consistent with slow absorption from the lung being the dominant process controlling systemic kinetic behavior. The long t½ and 2-fold accumulation ratio observed on repeat dosing supports once daily dosing in subsequent studies.

1336. Assessment of the *In Vivo* Efficacy of WCK 5222 (Cefepime-Zidebactam) Against Carbapenems-Resistant *Acinetobacter baumannii* (CR-ACBN) in the Neutropenic Murine Thigh Infection Model

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Background. Zidebactam (ZID) is a novel β-lactam enhancer with high binding affinity to PBP2 and intrinsic activity against many Gram-negative pathogens, with the exception of ACBN. ZID also inhibits β-lactamases but not OXA carbapenemases associated with ACBN or metallo-β-lactamases. However, WCK 5222 (a combination of cefepime [FEP] and ZID) has shown *in vitro* activity against ACBN, including OXA producers. Moreover, we have previously shown that WCK 5222 human-simulated regimen (HSR) causes extensive (i.e., >2 log) eradication of ACBN from neutropenic mice lung. This study aimed to evaluate the *in vivo* efficacy of the HSR of WCK 5222 compared with FEP HSR or ZID HSR alone against ACBN in the neutropenic murine thigh infection model.

Methods. Six CR-ACBN clinical isolates, including five isolates expressing OXA-23 or OXA-24, were studied. FEP and WCK 5222 MICs were 128 to >512 and 16 to 64 mg/L, respectively. The ZID MIC was >512 mg/L for all isolates. ICR mice were rendered transiently neutropenic via cyclophosphamide prior to thigh inoculation with bacterial suspensions of 10^7 CFU/mL. Treatment mice received either FEP HSR (equivalent to a clinical dose of 2 g IV q8h as a 1 hour infusion), ZID HSR (equivalent to a clinical dose of 1 g IV q8h as 1 hour infusion), or WCK 5222 HSR (FEP HSR + ZID HSR). Control mice were vehicle-dosed. Changes in $\log_{10}$ CFU/mL at 24 hours compared with 0 hours controls were measured to assess efficacy.

Results. The average $\log_{10}$ CFU/thigh at 0 hours across all isolates was 5.85 ± 0.22. Compared with 0 hours control, the mean bacterial growth at 24 hours in the untreated control mice, FEP HSR, and ZID HSR were 2.34 ± 0.93, 1.36 ± 1.40, and 2.04 ± 0.80 $\log_{10}$CFU/thigh, respectively. The WCK 5222 HSR produced a decline in bacterial burden for all isolates [mean reduction of -2.09 ± 1.01 $\log_{10}$CFU/thigh]; 4/6 isolates achieved ≥ 2-log reduction while ≥1-log reduction was attained with the remaining two isolates.

Conclusion. HSR of WCK 5222 showed potent *in vivo* activity against CR-ACBN expressing OXA carbapenemases in the murine thigh model which is attributed to the β-lactam enhancing effect of ZID, driven by the complementary PBP binding of FEP and ZID. These results support the clinical evaluation of WCK 5222 for the management of infections due to CR-ACBN.

1337. SYN-004 (Ribaxamase) Protects the Gut Microbiome of Patients Treated With Ceftriaxone From Disruption and Reduces the Emergence of Antimicrobial Resistance

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Background. When β-lactam antibiotics are administered intravenously, a significant portion of each dose can be excreted through the bile into the intestine. This excess antibiotic disrupts the balance of the gut microbiome making the recipient more susceptible to certain infections and can lead to the emergence of antimicrobial resistance. SYN-004 (ribaxamase) is an orally administered β-lactamase designed to be given with IV β-lactam antibiotics (penicillins and cephalosporins) to degrade excess antibiotics excreted into the upper GI tract before they can disrupt the gut microbiome and resistome.

Methods. During a Phase 2b, clinical study with ribaxamase which demonstrated a significant reduction in *Clostridium difficile* infection in patients receiving ceftriaxone + ribaxamase, longitudinal fecal samples were collected from the patients. DNA extracted from these samples was 16S rRNA and whole genome sequenced, and the sequences were analyzed for changes in the gut microbiome and resistome. Statistical analyses were performed to determine correlations between changes in the gut microbiome and resistome and clinical study data.

Results. Sequence analyses revealed that ribaxamase protected the integrity of the gut microbiome, including preventing enterococcal mono-domination (defined as >30% of the microbiome being from one genus), and identified over 1,300 AMR genes in the gut resistome. LefSe analysis of the gut resistome identified a family of β-lactamases (CfxA) and vancomycin resistance genes which demonstrated a significant increase in placebo-treated vs. ribaxamase-treated patients from pre-to post-antibiotics. Analysis by

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This abstract has been withdrawn at the author's request.

1335. Safety and Pharmacokinetic Profile of PC786, a Novel Inhibitor of Respiratory Syncytial Virus L-protein Polymerase, in a Single and Multiple-Ascending Dose Study in Healthy Volunteer and Mild Asthmatics

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Background. RSV is the most common cause of bronchiolitis in infants and is responsible for severe respiratory infections in the elderly and immunocompromised populations. RSV replicates in the columnar epithelial cells of the proximal and distal airways which are accessible to inhaled therapies. PC786 is a potent non-nucleoside RSV L-protein polymerase inhibitor designed for inhaled delivery. In preclinical studies, PC786 exhibits prolonged lung tissue residence with minimal systemic exposure, thus limiting the potential for adverse systemic effects.

Methods. A phase 1 study was conducted to evaluate the safety and pharmacokinetics of PC786 delivered in a suspension formulation by nebulizer (PARI LC SPRINT device). Healthy volunteers (HVs) received placebo or PC786 as single ascending doses (0.5–20 mg, Cohort (C) 1), 5 mg BD for 7 days (C2), or 10 mg BD for 7 days (C3). Mild asthmatics received a single dose of PC786 5 mg or placebo (C4). PC786 PK was measured in plasma and in nasal mucosal lining fluid (MLF) collected using a synthetic absorptive matrix.

Results. PC786 was well tolerated, with no significant adverse clinical nor laboratory findings. Following single inhaled doses PC786 appeared rapidly in the plasma; mean plasma C_{max} of 190, 571, 1,760, and 3,270 pg/mL, for the 0.5, 2, 8, and 20 mg doses, respectively, were measured on average at 0.68 to 0.93 hours (T_{max}) post-inhalation. Following administration of 5 mg BD (C2) the extent of accumulation was approximately 2-fold. The geometric mean apparent terminal half-life measured following 10 mg BD (C3) was 97 hours. The ratio of MLF:plasma concentrations ranged from 6,347 (+2 hours) to 1,050 (+24h).

Conclusion. PC786 was well tolerated by HVs and asthmatics. The compound showed a rapid T_{max}, suggesting rapid exposure of the respiratory epithelium. The PC786 concentrations in MLF exceed the IC_{90} for RSV, but circulating plasma concentrations were low. The MLF:plasma measured in this study was consistent with lung:plasma ratios measured in preclinical studies. The long plasma half-life is

qPCR supported both new acquisition of these genes and expansion of existing AMR pools. Further statistical analyses demonstrated significant correlations between changes in the gut resistome 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 ribaxamase with IV β-lactam antibiotics can protect 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 Iclaprim Vs. Vancomycin for trEatment of Acute Bacterial Skin and Skin Structure Infections

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Background. The objective of this evaluation was to provide an analysis of pooled efficacy data from two parallel Phase 3 trials of iclaprim, a diaminopyrimidine dihydrofolate reducatase 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 of these studies was to determine whether iclaprim was noninferior (NI; 10% margin) to vancomycin in achieving a ≥20% 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).

	REVIVE-1		REVIVE-2		Combined REVIVE-1/2	
	Iclaprim *(N = 182)*	Vancomycin *(N = 158)*	Iclaprim *(N = 127)*	Vancomycin *(N = 135)*	Iclaprim *(N = 309)*	Vancomycin *(N = 293)*
Early Clinical Response, *n* (%)	152 (83.5)	126 (79.7)	105 (82.7)	103 (76.3)	257 (83.2)	229 (78.2)
% Difference (iclaprim–vancomycin)	3.77		6.38		5.01	
95% CI	−4.50, 12.04		−3.35, 16.12		−1.29, 11.32	

Conclusion. In this post-hoc analysis of the REVIVE studies, iclaprim achieved NI to vancomycin in both studies, based on ECR at 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. Motif Bio: Consultant and Scientific Advisor, Consulting fee. Theravance: Consultant, Speaker honorarium. Genentech: Consultant, Consulting fee. **T. P. Lodise Jr.**, Motif BioSciences: Board Member, Consulting fee. **W. O'Rirodan**, Motif BioSciences: Board Member, Consulting fee. **M. Wilcox**, Motif BioSciences: Board Member, Consulting fee. **T. M. File Jr.**, Motif BioSciences: Board Member, Consulting fee. **M. Dryden**, 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/Relebactam (IMI/REL) vs. Imipenem/Cilastatin Plus Colistin (IMI+CST) in Patients with Imipenem-Nonsusceptible (NS) Bacterial Infections

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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 MIC; 12/41 (29%) had HABP/VABP, 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. Baseline 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 cIAI were higher in SmMITT (table).

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.

Table. Efficacy outcomes in pts in the mMITT and SmMITT populations				
	IMI/REL[a] n/m (%)	**IMI+CST[b]** n/m (%)	**Unadjusted Difference** % (90% CI)	**Adjusted Difference** % (90% CI)[c]
Favorable Overall Response[d]				
mMITT	15/21 (71.4)	7/10 (70.0)	1.4	−7.3 (−27.5, 21.4)
HABP/VABP	7/8 (87.5)	2/3 (66.7)	20.8	-
cIAI	0/2 (0.0)	0/2 (0.0)	0.0	-
cUTI	8/11 (72.7)	5/5 (100.0)	−27.3 (−52.8, 12.8)[e]	-
SmMITT	21/28 (75.0)	10/13 (76.9)	−1.9	−4.5 (−24.2, 20.7)
HABP/VABP	7/8 (87.5)	3/4 (75.0)	12.5 (−25.4, 56.6)[e]	-
cIAI	2/5 (40.0)	1/3 (33.3)	6.7	-
cUTI	12/15 (80.0)	6/6 (100.0)	−20.0 (−41.4, 14.2)[e]	-
Favorable Clinical Response (Day 28)				
mMITT	15/21 (71.4)	4/10 (40.0)	31.4	26.3 (1.3, 51.5)
SmMITT	21/28 (75.0)	7/13 (53.8)	21.2	17.6 (-5.9, 42.5)
All-Cause Mortality (Through Day 28)				
mMITT	2/21 (9.5)	3/10 (30.0)	−20.5	−17.3 (-46.4, 6.7)
SmMITT	3/28 (10.7)	3/13 (23.1)	−12.4	−10.5 (-35.2, 9.6)

[a]IMI/REL (500 mg imipenem/cilastatin and 250 mg relebactam) every 6 hours. [b]CST provided as colistimethate sodium (loading dose of 300 mg colistin base activity [CBA] followed by 150 mg CBA [corresponding to =360 mg colistimethate sodium or =4.5 million IU] every 12 hours). imipenem/cilastatin (500 mg every 6 hours). [c]Adjusted differences and 90% CIs are based on Miettinen & Nurminen method stratified by infection-site stratum. [d]Overall response: (a) survival status through day 28 postrandomization in pts with HABP/VABP, (b) clinical response at day 28 postrandomization for pts with cIAI, and (c) the composite clinical and microbiological response at early follow-up for pts with cUTI. [e]90% CIs are based on Miettinen & Nurminen method.
n/m, number of pts with a favorable response or all-cause mortality/number of evaluable pts.

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, MotifBio, Nabriva, 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. **I. 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

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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 yeast and fungi, including echinocandin- and azole-resistant *Candida* species. Given this activity, intravenous (IV) and oral (PO) formulations of APX001 are being developed for