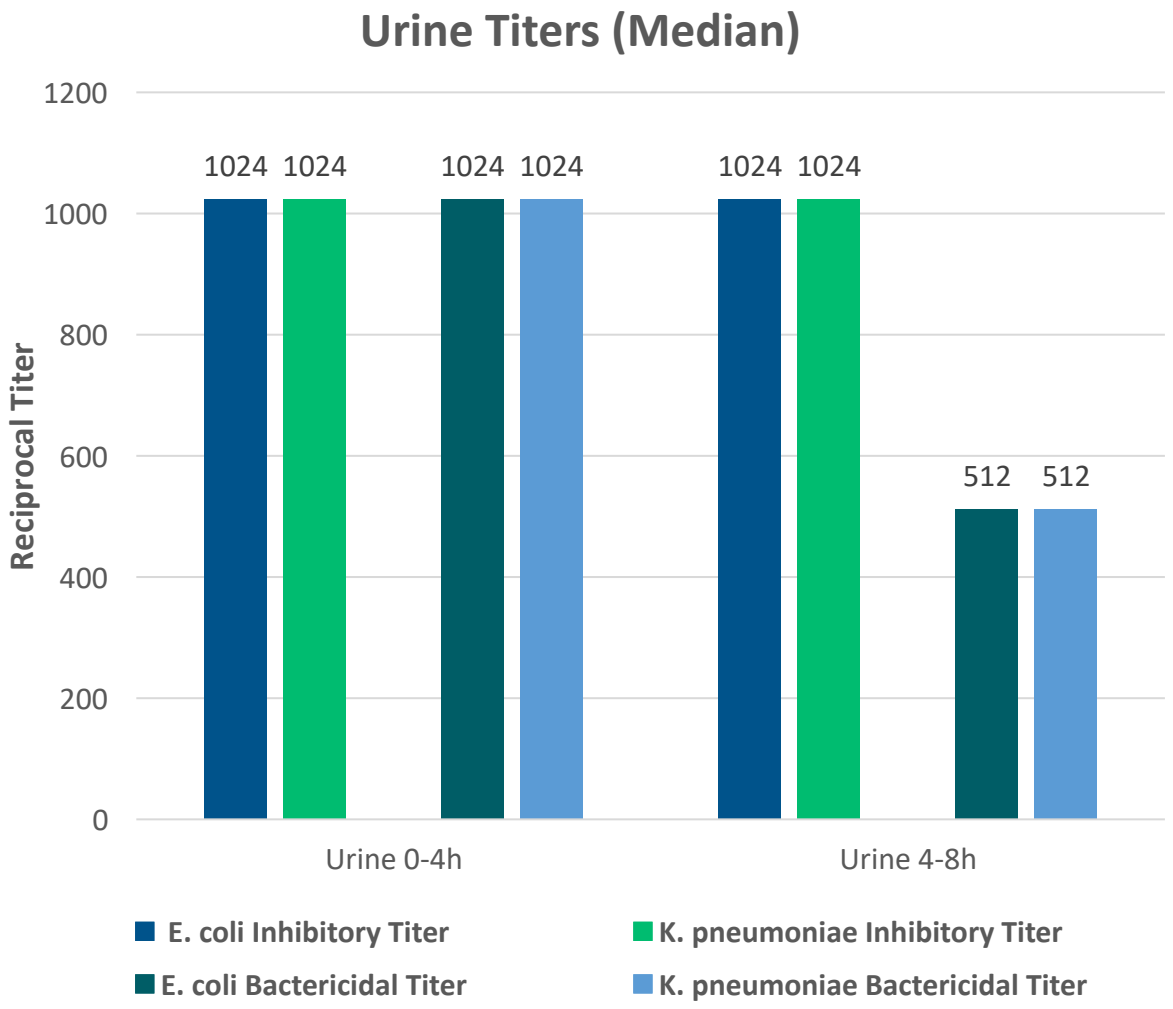
Serum and Urine Titers (ceftibuten-ledaborbactam etzadroxil 400mg/300mg q8h)



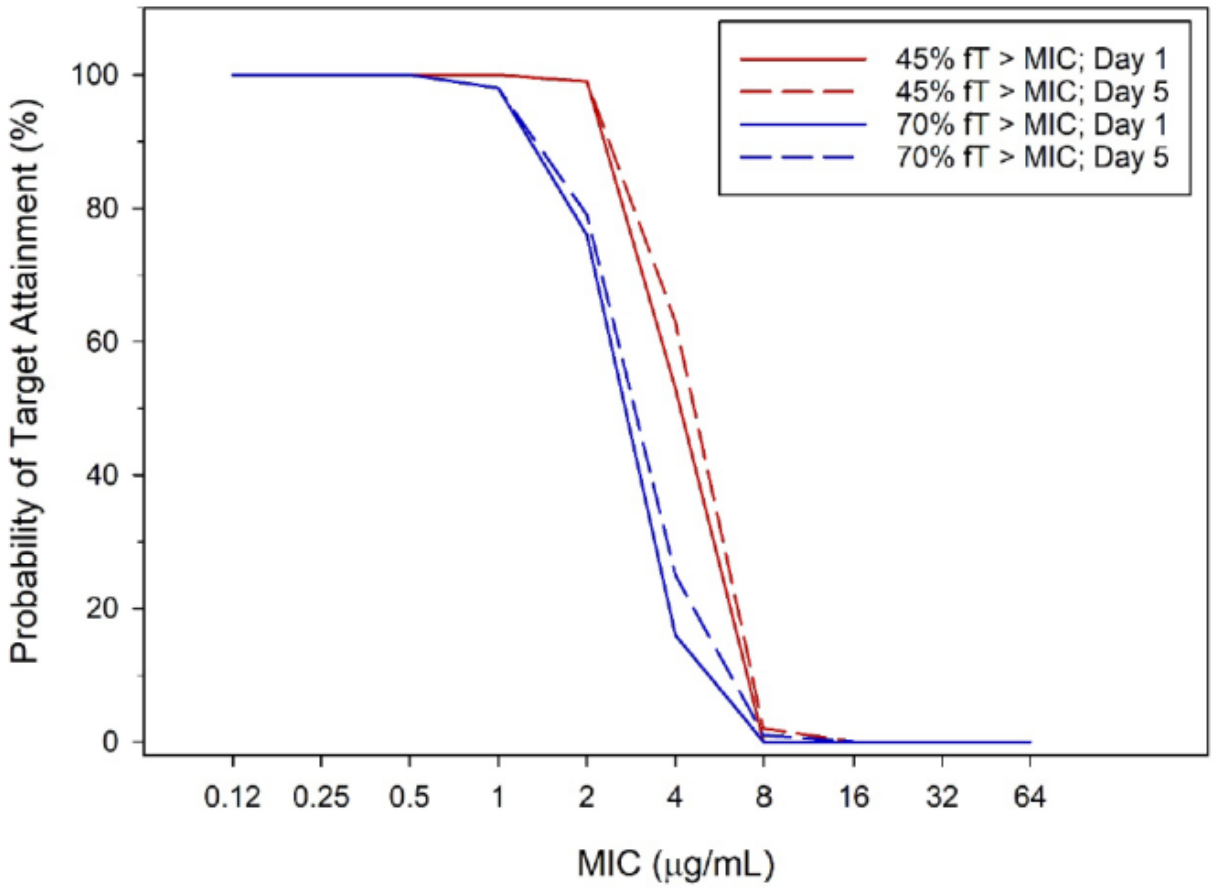
Pre-dose urine titers =1

E. coli (ATCC BAA-2523; OXA-48); *K. pneumoniae* (ATCC 700603; SHV-18, OXA-2)

Data on file, Venatorx Pharmaceuticals

Probability of Target Attainment

Ceftibuten 400mg q8h



Ledaborbactam

Regimen	*f*AUC:MIC = 5		
MIC TARGET	MIC = 0.5 ug/mL	MIC= 1 ug/mL	MIC= 2 ug/mL
300 mg Q12h	100	100	93
400 mg Q12h	100	100	99.6
500 mg Q12h	100	100	99.8
600 mg Q12h	100	100	100
200 mg Q8h	100	100	93.2
300 mg Q8h	100	100	99.6
400 mg Q8h	100	100	100
800 mg Q24h	100	100	99.6

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30% inflated variability

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Ceftibuten-Ledaborbactam Etzadroxil Summary and Next Steps

- **Ceftibuten-ledaborbactam has in vitro and in-vivo activity against clinically relevant resistant Enterobacterales including those expressing serine-β-lactamases**
  - Extended spectrum β-lactamase (ESBL) producing Enterobacterales
  - Carbapenem-resistant Enterobacterales (CRE)
- **Acceptable Phase 1 Safety Profile**
  - Ceftibuten safety profile at higher doses similar to registered 400mg dose
  - Combination with similar profile to ceftibuten including GI effects
- **Complete Phase 1 studies and Final Modeling and Simulation leading to dose selection for Phase 3**