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.

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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.

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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]	IMI+CST[b]	Unadjusted Difference	Adjusted Difference
	n/m (%)	n/m (%)	% (90% CI)	% (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 cIAI cUTI	7/8 (87.5) 0/2 (0.0) 8/11 (72.7)	2/3 (66.7) 0/2 (0.0) 5/5 (100.0)	20.8 0.0 -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 cIAI cUTI	7/8 (87.5) 2/5 (40.0) 12/15 (80.0)	3/4 (75.0) 1/3 (33.3) 6/6 (100.0)	12.5 (-25.4, 56.6)[e] 6.7 -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.

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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

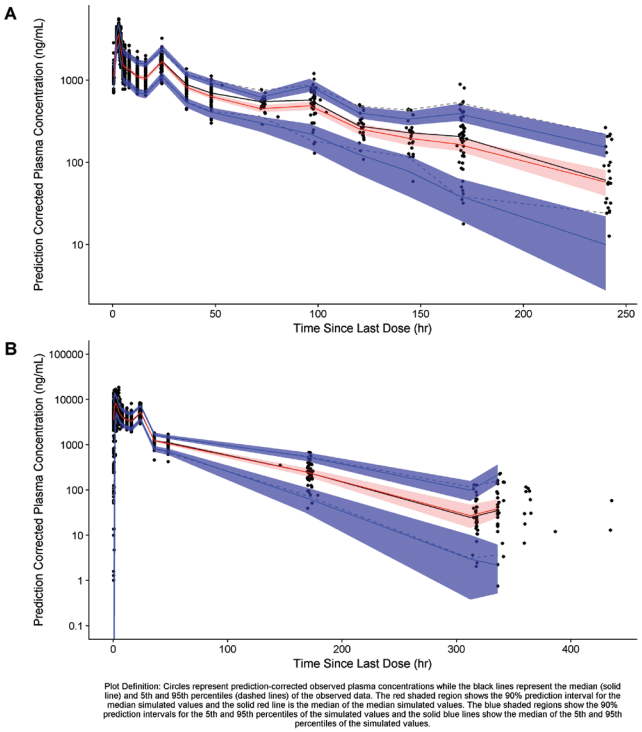
the treatment of patients with candidemia or invasive candidiasis. Phase 1 data were used to develop a population PK (PPK) model to describe the time-course of APX001A in plasma.

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 PK 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 (IIV) 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 IIV 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 (r^2 = 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 APX001 dose selection.

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



Plot Definition: Circles represent prediction-corrected observed plasma concentrations while the black lines represent the median (solid line) and 5th and 95th percentiles (dashed lines) of the observed data. The red shaded region shows the 90% prediction interval for the median simulated values and the solid red line is the median of the median simulated values. The blue shaded regions show the 90% prediction intervals for the 5th and 95th percentiles of the simulated values and the solid blue lines show the median of the 5th and 95th percentiles of the simulated values.

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This abstract has been withdrawn at the author's request.

1342. Comparison of Lysin CF-301 (Exebacase) Activity Against *S. aureus* Isolates From Bacteremic Patients Enrolled in a Phase 2 Study (CF-301-102) to Contemporary Surveillance Isolates

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Background. CF-301 (exebacase) is a novel, recombinantly produced, bacteriophage-derived lysin (cell wall hydrolase) which is the first lysin to enter Phase 2 (Ph2) in the United States and is being studied for the treatment of *S. aureus* bacteremia including endocarditis. We examined the activity of CF-301 against methicillin-sensitive and methicillin-resistant *S. aureus* (MSSA and MRSA) isolates from participants in the ongoing, CF-301 "first in-patient' Ph2 study (NCT03163446) in comparison to activity reported in a recent surveillance study.

Methods. Patients with complicated bacteremia or endocarditis caused by *S. aureus* were enrolled into Study CF-301-102 at study centers in the United States and Guatemala between 2017 and 2018. Baseline isolates from blood cultures were collected prior to administration of CF-301. The activity of CF-301 activity against the first 36 isolates of MRSA (14) and MSSA (22) was determined at a central laboratory. Surveillance data for CF-301 were generated against 300 isolates of MRSA (150) and MSSA (150) collected between 2016 and 2017 from patients with various infection types at US centers. CF-301 MICs were determined using the modified broth microdilution method approved by the CLSI for CF-301.

Results. *In vitro* activity of CF-301 against *S. aureus* isolates from Ph2 Study CF-301-102 and surveillance

			MIC (µg/mL)						
Organism	Source	N	0.125	0.25	0.5	1	2	MIC_{50}	MIC_{90}
MSSA	Ph2	22	1	6	13	2		0.5	0.5
	Surveillance	150		2	91	57		0.5	1
MRSA	Ph2	14		3	10	1		0.5	0.5
	Surveillance	150		5	108	37		0.5	1

The CF-301 MICs of baseline patient isolates from the Ph2 study ranged from 0.125 – 1 µg/mL. CF-301 $MIC_{50/90}$ values for all MSSA and MRSA isolates were 0.5 µg/mL. CF-301 MICs reported in a recent the surveillance study ranged from 0.25–1 µg/mL, with $MIC_{50/90}$ values of 0.5/1 µg/mL.

Conclusion. The activity of CF-301 against baseline *S. aureus* isolates from blood cultures obtained from bacteremic patients enrolled in the Ph2 study was similar to that observed in the surveillance study. Based on data from previously presented exposure target attainment animal studies, PK/PD modeling and preliminary non-clinical breakpoint assessments, we expect that strains with MIC values of ≤1 µg/mL will be susceptible to the clinical CF-301 dose (0.25mg/kg) under study in Ph2.

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