gPCR supported both new acquisition of these genes and expansion of existing AMR pools. Further statistical analyses demonstrated significant correlations between changes in gut resistance and clinical study parameters including β-lactamase gene frequency and study drug assignment, and efflux pump gene frequency and vancomycin resistance. **Conclusion.** Taken together, these findings demonstrated that coadministration of rifampin with IV β-lactam antibiotics can interfere with the integrity of the gut microbiome and may help limit the emergence of AMR induced by these antibiotics.

**Disclosures.** J. Kokai-Kun, Synthetic Biologics, Inc.: Employee, Salary. C. Le, Synthetic Biologics, Inc.: Employee, Salary. K. Trout, Synthetic Biologics, Inc.: Employee, Salary. J. Sliman, Synthetic Biologics, Inc.: Employee, Salary.

1338. A Pooled Analysis of Patients With Wound Infections in the Phase 3 REVIVE Trials: Randomized, Double-blind Studies to Evaluate the Safety and Efficacy of I claprim vs. Vancomycin for Treatment of Acute Bacterial Skin and Skin Structure Infections

David Huang, MD, PhD, FIDSA, FACP; G. Ralph Corey, MD; Thomas L. Holland, MD; Thomas P. Lodise Jr., PharmD, PhD; William O’Riodan, MD; Mark Wilcox, MD; Thomas M. File Jr., MD; Matthew Dryden, MD, FRCPath, FRCPs; Antonio Torres, MD, PhD, FERS; Barbara Balser, DVM; and Eve Desplats, BS; Motif BioSciences, Inc., Framingham, N. Jersey. Duke University Medical Center, Durham, North Carolina; Albany College of Pharmacy and Health Sciences, Albany, New York; eStudy Sites, San Diego, California; Leeds Teaching Hospitals and University of Leeds, Leeds, United Kingdom; Northeast Ohio Medical University, Rootstown, Ohio; Royal Hampshire County Hospital, Winchester, United Kingdom; August Pi i Sunyer Biomedical Research Institute (IDIBAPS), CIBERES, Barcelona, Spain; Veristat, Southborough, Massachusetts

**Session:** 144. Novel Agents

**Friday, October 5, 2018: 12:30 PM**

**Background.** The objective of this evaluation was to provide an analysis of pooled efficacy data from two parallel phase 3 trials of iclaprim, a diaphoridyl phosphate reductase inhibitor, compared with vancomycin for the treatment of patients with wound infections including surgical site infections (SSI).

**Methods.** A pooled analysis of patients with wound infections was conducted from two parallel Phase 3, double-blind, randomized (1:1), active-controlled, multinational, multicenter trials (REVIVE-1 and REVIVE-2), which included a total of 602 patients with wound infections. The data were analyzed separately and then pooled to determine the efficacy of iclaprim 80 mg fixed dose compared with vancomycin 15 mg/kg. Both drugs were administered intravenously every 12 hours for 5 to 14 days according to the investigator assessment of clinical response. The primary endpoint for these studies was to determine whether iclaprim was noninferior (NI; 10% margin) to vancomycin in achieving a 22% reduction in lesion size (early clinical response [ECR]) at 48 to 72 hours after initiation of the study drug (early time point [ETP]), compared with baseline in the intent-to-treat (ITT) population.

**Results.** Iclaprim had similar ECR rates at ETP compared with vancomycin among the subset of patients with wound infections (see table). The median treatment duration for both iclaprim and vancomycin was 7 days (range 5–14 days).

| Table: Efficacy outcomes in patients with wound infections in the SmMITT and OFMITT populations |
|-------------------------------------------------|----------|----------|----------|----------|----------|
| SmMITT vs. OFMITT | | | | | |
| | INClude | Excluded | InClude | Excluded | InClude | Excluded |
| Early Clinical Response, % | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 |
| Difference | -0.5 | 0.0 | -0.5 | -0.5 | 0.0 | 0.0 |
| Iclaprim vs. Vancomycin | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 |

**Conclusion.** In this post-hoc analysis of the REVIVE studies, iclaprim achieved NI to vancomycin in both studies, based on ETP in the subgroup of patients with wound infections. These results suggest that iclaprim may be a valuable treatment option for patients with wound infections, including SSI, suspected or confirmed to be due to Gram-positive pathogens.

**Disclosures.** D. Huang, Motif BioSciences: Employee, Salary. G. R. Corey, Motif BioSciences: Board Member, Consulting fee. T. L. Holland, Basilea: Consultant, Consulting fee. W. O’Riodan, Motif BioSciences: Board Member, Consulting fee. M. Wilcox, Motif BioSciences: Board Member, Consulting fee. M. Dryden, Motif BioSciences: Board Member, Consulting fee. T. P. Lodise Jr., Motif BioSciences: Board Member, Consulting fee. W. O’Riodan, Motif BioSciences: Board Member, Consulting fee. M. Wilcox, Motif BioSciences: Board Member, Consulting fee. B. Balser, Motif BioSciences: Consultant, Consulting fee. E. Desplats, Motif BioSciences: Consultant, Consulting fee.

1339. Results for the Supplemental Microbiological Modified Intent-to-Treat (SmMITT) Population of the RESTORE-IMI 1 Trial of Imipenem/Cilastatin/Relebacatam (IMI/REL) vs. Imipenem/Cilastatin Plus Collistin (IMI+ CST) in Patients With Imipenem-Nonsusceptible (NS) Bacterial Infections

Keith Kim, MD, MPH; Thomas File Jr., MD; Helen W. Boucher, MD, FIDSA; Michelle Brown, RN; Angela Aggrey, PhD; Ireen Khan, MD; Hee-Koung Joeng, PhD; Robert Tipping, MS; Jejun Du, PhD; Katherine Young, MS; Joan Butterton, MD; Nicholas A. Kartsonis, MD and Amanda Paschke, MD, MSC, C. University of Michigan, Ann Arbor, Michigan; Summa Health System, Akron, Ohio; Infectious Diseases, Tufts Medical Center, Boston, Massachusetts; Merck & Co., Inc., Kenilworth, New Jersey

**Session:** 144. Novel Agents

**Friday, October 5, 2018: 12:30 PM**

**Background.** Clinical trials of new antibacterial agents in patients with carbapenem-resistant infections are critical but challenging to conduct. One challenge is identifying the study population by microbiological (micro) criteria; patients need to be identified locally to initiate effective treatment rapidly, but data standardization requires central laboratory confirmation. REL is a novel β-lactamase inhibitor that can restore imipenem activity against many imipenem-NS Gram-negative pathogens. Here we compare a supplemental analysis population based on local microbiology data (SmMITT eligibility) with the primary analysis population (mMITT) from the RESTORE-IMI 1 trial (NCT02452047) of IMI/REL vs. IMI+CST.

**Methods.** Randomized, active-controlled, double-blind, phase 3 trial enrolled adults with hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), complicated intra-abdominal infection (cIAI), or complicated urinary tract infection (cUTI). Patients were mMITT-eligible if pathogens were imipenem-NS (but CST- and IMI/REL-susceptible) based on central laboratory minimum inhibitory concentration (MIC). SmMITT comprised mMITT plus all patients who met inclusion criteria only based on local laboratory MIC.

**Results.** The SmMITT population (n = 41 [28 IMI/REL; 13 IMI+CST]) comprised 31 from mMITT plus 10 based on local MAC (8/41 [20%] cIAI and 21/41 [51%] cUTI). The majority of differences in central vs. local MIC were 1–2 dilutions; similar numbers of patients were excluded from mMITT due to imipenem susceptibility (n = 5) or IMI/REL-NS (n = 4); 1 patient was cST-NS. Based on ≥1 characteristics, including infecting pathogens, were comparable in SmMITT and mMITT: SmMITT: 68% male; 46% ≥65 y; 24% APACHE II score >15; 22% creatinine clearance <60 mL/minute. Rates of efficacy outcomes (overall response, day 28 clinical response, day 28 mortality) were comparable between populations, except that response rates in patients with cUTI were higher in SmMITT (91% vs. 73%).

**Conclusion.** Consistency of results was demonstrated across two analysis populations in a trial of resistant pathogens. This analysis provides results supportive of expected future clinical use of IMI/REL when treatment decisions will be made based on local laboratory results.

**Disclosures.** K. Kaye, Merck & Co., Inc.: Consultant and Research Contractor, Research grant. Melinta, Achaogen, Allergan: Consultant, Consulting fee. T. File, Bio Merieux, Curetis, Melinta, Merck, Metfillio, Ndgravit, Paratek, Pfizer: Consultant, Consulting fee. H. W. Boucher, Merck & Co., Inc.: Scientific Advisor, Consulting fee. M. Brown, Merck & Co., Inc.: Employee, Salary. A. Aggrey, Merck & Co., Inc.: Employee, Salary. L. Khan, Merck & Co., Inc.: Employee, Salary. H. K. Joeng, Merck & Co., Inc.: Employee, Salary. R. Tipping, Merck & Co., Inc.: Employee, Salary. J. Du, Merck & Co., Inc.: Employee, Salary. K. Young, Merck & Co., Inc.: Employee, Salary and Stock options. J. Butterton, Merck & Co., Inc.: Employee, Salary and Stock. N. A. Kartsonis, Merck & Co., Inc.: Employee, Salary and Stocks. A. Paschke, Merck & Co., Inc.: Employee and Shareholder, Salary.

1340. Population Pharmacokinetic (PK) Analysis of APX001 Using Phase 1 Data Michael Trang, PharmD; Justin C. Bader, PharmD, MBA; Eric A. Ople, BSc; William G. Kramer, PhD; Michael R. Hodges, MBRs, BSc; Soujata M. Bharmann, PharmD, MS and Christopher M. Rubino, PharmD; ICMP, Schoenheyde, New York

**Session:** 144. Novel Agents

**Friday, October 5, 2018: 12:30 PM**

**Background.** APX001 is a novel antifungal agent which is rapidly converted to the active metabolite APX001A. APX001A exhibits in vitro activity against many clinically important yeasts and fungi, including echinocandin- and azole-resistant Candida species. Given this activity, intravenous (IV) and oral (PO) formulations of APX001 are being developed for...
the treatment of patients with candidemia or invasive candidiasis. Phase 1 data were used to develop a population PK (PPK) model to describe the time-course of APX001A in plasma.

Methods. The PPK model was developed using 3,736 plasma PK samples collected from 128 healthy subjects who received APX001 single and multiple IV and PO doses ranging from 10 to 1,000 mg. Instantaneous conversion was assumed by scaling input doses by the molecular weight ratio of APX001A to APX001. After development of the structural PPK model, stepwise forward and backward selection procedures were used to identify significant covariate relationships. Model qualification included standard goodness-of-fit metrics and prediction-corrected visual predictive check (PC-VPC) plots.

Results. A two-compartment model with zero-order IV input, or first-order PO absorption with lag time to account for the apparent delay in oral absorption, best described APX001A plasma PK. Exponential error models were used to estimate interindividual variability (IVV) for all parameters. Interoccasion variability was estimated for the absorption rate constant, bioavailability, and lag time. Body weight was identified as a statistically significant predictor of the IVV on the volume of the central and peripheral compartments. The PPK model provided an accurate and unbiased fit to the plasma data based on individual and population-predicted concentrations (r² = 0.977 and 0.873, respectively). The PC-VPC plots for the final PPK model (Figure 1) demonstrated good alignment between observed concentrations and the model predicted 5th, 50th, and 95th percentiles.

Conclusion. A PPK model describing APX001A plasma PK following IV or PO doses was successfully developed. This model will be useful for generating simulated APX001A exposures for use in pharmacokinetic–pharmacodynamic target attainment analyses to support APX001A dose selection.

Figure 1. PC-VPC for the final population PK model for APX001A following IV (A) and PO (B) doses of APX001

Disclosures. M. Trang, Amplyx Pharmaceuticals, Inc.: Research Contractor, Research support. J. C. Bader, Amplyx Pharmaceuticals, Inc.: Research Contractor, Research support. E. A. Ople, Amplyx Pharmaceuticals, Inc.: Employee, Salary. W. G. Kramer, Amplyx Pharmaceuticals, Inc.: Scientific Advisor, Consulting fee. M. R. Hodges, Amplyx Pharmaceuticals, Inc.: Employee, Salary. S. M. Bhavnani, Amplyx Pharmaceuticals, Inc.: Research Contractor, Research support. C. M. Rubino, Amplyx Pharmaceuticals, Inc.: Research Contractor, Research support.