**LB3. Exebacase (EXE) Reduced Length of Stay and 30-Day Readmission Rates for US Patients with Methicillin-Resistant Staphylococcus aureus (MRSA) Bacteremia Including Endocarditis Compared with Standard of Care Antibiotics (SoC) Alone in a Phase 2 Study**

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*Thursday, October 3, 2019: 2:05 PM*

***Background.*** Exebacase, a lysin (cell wall hydrolase), is the first direct lytic agent to report Phase 2 study results in *Staphylococcus aureus* bacteremia including endocarditis. Among MRSA patients enrolled in this randomized, double-blind, placebo, controlled study, EXE used in addition to standard of care antibiotics (SoC), had 42.8% higher clinical responder rates (CRRs) compared SoC alone. We sought to determine whether these differences in CRRs translated into reductions in health resource utilization (HRU) in this population of critically ill, hospitalized patients.

***Methods.*** The microbiological intent-to-treat population included 116 patients (71 EXE, 45 SoC) with documented *S. aureus* who received a single 2-hour infusion of blinded study drug dosed based on target attainment. The primary efficacy endpoint was CRR at Day 14. Diagnoses and clinical outcomes were determined by a blinded Adjudication Committee. HRU including length of stay (LOS), and 30-day hospital readmission rates (HRR) for all causes (AC) and for *S. aureus* (SA) were evaluated in MRSA patients who were alive at the time of discharge.

***Results.*** The average patient was white, male and ~56 years old (67.8%). Twenty-seven EXe patients (38.0%) and 16 SoC patients (35.6%) had MRSA. All but 2 MRSA patients (1 EXE, 1 SoC) were enrolled in the United States. The Day 14 CRR were 70.4% for EXE and 60.0% for SoC groups (p=0.314) overall. In a prespecified analysis of MRSA patients, the CRR with EXE was 74.1% vs. 31.3% with SoC ($P = 0.010$). Among MRSA patients who received study drug, incidence of treatment emergent adverse events (TEAEs) was balanced between groups (24 (88.9%) in EXE and 15 (98.3%) in SoC) as were serious TEAEs (17(63.0%) in EXE, 12 (75%) in SoC). 1 EXE and 2 SoC US MRSA patients died in hospital. Among US MRSA patients discharged alive from the hospital, the median LOS after study drug was 6 vs. 10 days for EXE and SoC, respectively. Thirty-day AC HRR were 16% vs. 30.8%, for EXE vs. SoC, respectively, and 30-day SA HRR were 8% vs. 15.4%, respectively.

***Conclusions.*** Exebacase used in addition to SoC was associated with a reduction in length of hospital stay and 30-day readmission rates for all causes and for *S. aureus* compared with SoC alone in patients being treated for MRSA bacteremia/endocarditis.

***Disclosures.*** Cara Cassino, MD, ContraFect Corporation (Employee), Hemal Shah, PharmD, Boehringer Ingelheim (Consultant), ContraFect Corp (Consultant), DBV Technologies (Consultant), Mylan specialty (Consultant), Nabriva (Consultant), Joy Lipka-Diamond, MS, ContraFect Corporation (Consultant), Anita F. Das, PhD, Achaogen (Consultant), AntiobioTx (Consultant), Boston Pharmaceuticals (Consultant), Cempra (Consultant), ContraFect Corporation (Consultant), Iterum Therapeutics (Consultant), Nabriva (Consultant), Paratek (Consultant), Tetraphase (Consultant), UTILITY (Consultant), Wockhardt (Consultant).

**LB4. Efficacy and Safety of Cefiderocol vs. High-Dose Meropenem in Patients with Nosocomial Pneumonia—Results of a Phase 3, Randomized, Multicenter, Double-Blind, Non-Inferiority Study**

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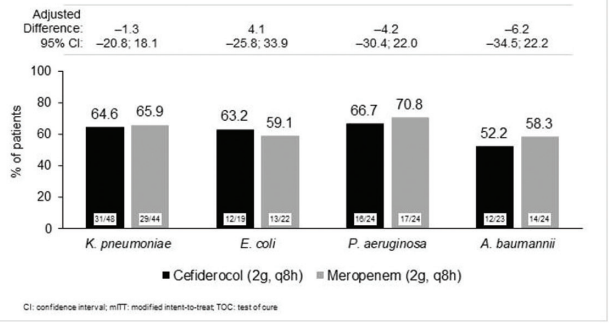
***Background.*** Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against a broad range of Gram-negative bacteria. In this study, Day 14 all-cause mortality (ACM) rates were compared between CFDC and meropenem (MEM) in patients with nosocomial Gram-negative pneumonia.

***Methods.*** The study (NCT03032380) was a Phase 3, international, double-blind, randomized, non-inferiority study in hospitalized patients with ventilator-associated, hospital-acquired, or healthcare-associated pneumonia caused by suspected Gram-negative bacteria. Patients were treated with CFDC (2 g, q8h) or MEM (2 g, q8h), both infused for 3 hours, for 7–14 days. Adjunctive linezolid (600 mg, q12h, ≥5 days) was given in both arms to cover Gram-positive bacteria. The primary endpoint was non-inferiority of CFDC to MEM for Day 14 ACM rate in the modified intent-to-treat population (mITT; non-inferiority margin: –12.5%). Key secondary endpoints were clinical and microbiological outcomes at test of cure (TOC), and Day 28 mortality. Safety was investigated up to 28 days after the end of treatment.

***Results.*** In the ITT population, 148 patients were randomized to CFDC and 150 to MEM: 59.7% were ventilated, 32.6% had failure of prior therapy, the median APACHE II score was 15, and 6.0% had concomitant Gram-negative bacteremia at baseline. In the mITT population, non-inferiority of CFDC to MEM for Day 14 ACM was demonstrated; CFDC: 12.4% (18 out of 145 patients) vs. MEM: 11.6% (17 out of 146 patients); treatment difference: 0.8; 95% confidence interval: –6.6; 8.2. Comparable Day 28 ACM (CFDC: 21.0% vs. MEM: 20.5%), clinical cure (CFDC: 64.8% vs. MEM: 66.7%), and microbiological eradication (CFDC: 47.6% vs. MEM: 48.0%) rates were demonstrated in the mITT population at TOC. Clinical cure rates for major target pathogens at TOC were similar between CFDC and MEM arms (figure). The rates of treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious AEs, discontinuation due to TEAEs, and deaths were similar between treatment arms (table).

***Conclusion.*** This study demonstrated the non-inferiority of CFDC to high-dose MEM for the pre-specified endpoint of Day 14 ACM. No unexpected safety signals were observed in the study.

Figure. Clinical cure rates in mITT population for the most frequently isolated pathogens at TOC




CI: confidence interval; mITT: modified intent-to-treat TOC: test of cure

Table. Incidence of TEAEs in the safety population

| Adverse event category | Cefiderocol (2g, q8h) N=148 | Meropenem (2g, q8h) N=150 |
|---|---|---|
| TEAEs, n (%) | 130 (87.8) | 129 (86.0) |
| Drug-related TEAEs, n (%) | 14 (9.5) | 17 (11.3) |
| Treatment-emergent SAEs, n (%) | 54 (36.5) | 45 (30.0) |
| Drug-related SAEs, n (%) | 3 (2.0) | 5 (3.3) |
| Discontinuation due to TEAEs, n (%) | 12 (8.1) | 14 (9.3) |
| Discontinuation due to drug-related TEAEs, n (%) | 2 (1.4) | 2 (1.3) |
| TEAEs leading to death, n (%) | 39 (26.4) | 35 (23.3) |

***Disclosures.*** Richard G. Wunderink, MD, Merck (Consultant, Grant/Research Support), Shionogi Inc. (Consultant), Yuko Matsunaga, MD, Shionogi Inc. (Employee), Mari Ariyasu, BPharm, Shionogi & Co., Ltd. (Employee), Roger Echols, MD, Shionogi Inc. (Consultant), Anju Menon, PhD, Shionogi Inc. (Employee), Tsutae Den Nagata, MD, Shionogi & Co., Ltd. (Employee).

**LB5. A Long-Time Coming: Final 2-year Analysis of Efficacy, Durability, and Microbiome Changes in a Controlled Open-Label Trial of Investigational Microbiota-Based Drug RBX2660 for Recurrent Clostridioides difficile Infections**

Robert Orenstein, DO[1]; Sarah Mische, PhD[2]; Sarah Mische, PhD[2]; Ken Blount, PhD[2]; Ken Blount, PhD[2]; Lindy Bancke, PharmD[2]; Xin Su, MD, MSc[3]; Dana Walsh, PhD[2]; Adam Harvey, PhD[3]; Carlos Gonzalez, MS[4]; Dale N. Gerding, MD[5]; Dale N. Gerding, MD[5]; [1]Mayo Clinic in Arizona, Phoenix, Arizona,; [2]Rebiotix Inc., Roseville, Minnesota,; [3]Rebiotix Inc., Roseville, Minnesota,; [4]BioRankings, LLC, St. Louis, Missouri,; [5]Edward Hines Jr. VA Hospital, Hines, Illinois

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***Background.*** Recurrent *Clostridioides difficile* infection (rCDI) is an urgent public health threat associated with significant mortality and medical cost. Microbiota therapy is gaining acceptance as a strategy to reduce rCDI recurrence. We present the final 24-month analysis of clinical safety, efficacy, and microbiome restoration from a Phase 2 open-label trial of RBX2660 for prevention of CDI recurrence.

***Methods.*** Participants with multi-recurrent CDI received <2 doses of RBX2660 delivered via enema 7 days apart in this multicenter, open-label Phase 2 study. Efficacy was defined as the absence of CDI recurrence through 56 days after the last dose and was compared with 8-week recurrence-free rates for a historical control cohort that received standard-of-care antibiotic therapy. Fisher exact test compared the proportion of treatment participants who were CDI-free by age and sex. Durability was defined as continued absence of CDI episodes beyond 8 weeks. Safety and durability assessments occurred at 3, 6, 12, and 24 months. Participant stool samples were collected prior to and for up to 720 days after treatment, and microbiome changes were assessed by shallow shotgun sequencing.

***Results.*** The efficacy of RBX2660 to prevent rCDI at 8 weeks (78.9%; 112/142) was higher than the CDI-free rate in the historical control group (30.7%, 23/75; $P < 0.0001$). Age and sex did not impact efficacy. Among participants who achieved treatment success at 8 weeks and were evaluable for long-term durability ($n = 95$), 8 experienced a new CDI episode by the 24-month follow-up for an overall durability of 91.6%. The safety profile was consistent with previous reports for RBX2660. In total, 503 stool samples from 110 treatment responders were analyzed. Within 7 days of treatment, the relative abundance of Bacteroidia and Clostridia remained shifted

higher than pre-treatment levels while Gammaproteobacteria and Bacilli declined sharply after treatment, and these changes persisted to at least 24 months.

***Conclusion.*** RBX2660, a microbiota-based drug, was safe and efficacious for preventing rCDI with clinical durability to 24 months after treatment, independent of age or sex, and RBX2660 durability associated with durable microbiome shifts from pre-treatment to a healthier composition.

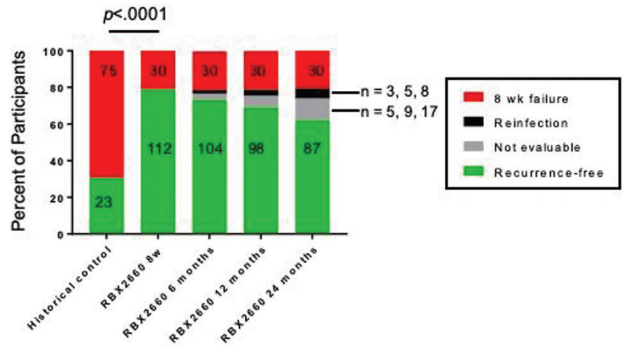


**Figure 1**: Primary outcome and durability, reported as percentages with number of participants shown as numbers

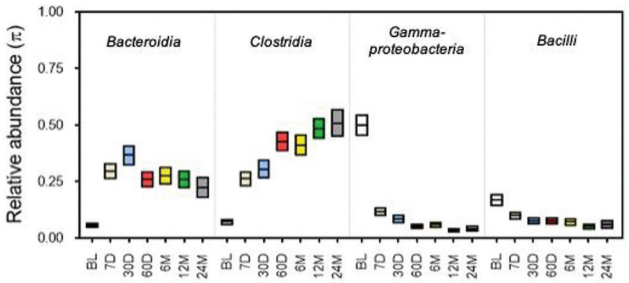


**Figure 2**: Mean relative abundance (π) with confidence intervals at the taxonomic class level before treatment (BL) and at time points after treatment.

***Disclosures.*** Robert Orenstein, DO, Rebiotix Inc. (Advisor or Review Panel member), Sarah Mische, PhD, Rebiotix Inc. (Employee), Ken Blount, PhD, Rebiotix Inc. (Employee), Lindy Bancke, PharmD, Rebiotix Inc. (Employee), Xin Su, MD, MSci, Rebiotix Inc. (Employee), Dana Walsh, PhD, Rebiotix Inc. (Employee), Adam Harvey, PhD, Rebiotix Inc. (Employee), Carlos Gonzalez, MS, Rebiotix Inc. (Consultant), Dale N. Gerding, MD, Rebiotix Inc. (Board Member).

### LB6. EDP-938, a Novel RSV N-Inhibitor, Administered Once or Twice Daily Was Safe and Demonstrated Robust Antiviral and Clinical Efficacy in a Healthy Volunteer Challenge Study

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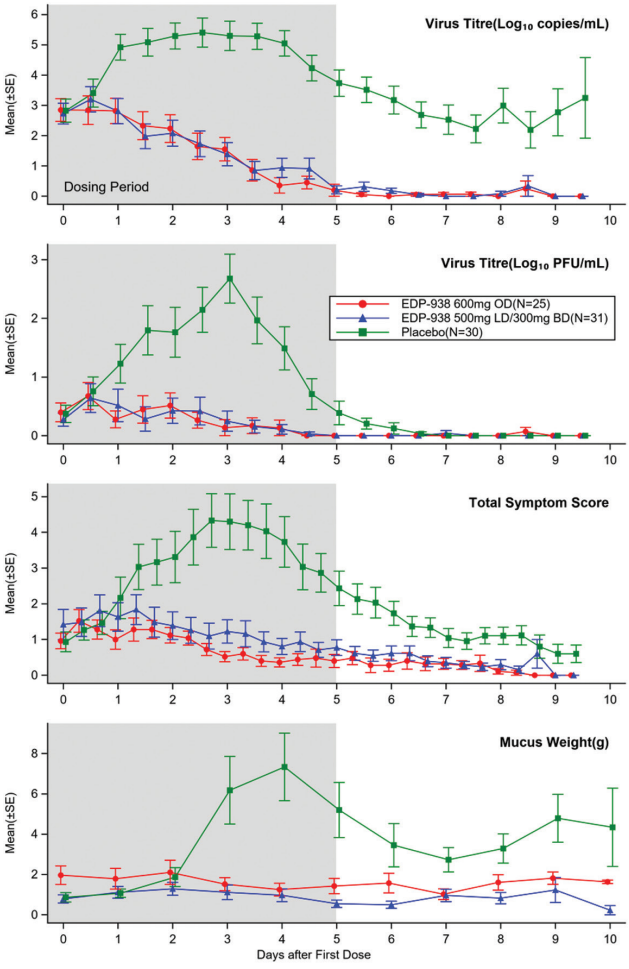
***Background.*** Respiratory syncytial virus (RSV) represents an important global health challenge with significant morbidity and mortality in infants, elderly, and immunocompromised adults. No effective therapy is currently available. EDP-938 demonstrates potent *in vitro* activity against RSV Subtypes A and B. We report data from EDP 938-101, a double-blind, placebo-controlled, Phase 2a study that evaluated EDP-938 in adult volunteers inoculated with RSV-A Memphis 37b.

***Methods.*** Subjects were healthy volunteers, 18–45 years, who were sero-suitable (i.e., lower 25th percentile). After RSV inoculation on Study Day 0, subjects had 12 hourly nasal wash monitored for RSV infection by qualitative RSV RT–PCR. On Study Day 5 or previously if qualitative RT–PCR was RSV+, subjects were randomized to receive 5 days of EDP-938 600 mg once daily (QD arm) or 500 mg loading dose then 300 mg twice daily (BID arm), or placebo twice daily. Assessments included 12 hourly nasal wash for quantitative RSV viral load, 8 hourly RSV Total Symptom Scoring (TSS) and daily mucus weights. Safety assessments were continued though Day 28 (last follow-up). The primary endpoint was the RSV viral load area under the curve (AUC) from first dose through Day 12 among RSV-infected subjects, defined as the Intent To Treat-Infected (ITT-I) population. The study was fully powered for both RSV viral load and TSS endpoints.

***Results.*** A total of 115 subjects were randomized and inoculated; 86 were included in the ITT-I analysis. The primary and secondary efficacy endpoints were achieved with high statistical significance in QD and BID arms (figure and table). Among EDP-938 recipients all adverse events (AEs) were mild except for a single AE of moderate dyspepsia in the BID arm and events of moderate headache ($n$ = 2) and hypoacusis ($n$ = 1) in the placebo arm. All AEs resolved in follow-up.

***Conclusions.*** In the RSV Challenge study, EDP-938 administered once or twice daily achieved primary and key secondary endpoints with robust reductions in RSV viral load (by both qRT–PCR and plaque assays), symptom scores and mucus weights. These data support the further clinical evaluation of EDP-938 in populations at risk of severe RSV disease.

| Endpoint (Mean (±SD)) | EDP-938 600 mg QD N=25 | EDP-938 500 mg x1 + 300 mg BID N=31 | Placebo N=30 | P-value EDP-938 vs placebo |
|---|---|---|---|---|
| AUC by Quantitative RT-PCR (hours x $\log_{10}$ copies/mL) | 203.95 (173.50) | 217.71 (217.55) | 790.15 (408.80) | Both P<0.001 |
| AUC by Plaque Assay (hours x $\log_{10}$ PFU/mL) | 34.05 (63.58) | 35.91 (78.04) | 185.55 (161.71) | Both P<0.001 |
| AUC TSS (hours x Score) | 124.47 (115.60) | 181.75 (248.42) | 478.75 (422.29) | Both P<0.001 |
| Nasal Mucus Weight (grams) | 12.965 (13.03) | 7.428 (11.13) | 33.416 (37.81) | Both P<0.001 |




***Disclosures.*** Eoin Coakley, MD, Enanta Pharmaceuticals (Employee), Alaa Ahmad, PhD, Enanta Pharmaceuticals (Employee), Kajal Larson, PhD, Enanta Pharmaceuticals (Employee), Ty McClure, PhD, Enanta Pharmaceuticals (Employee), Kai Lin, PhD, Enanta Pharmaceuticals (Employee), Kursten Tenhoor, n/a, Enanta Pharmaceuticals (Consultant), Kingsley Eze, n/a, hVIVO Services Ltd. (Employee), Nicolas Noulin, PhD, No financial relationships or conflicts of interest, Veronika Horvathova, MBChB, MSc, hVIVO Services Limited (Other Financial or Material Support, Employed by hVIVO during the conduct of the study), Bryan Murray, MBBS, No financial relationships or conflicts of interest, Mark Baillet, PhD, S-CUBED (Employee), Julie Mori, PhD, hVIVO (Employee, Shareholder) Nathalie Adda, MD, Enanta Pharmaceuticals (Employee).

### LB7. A Randomized, Blinded, Placebo- and Vancomycin-Controlled, First-In-Human (FIH) Study of the Safety, Pharmacokinetics (PK), and Fecal Microbiome Effects of ACX-362E, a Novel Anti-Clostridial DNA Polymerase IIIC (polIIIC) Inhibitor

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