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). 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

| Population | ZTI-01 | PIP-TAZ | Difference (%) | 95% CI |
|------------|--------|---------|----------------|-------|
| m-MITT     | 233    | 233     | -1.2 (-6.8, 4.4) |       |
| Cure       | 212 (90.6) | 212 (91.8) | -1.2 (-6.8, 4.4) |       |
| Failure    | 11 (4.7)  | 16 (6.9)  | 5.5 (1.7, 9.3)   |       |
| Indeterminate | 11 (4.7) | 3 (1.3)  | 3.7 (1.1, 6.3)   |       |

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

Disclosures.
K. Kaye, Zavante Therapeutics, Inc.: Scientific Advisor, Consulting fee.
L. B. Rice, Zavante Therapeutics, Inc.: Scientific Advisor, Consulting fee.
Y. Stus, Zavante Therapeutics, Inc.: Investigator, Research support.
O. Sagan, Zavante Therapeutics, Inc.: Investigator, Research support.
C. Bissantz, Zavante Therapeutics, Inc.: Employee, Salary.
P. B. Eckburg, Zavante Therapeutics, Inc.: Employee and Shareholder, Salary.
K. Garey, Zavante Therapeutics, Inc.: Employee and Shareholder.
S. Persichetti, Zavante Therapeutics, Inc.: Employee.
J. Ellis-Grosse, Zavante Therapeutics, Inc.: Employee and Shareholder.
E. Bassères, Zavante Therapeutics, Inc.: Employee and Shareholder.

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

Tomoca E. Asempra, PharmD1; Ana Motos, MSc; Kamila Abdelraouf, PhD; Caterina Bassi, PhD; Claudia Zampaloni, PhD and David P. Nicolau, PharmD, FCCP, FIDSA, A. Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, 1Roche Pharma Research and Early Development Pharmaceutical Science, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland, Roche Pharma Research and Early Development, Innominato, Immunology and Infectious Diseases, Roche Innovation Center Basel, 2Roche Innovation Center Basel, 3Roche Innovation Center Basel, 4Division 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 Enterobacteriaceae. 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 neutrophilic 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 10⁶ CFU/mL. Regimens in mice that simu-
lated 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 was started 2 hours after inoculation and continued for 24 hours. Efficacy was assessed as the change in log₇ 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 log₇ 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 log₇ CFU/lung, respectively; MEM/NAC HSR resulted in up to 2-log bacterial reduction in isolates with MEM/NAC MIC ≥64 mg/L.

Conclusion. MEM/NAC human-simulated ELF exposure produced enhanced efficacy against MEM-resistant β-lactamase-producing Enterobacteriaceae isolates with MEM/ NAC MIC ≥64 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 BARDCA Contract HHSHO100201600038C.

Disclosures.
C. Bissantz, F Hoffmann La Roche Ltd.: Employee, Salary.
C. Zampaloni, F Hoffmann-La Roche Ltd.: Employee, Salary.
P. B. Eckburg, Hoffmann La Roche Ltd.: Grant Investigator, Grant recipient.

1370. Cefepime/VRX-5133 Broad-Spectrum Activity Is Maintained Against Emerging KPC-3 and PDC-Variants in Multidrug-Resistant K. pneumoniae and P. aeruginosa
Denis Daigle, PhD1; Jodie Hamrick, BSc1; Cassandra Chatwin, BSc1; Natalia Kurepina, PhD1; Barry N. Kreiswirth, PhD1; Ryan K. Shields, PharmD1; Antonio Oliver, PhD1; Cornelius J. Clancy, MD2; Minh-Hong Nguyen, MD3; David Peviar, PhD1 and Luigi Xerri, PhD1; VenatoRx Pharmaceuticals Inc., Malvern, Pennsylvania, 1Public Health Research Institute, Rutgers New Jersey Medical School, Newark, New Jersey, 2University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, 3Hospital Son Espases, Palma de Mallorca, Spain, 4Infecctious Diseases, University of Pittsburgh, Pittsburgh, Pennsylvania

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

Background. VRX-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-βL) 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 ceftazidime/tazobactam.

**Methods.** Susceptibility testing was performed according to CLSI methods with cefepime, ceftazidime, 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 ceftazidime/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 ceftazidime/tazobactam-resistant P. aeruginosa, where 4/5 isolates had MIC of 4–8 mg/L relative to ceftazidime/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-βLs, clinically evolving variants of Ser-βLs (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. Chavkin, 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.: Employee, Salary. D. Pevear, VenatoRx Pharmaceuticals Inc.: Employee, Salary. L. Xerri, VenatoRx Pharmaceuticals Inc.: Employee and Shareholder, Salary.

### Table: TP-6076 Dose (mg) and AUC_{0-24} / mg hours/mL and T_{1/2} (hours)

| TP-6076 Dose (mg) | AUC_{0-24} (mg 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**

Krysyna Kazmierczak, PhD; Boudewijn De Jonge, PhD; Gregory G. Stone, PhD; and Dan Sahm, PhD, IHMA, Inc., Schaumburg, Illinois, 3Formerly of AstraZeneca Pharmaceuticals, Waltham, Massachusetts, 2Pfizer, Inc., New York, New York, 5International Health Management Associates, Inc., Schaumburg, Illinois.

**Session.** 144, Novel Agents

Friday, October 5, 2018: 1:30 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 in 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.** Nonuplicate 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 Ebs (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 (Carb) (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 Carb-positive MBL-negative and Carb-negative Ebs and against all MEM-Ns Ebs, but was not active against MBL-positive Ebs. 100% of MEM-Ns Ebs were inhibited by ≤8 µg/mL of ATM-AVI.

**Conclusion.** CAZ-AVI and ATM-AVI displayed potent in vitro activity against MEM-Ns Ebs 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.

---

S420 • OFID 2018:5 (Suppl 1) • Poster Abstracts