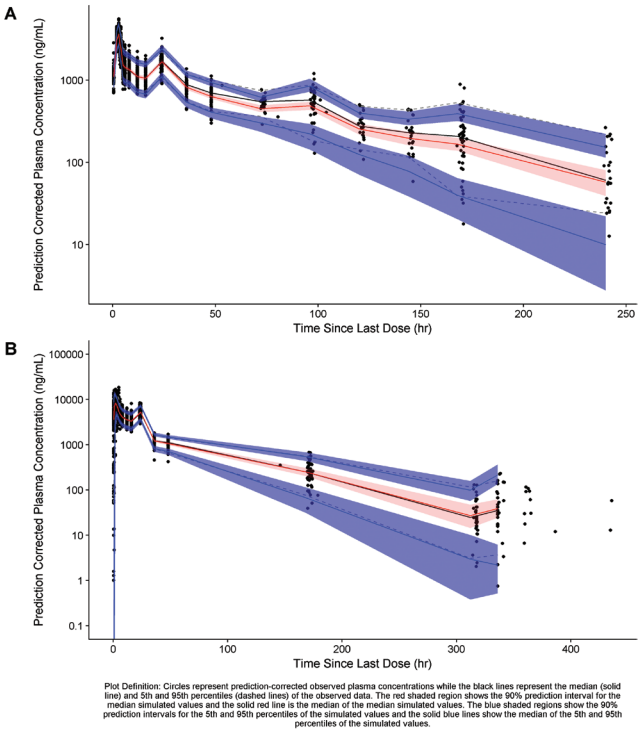
the treatment of patients with candidemia or invasive candidiasis. Phase 1 data were used to develop a population PK (PPK) model to describe the time-course of APX001A in plasma.

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.

Disclosures. **D. Anastasiou**, ContraFect Corporation: Consultant, Consulting fee. **A. Jandourek**, ContraFect Corporation: Employee, Salary. **C. Cassino**, ContraFect Corporation: Employee, Salary. **R. Schuch**, ContraFect Corporation: Employee, Salary.

1343. Prophylactic Dosing of Baloxavir Acid Eliminates Mortality in Mice Lethal Influenza A Virus Infection Model

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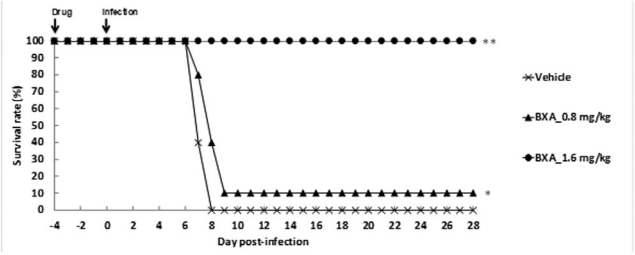
Background. Baloxavir acid (BXA), an active form of orally available prodrug baloxavir marboxil (BXM, formerly S-033188), is a novel small molecule inhibitor of cap-dependent endonuclease (CEN) of influenza A and B virus, and was recently launched for the treatment of acute and uncomplicated influenza with single dosing of BXM (the trade name XOFLUZA™) in Japan in March 2018. Here, we evaluated the prophylactic efficacy of BXA in mice lethally infected with influenza A virus.

Methods. $T_{1/2}$ of BXA in human is more than 10 times longer than that in mice. Therefore, suspension of BXA was subcutaneously administered at 0.8 or 1.6 mg/kg in mice to maintain the plasma concentration of BXA as seen in humans, and then mice were intranasally inoculated with a lethal dose of A/PR/8/34 strain at 48, 72, or 96 hours after the administration of BXA. Survival time and body weight change were then monitored through a 28-day period after virus infection. Mice were euthanized and regarded as dead if their body weights were lower than 70% of the initial body weights according to humane endpoints.

Results. Single dosing of BXA (1.6 mg/kg) completely eliminated mortality in mice, when the mice were administrated the drug at 48, 72, or 96 hours before virus infection (Figure 1). BXA treatment also significantly prevented body weight loss, consistent with the prolonged survival.

Conclusion. Prophylactic dosing of BXA exhibited significant protective efficacy against mortality and body weight loss in mice following a lethal infection with influenza A virus. The significant prophylactic efficacy observed in our mouse model suggests the potential utility of BXM for the prophylaxis of influenza in human.

Figure 1 Effect of prophylactic treatment with baloxavil acid on mortality due to infection witha lethal dose fo A/PR/8/34 strain in mice



BXA,baloxavir acid. The following P values were calculated by log-rank test and the fixed-sequence procedure: *P<0.05, **P<0.0001 vs vehicle

Disclosures. **S. Shano**, Shionogi & Co., Ltd.: Employee, Salary. **K. Fukao**, Shionogi & Co., Ltd.: Employee, Salary. **T. Noshi**, Shionogi & Co., Ltd.: Employee, Salary. **K. Sato**, Shionogi & Co., Ltd.: Employee, Salary. **M. Sakuramoto**, Shionogi & Co., Ltd.: Employee, Salary. **K. Baba**, Shionogi TechnoAdvance Research & Co., Ltd.: Employee, Salary. **T. Shishido**, Shionogi & Co., Ltd.: Employee, Salary. **A. Naito**, Shionogi & Co., Ltd.: Employee, Salary.

1344. Ridinilazole (RDZ) for *Clostridium difficile* Infection (CDI): Impact of Diagnostic Method on Outcomes From a Phase 2 Clinical Trial

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Background. Diagnosis of CDI includes fecal detection of a *C. difficile* toxigenic strain (TS) or free toxins (FT). TS detection does not distinguish infection from colonization. Guidelines recommend an FT test be part of diagnostic algorithms. Here we report outcome differences, based on diagnostic method at enrollment, from a Phase 2 clinical trial of RDZ, a novel CDI antibiotic designed to treat CDI and reduce recurrence of CDI (rCDI).

Methods. This double-blind study randomized 100 patients 1:1 to 10 days RDZ 200 mg BID or vancomycin (VAN) 125 mg QID treatment. Subjects were enrolled with CDI symptoms and a positive diagnostic result (FT or TS). Baseline (BL) stool samples were assessed for the presence of FT. All subjects entered the intent to treat (ITT) population; those subjects positive for FT entered a modified ITT (mITT), the primary analysis population. Primary endpoint was sustained clinical response (SCR) defined as cure at end of therapy and no rCDI for the next 30 days. rCDI was defined as CDI symptoms, a positive diagnostic test and need for therapy; a sensitivity analysis considered positive FT rCDI cases. BL fecal concentrations of lactoferrin and calprotectin were determined by enzyme immunoassay.

Results. Of 100 subjects enrolled, 69 (36 RDZ: 33 VAN) were FT positive at BL. RDZ compared with VAN recipients had improved SCR rates via reduced rCDI. Absolute differences in SCR between RDZ and VAN (prespecified 90% CI) for MITT (FT positive) and ITT subjects were 24.3% (3.1, 39.1) and 14.0% (−1.8, 28.8), respectively. Absolute SCR differences between the MITT and ITT subjects from the sensitivity analysis were 26.2% (4.6, 40.6) and 14.3% (−1.7, 29.1). Median BL calprotectin and lactoferrin levels (µg/mL) were significantly higher for FT positive subjects at 1,002 and 87, than for FT negative subjects at 53 and 4, respectively.

Conclusion. RDZ showed improved SCR in comparison with VAN. Treatment differences were greater in MITT subjects. Lower SCR improvement in RDZ ITT subjects is likely due to enrollment of some colonized rather than infected subjects; this explanation is supported by higher calprotectin and lactoferrin levels in FT-positive samples. These data demonstrate the importance of FT testing in-line with CDI guideline recommendations.

Disclosures. **R. Vickers**, Summit Therapeutics: Employee, Salary and Stock options. **S. Chowdhury**, Summit Therapeutics: Employee, Salary and Stock options. **M. Wilcox**, Summit Therapeutics: Consultant, Research Contractor and Scientific. Advisor, Consulting fee, Research grant and Research support.

1345. Comparative Activity of Plazomicin and Other Aminoglycosides Against *Enterobacteriaceae* Isolates From Various Infection Sources From Hospitalized Patients in the United States

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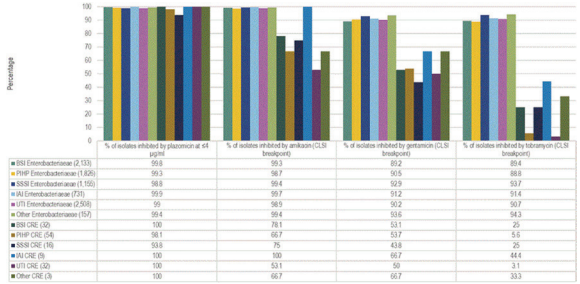
Background. Plazomicin is a next-generation aminoglycoside that is currently under review at the United States Food and Drug Administration for complicated urinary tract infections (cUTIs), including acute pyelonephritis, and bloodstream infections (BSIs) due to certain *Enterobacteriaceae* (ENT) in patients who have limited or no alternative treatment options. We evaluated the activity of plazomicin and aminoglycosides against ENT isolates collected in US hospitals during 2014 to 2017 by site of infection.

Methods. A total of 8,510 ENT isolates were collected from BSIs (2,133), pneumonia in hospitalized patients (PIHP; 1,826), skin and skin structure infections (SSSIs; 1,155), intra-abdominal infections (IAIs; 731), UTIs (2,508), and other or unknown infection sites (others; 157) in 71 US hospitals during 2014 to 2017. Isolates were susceptibility (S) tested by reference broth microdilution methods and results were interpreted using CLSI breakpoints.

Results. Plazomicin ($MIC_{50/90}$ ranges, 0.25–0.5/1–2 µg/mL) inhibited 98.8–99.9% of the ENT isolates at ≤4 µg/mL across all infection types (figure). At ≤4 µg/mL, plazomicin inhibited 93.8–100% of the carbapenem-resistant ENT (CRE) isolates stratified by infection type. The S rates for amikacin ranged from 98.7% to 99.7% against ENT isolates overall. However, amikacin S rates for CRE ranged from 53.1% for UTI to 100% for IAI isolates. Gentamicin (89.2–93.6%S) and tobramycin (88.8–94.3%S) were slightly less active than plazomicin and amikacin against the ENT isolates stratified by infection source. Gentamicin S rates against CRE isolates ranged from 43.8% to 66.7% while tobramycin inhibited <45% of the CRE isolates from the different infection sources.

Conclusion. The activity of plazomicin and amikacin was similar against ENT isolates from US hospitals and did not vary by infection type; however, amikacin activity against CRE isolates varied by infection source while plazomicin remained active against CRE isolates regardless of infection source. These results highlight the potential role of plazomicin for treating serious infections caused by CRE. This project was partially funded under BARDA Contract No. HHSO100201000046C.



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1346. The Tetrazole VT-1598 Is Efficacious in a Murine Model of Invasive Aspergillosis with a PK/PD Expected of a Mold-Active CYP51 Inhibitor

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Background. VT-1598 is a novel fungal CYP51 inhibitor with potent *in vitro* activity against yeast, mold, and endemic pathogenic fungi (Wiederhold, JAC, 2017). Its tetrazole-based rational drug design imparts much greater selectivity vs. human CYPs (Yates, BMCL, 2017), which could reduce human CYP-related side effects and DDIs. We report here VT-1598's *in vivo* activity in an invasive aspergillosis (IA) model.

Methods. MIC was determined as outlined in CLSI M38-A2. Plasma PK was measured after 4 days of oral doses in neutropenic ICR mice without fungal