P. aeruginosa (PSA). VNRX-5133 has direct inhibitory activity against serine-active site β-lactamases (Ser-BL) and emerging VIM/NDM metallo-β-lactamases (MBL). We show herein that cefepime/VNRX-5133 is highly active against MDR-*K. pneumoniae* and *P. aeruginosa* clinical isolates producing BL-variants evolved during therapy that compromise activity of ceftazidime/avibactam and ceftolozane/tazobactam.

Methods. Susceptibility testing was performed according to CLSI methods with cefepime, ceftolozane, and ceftazidime alone or in combination with VNRX-5133, avibactam, or tazobactam, respectively, fixed at 4 mg/L. Five clinical isolates of *K. pneumoniae* producing KPC variants impacting ceftazidime/avibactam and five clinical isolates of *P. aeruginosa* producing *Pseudomonas*-derived cephalosporinase variants impacting ceftolozane/tazobactam activity were collected in 2016 and 2017, respectively, from United States and Spanish hospitals. All other clinical isolates of *Enterobacteriaceae* and *P. aeruginosa* (n = 40) were collected in 2016.

Results. Cefepime/VNRX-5133 was highly active against five ceftazidime/avibactam-resistant *K. pneumoniae* clinical isolates producing KPC variants with MIC ranging from 0.5 to 4 mg/L relative to ceftazidime/avibactam MIC range of 16 to >128 mg/L. Cefepime/VNRX-5133 was also active against all five clinical isolates of ceftolozane/tazobactam-resistant *P. aeruginosa*, where 4/5 isolates had MIC of 4–8 mg/L relative to ceftolozane/tazobactam MIC range of 32–128 mg/L. The elevated cefepime/VNRX-5133 MIC (16 mg/L) in the remaining *P. aeruginosa* isolate was not due to the PDC-221 variant, as an engineered strain of *P. aeruginosa* producing this enzyme had a cefepime/VNRX-5133 MIC of 1 mg/L.

Conclusion. VNRX-5133 is a potent BLI possessing a unique broad spectrum of activity, including Class A, C, and D Ser-BLs, clinically evolving variants of Ser-BLs (e.g., KPC, PDC) and emerging VIM/NDM-type MBLs. Cefepime/VNRX-5133 is highly active against emerging multidrug-resistant *Enterobacteriaceae* and *P. aeruginosa*.

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1371. Safety, Tolerability, and Pharmacokinetics of Multiple Doses of TP-6076, a Novel, Fully Synthetic Tetracycline, in a Phase 1 Study

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Background. TP-6076 is a novel, fully synthetic tetracycline being developed for the treatment of serious bacterial infections, including those caused by multidrug-resistant *Acinetobacter baumannii*. TP-6076 has demonstrated potent activity *in vitro* against carbapenem-resistant strains of *A. baumannii*, with MIC_{90} 64 times lower compared with tigecycline and 256 times lower compared with minocycline. We now report the results of a multiple ascending dose study in normal healthy volunteers.

Methods. This was a phase 1, single-site, randomized, double-blind, placebo-controlled dose-escalating, multiple dose study in healthy adults who met the inclusion/exclusion criteria and provided informed consent prior to any study procedure. Cohorts of eight subjects each (six active and two placebo) received daily doses of 6.0 to 40.0 mg TP-6076 or placebo for 7 days. Plasma and urine samples for pharmacokinetic (PK) analyses were collected starting immediately prior to dosing until 96 hours after the last dose. Safety was assessed through collection of adverse events (AEs), clinical laboratories, vital signs, ECG, and physical examination data.

Results. The geometric mean derived PK parameters for TP-6076 were:

TP-6076 Dose (mg)	$AUC_{0\text{-}tau}$ (ng hours/mL)		$T_{1/2}$ (hours)
	Day 1	Day 7	Day 7
6.0	1043	1621	21.2
20.0	4871	7139	27.7
30.0	6382	10149	28.4
35.0	7842	10825	28.8
40.0	9433	12698	25.8

There were no serious or severe AEs reported. The most frequently reported AEs were gastrointestinal events, including nausea and vomiting, and localized infusion site reactions. There were no clinically significant changes in clinical laboratory values, ECG parameters, or physical examination findings.

Conclusion. Following multiple IV doses of TP-6076, plasma exposure increased as dose increased. Multiple IV doses of TP-6076 were generally well tolerated, with higher gastrointestinal adverse event rates in the higher dose groups.

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1372. *In Vitro* Activity of Novel Ceftazidime–Avibactam and Aztreonam–Avibactam Combinations Against Carbapenem-Nonsusceptible *Enterobacteriaceae* Isolates by Phenotype Collected in Latin America From 2014 to 2017 as Part of the INFORM Surveillance Program

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Background. Carbapenem-nonsusceptible *Enterobacteriaceae* (CRE) are often multidrug-resistant and infections caused by these organisms are associated with increased morbidity and mortality. The combination of avibactam (AVI), a non-β-lactam/β-lactamase inhibitor of Class A, C, and some D serine β-lactamases, with ceftazidime (CAZ) and aztreonam (ATM) is being developed to treat infections caused by CRE. CAZ-AVI reveals potent *in vitro* activity against CRE, except those producing metallo-β-lactamases (MBLs), whereas ATM-AVI inhibits growth of both MBL-positive and MBL-negative CRE. We evaluated the *in vitro* activity of CAZ-AVI and ATM-AVI against *Enterobacteriaceae* isolates nonsusceptible to meropenem (MEM-NS) collected in 2014–2017 in Latin America through the INFORM global surveillance program.

Methods. Nonduplicate clinically significant isolates were collected from 29 hospital laboratories located in Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela. Susceptibility testing was performed by CLSI broth microdilution. AVI was tested at a fixed concentration of 4 μg/mL in combination with CAZ and ATM. MEM-NS *Eba* (MIC >1 μg/mL) were screened for the presence of β-lactamase genes by PCR and sequencing.

Results. Five hundred fifty-seven MEM-NS isolates were identified (440 *Klebsiella pneumoniae* and 117 isolates of 13 other species). Of these, 441 (79.2%) carried carbapenemases (Cpase) (KPC only, n = 383; MBL only, n = 48; OXA-48-like only, n = 5; KPC and OXA-48-like, n = 2; MBL and GES, n = 2; MBL and KPC, n = 1). CAZ-AVI showed potent *in vitro* activity against Cpase-positive MBL-negative and Cpase-negative *Eba* and against all MEM-NS *Eba*, but was not active against MBL-positive *Eba*. 100% of MEM-NS *Eba* were inhibited by ≤8 μg/mL of ATM-AVI.

Phenotype/Enzyme content (n)	MIC_{90} [mg/L]/% Susceptible[a]							
	CAZ		CAZ-AVI		ATM		ATM-AVI	
	MIC_{90}	% S	MIC_{90}	% S	MIC_{90}	% S	MIC_{90}	% S
All *Eba* (9891)	64	70.2	0.5	99.4	128	68.5	0.12	NA
MEM-NS *Eba* (557)	>128	6.1	8	90.7	>128	5.9	0.5	NA
Cpase- (116)	>128	9.6	4	100	>128	9.6	1	NA
KPC+, MBL- (385)[b]	>128	5.5	2	100	>128	0.3	0.5	NA
OXA-48+, MBL- (5)	--	40	--	100	--	40	--	NA
MBL+ (51)[c]	>128	0	>128	0	>128	37.3	0.25	NA

NA, no breakpoints available; n, number of isolates

[a] % Susceptible defined using CLSI 2018 breakpoints. MIC_{90} was not determined for n <10 isolates

[b] Included two isolates co-carrying KPC and OXA-48-like Cpases

[c] Included two isolates co-carrying MBL and GES Cpases and 1 isolate co-carrying MBL and KPC Cpases

Conclusion. CAZ-AVI and ATM-AVI displayed potent *in vitro* activity against MEM-NS *Eba* collected in LA. These agents could serve as promising options for treatment of infections caused by CRE.

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IHMA, Inc.: Employee, Salary.