with baseline bacteremia could receive up to 14 days; study continued to late follow-up (LFU, 26 ± 2 days). Oral step-down therapy was prohibited. ZTI-01 met the primary endpoint of noninferiority to PIP-TAZ. Secondary objectives included comparing clinical cure rates (assessed by investigator) in the modified intent-to-treat (MITT), microbiologic MITT (m-MITT), clinical evaluable (CE), and microbiologic evaluable (ME) populations at test-of-cure (TOC, Day 19 ± 2 days).

Results. There were 464 patients randomized who received study drug. In all populations, clinical cure rates at TOC were high and similar between treatment groups (>90%) (table).

Conclusion. These results demonstrate consistent efficacy in multiple secondary efficacy populations for patients with cUTI and AP who were treated with either ZTI-01 or PIP-TAZ. If approved by FDA, ZTI-01 may provide a new IV option with a differentiated MOA for patients in the United States with serious Gram-negative infections.

Table: Clinical Response at TOC

	ZTI-01	PIP-TAZ		
Population	*n* (%)	*n* (%)	Difference (%)	95% CI
MITT	233	231		
Cure	211 (90.6)	212 (91.8)	−1.2	(−6.8, 4.4)
Failure	11 (4.7)	16 (6.9)		
Indeterminate	11 (4.7)	3 (1.3)		
m-MITT	184	178		
Cure	167 (90.8)	163 (91.6)	−0.8	(−7.2, 5.6)
Failure	9 (4.9)	12 (6.7)		
Indeterminate	8 (4.3)	3 (1.7)		
CE	199	196		
Cure	188 (94.5)	182 (92.9)	1.6	(−3.7, 6.9)
Failure	11 (5.5)	14 (7.1)		
ME	155	145		
Cure	148 (95.5)	135 (93.1)	2.4	(−3.5, 8.3)
Failure	7 (4.5)	10 (6.9)		

95% confidence intervals (CIs, two-sided) were computed using a continuity-corrected Zstatistic.

Disclosures. **K. Kaye**, Zavante Therapeutics, Inc.: Scientific Advisor, Consulting fee. **L. B. Rice**, Zavante Therapeutics, Inc.: Scientific Advisor, Consulting fee. **V. Stus**, Zavante Therapeutics, Inc.: Investigator, Research support. **O. Sagan**, Zavante Therapeutics, Inc.: Investigator, Research support. **E. Fedosiuk**, Zavante Therapeutics, Inc.: Investigator, Research support. **A. Das**, Zavante Therapeutics, Inc.: Consultant, Consulting fee. **D. Skarinksy**, Zavante Therapeutics, Inc.: Employee and Shareholder, Salary. **P. B. Eckburg**, Zavante Therapeutics, Inc.: Consultant and Shareholder, Consulting fee. **K. Manvelian**, Zavante Therapeutics, Inc.: Employee and Shareholder, Salary. **E. J. Ellis-Grosse**, Zavante Therapeutics, Inc.: Employee and Shareholder, Salary.

1368. Assessment of the *In Vivo* Efficacy of Human-Simulated Epithelial Lining Fluid (ELF) Exposure of Meropenem/Nacubactam (MEM/NAC) Combination Against β-Lactamase-Producing Enterobacteriaceae in Neutropenic Lung Infection Model

Tomefa E. Asempa, PharmD[1]; Ana Motos, MSc[1]; Kamilia Abdelraouf, PhD[1]; Caterina Bissantz, PhD[2]; Claudia Zampaloni, PhD[3] and David P. Nicolau, PharmD, FCCP, FIDSA[1,4]; [1]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, [2]Roche Pharma Research and Early Development Pharmaceutical Science, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland, [3]Roche Pharma Research and Early Development, Immunology, Inflammation and Infectious Diseases, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland, [4]Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. NAC is a novel dual action β-lactamase inhibitor with *in vitro* activity against class A, class C, and some class D β-lactamases and antibacterial activity against *Enterobactaeriaceae*. NAC is being developed as a combination therapy with MEM for the treatment of serious Gram-negative bacterial infections. This study evaluated the efficacy of the human-simulated ELF exposure of MEM/NAC, compared with those of MEM or NAC alone against β-lactamase-producing *Enterobacteriaceae* isolates in the neutropenic murine lung infection model.

Methods. Eight clinical MEM-resistant *Enterobacteriaceae* isolates harboring various β-lactamases (IMI, KPC, OXA, TEM, SHV, and AmpC) were utilized in the study. MEM and MEM:NAC (1:1) combination MICs were determined in triplicate via broth microdilution. ICR mice were rendered transiently neutropenic, and lungs were inoculated with 50 µL bacterial suspensions of 10^7 CFU/mL. Regimens in mice that simulated the human ELF exposures following doses of MEM 2g q8h and NAC 2g q8h (1.5 hours infusions) as monotherapies and in combination were established. Treatment mice received MEM human-simulated regimen (HSR), NAC HSR, or MEM/NAC HSR and control mice were vehicle-dosed. Treatment was started 2 hours after inoculation and continued for 24 hours. Efficacy was assessed as the change in $\log_{10}$CFU/lung at 24 hours compared with 0 hours controls.

Results. MEM and MEM/NAC MICs were 8–512 and 0.5–8 mg/L, respectively. The average $\log_{10}$CFU/lung at 0 hours across all isolates was 6.26 ± 0.26. Relative to 0 hours control, the mean bacterial growth at 24 hours in the untreated control mice, MEM HSR, and NAC HSR treatment groups were 2.93 ± 0.29, 2.72 ± 0.42, and 1.75 ± 0.80 $\log_{10}$CFU/lung, respectively. MEM/NAC HSR resulted in up to 2-log bacterial reduction in isolates with MEM/NAC MIC ≤4 mg/L.

Conclusion. MEM/NAC human-simulated ELF exposure produced enhanced efficacy against MEM-resistant β-lactamase-producing *Enterobacteriaceae* isolates with MEM/NAC MIC ≤4 mg/L. These data support a potential role for MEM/NAC for treatment of lung infections due to β-lactamase-producing *Enterobacteriaceae* and warrant further studies.

This project has been funded in part under HHS BARDA Contract HHSO100201600038C.

Disclosures. **C. Bissantz**, F Hoffmann La Roche Ltd.: Employee, Salary. **C. Zampaloni**, F. Hoffmann-La Roche Ltd.: Employee, Salary. **D. P. Nicolau**, Hoffmann-La Roche Ltd.: Grant Investigator, Grant recipient.

1369. Combined Analysis of the In Vitro Activity of Ridinilazole (RDZ) Against More Than 500 *Clostridium difficile* (CD) Clinical Isolates and Impact of RDZ on Cell Morphology

Esther Duperchy, PhD[1]; Eugénie Bassères, PhD[2]; Kevin Garey, PharmD, MS[3] and Richard Vickers, PhD[1]; [1]R&D, Summit Therapeutics, Abingdon, UK, [2]University of Houston College of Pharmacy, Houston, Texas, [3]University of Houston College of Pharmacy, Houston, Texas

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. *Clostridium difficile* infection (CDI) is one of the most urgent bacterial healthcare threats in the United States. RDZ is a targeted spectrum, GI restricted, antibacterial currently in clinical development for the treatment of CDI and reducing the recurrence of CDI. Here we report the combined analysis of previously reported and new independent studies assessing the susceptibility of CD clinical isolates collected in North America and Europe between 2010 and 2015, and the effect of RDZ on cell morphology.

Methods. A total of 570 CD clinical isolates across seven independent studies were tested for susceptibility. The majority of isolates (>70%) were sourced from RDZ Phase 2 clinical trials and North American and European surveillance programs. Minimum inhibitory concentrations (MIC) were determined by agar dilution on Wilkins Chalgren agar plates after 48 hours incubation at 37°C, or, by agar or microbroth dilution using supplemented Brucella medium following the CLSI guidelines M11-A7/A8. Up to 11 comparator antibiotics were tested alongside RDZ. PCR ribotyping was performed on 549 isolates by capillary gel electrophoresis. To investigate the impact of RDZ on cell morphology, CD strain R20291 was incubated with RDZ at 0.125–0.5 × MIC concentrations for 24 hours. DAPI and FM4-64 staining was used to visualize DNA and cell membrane by confocal microscopy.

Results. RDZ was highly active against the isolates collected in North America and Europe with MICs distributed over a narrow range (0.015–0.5 µg/mL) and an overall MIC_{90} of 0.25 µg/mL. There was no variation in activity by geographic region or ribotype, including hypervirulent ribotype 027 isolates ($N = 83$). RDZ also maintained activity against antibiotic-resistant isolates, including isolates with reduced susceptibility to metronidazole and vancomycin. When treated with sub-MIC concentrations of RDZ, CD cells formed filamentous structures with a dose-dependent effect on cell length and decreased septum formation. This preliminary data suggest that RDZ may alter CD cell division.

Conclusion. These data show that RDZ was highly active against recent CD isolates independent of geographic origin, ribotype, and antibiotic resistance profile. Mechanism of action studies are ongoing and further susceptibility profiling will be undertaken during the Phase 3.

Disclosures. **E. Duperchy**, Summit Therapeutics: Employee, Salary. **E. Bassères**, Summit Therapeutics: Collaborator, Research support. **K. Garey**, Summit Therapeutics: Collaborator, Research support. **R. Vickers**, Summit Therapeutics: Employee, Salary and Stock options.

1370. Cefepime/VNRX-5133 Broad-Spectrum Activity Is Maintained Against Emerging KPC- and PDC-Variants in Multidrug-Resistant *K. pneumoniae* and *P. aeruginosa*

Denis Daigle, PhD[1]; Jodie Hamrick, BSc[1]; Cassandra Chatwin, BSc[1]; Natalia Kurepina, PhD[2]; Barry N. Kreiswirth, PhD[2]; Ryan K. Shields, PharmD[3]; Antonio Oliver, PhD[4]; Cornelius J. Clancy, MD[5]; Minh-Hong Nguyen, MD[3]; Daniel Pevear, PhD[1] and Luigi Xerri, PhD[1]; [1]VenatoRx Pharmaceuticals Inc., Malvern, Pennsylvania, [2]Public Health Research Institute, Rutgers New Jersey Medical School, Newark, New Jersey, [3]University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, [4]Hospital Son Espases, Palma de Mallorca, Spain, [5]Infectious Diseases, University of Pittsburgh, Pittsburgh, Pennsylvania

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. VNRX-5133 is a cyclic boronate β-lactamase inhibitor (BLI) currently in clinical development with cefepime to treat multidrug-resistant (MDR) infections caused by ESBL- and carbapenemase-producing Enterobacteriaceae (ENT) and

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*.

Disclosures. **D. Daigle**, VenatoRx Pharmaceuticals Inc.: Employee and Shareholder, Salary. **J. Hamrick**, VenatoRx Pharmaceuticals Inc.: Employee, Salary. **C. Chatwin**, VenatoRx Pharmaceuticals Inc.: Employee, Salary. **N. Kurepina**, VenatoRx Pharmaceuticals Inc.: Research Contractor, Research support. **B. N. Kreiswirth**, VenatoRx Pharmaceuticals Inc.: Research Contractor, Research support. **R. K. Shields**, VenatoRx Pharmaceuticals Inc.: Research Contractor, Research support. **A. Oliver**, VenatoRx Pharmaceuticals Inc.: Research Contractor, Research support. **C. J. Clancy**, VenatoRx Pharmaceuticals Inc.: Research Contractor, Research support. **M. H. Nguyen**, VenatoRx Pharmaceuticals Inc.: Research Contractor, Research support. **D. Pevear**, VenatoRx Pharmaceuticals Inc.: Employee, Salary. **L. Xerri**, VenatoRx Pharmaceuticals Inc.: Employee and Shareholder, Salary.

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

Larry Tsai, MD and Alison Moore, BS; Tetraphase Pharmaceuticals, Watertown, Massachusetts

Session: 144. Novel Agents

Friday, October 5, 2018: 12:30 PM

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.

Disclosures. **L. Tsai**, Tetraphase Pharmaceuticals: Employee and Shareholder, Salary. **A. Moore**, Tetraphase Pharmaceuticals: Employee, Salary.

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

Krystyna Kazmierczak, PhD[1]; Boudewijn De Jonge, PhD[2]; Gregory G. Stone, PhD[3] and Dan Sahm, PhD[4]; [1]IHMA, Inc., Schaumburg, Illinois, [2]Formerly of AstraZeneca Pharmaceuticals, Waltham, Massachusetts, [3]Pfizer, Inc., New York, New York, [4]International Health Management Associates, Inc., Schaumburg, Illinois

Session: 144. Novel Agents

Friday, October 5, 2018: 12:30 PM

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.

Disclosures. **K. Kazmierczak**, Pfizer Inc.: Consultant, Consulting fee. IHMA, Inc.: Employee, Salary. **B. De Jonge**, AstraZeneca: Shareholder, Dividends. Pfizer Inc: Employee, Salary. **G. G. Stone**, Pfizer Inc.: Employee, Salary. AstraZeneca: Former Employee and Shareholder, Salary. **D. Sahm**, Pfizer Inc.: Consultant, Consulting fee.

IHMA, Inc.: Employee, Salary.