Background. There is a pressing need for development of oral antibiotics with activity against SBL-EB, particularly carbapenemase-producers, for use in the community or as step-down therapy for complicated urinary tract infection. VNRX-7145 is a novel boronic acid-based SBL inhibitor with no intrinsic activity that was designed as an orally bioavailable prodrug. The active moiety (VNRX-5236) is known to restore in vitro susceptibility to (CTB), an oral cephalosporin, among CTB-resistant SBL-EB.

Methods. CTB-resistant SBL-EB (N = 21) with CTB MICs ≥23 µg/mL and VNRX-5236 MIC range 0.12–2 µg/mL (VNRX-5236 fixed at 4 µg/mL) were evaluated. Carbenapenemases were produced by 9 strains (4 OXA, 5 KPC). Bacterial suspensions (~10^7 CFU/mL) were used to inoculate the thighs of neutropenic mice. A human-simulated regimen of cefotibuten (CTB HSR) equivalent to a 400 mg q12h dosage was developed in infected mice. In dose ranging studies, groups of 3 animals each received the CTB HSR as monotherapy or combined with escalating VNRX-5236 exposures (CTB/VNRX-5236 dose ratios ranging from 10:1 to 1:4). Efficacy was assessed as the change in log_10 CFU/thigh at 24 hours from 0 hour burden. With previous in vivo dose fractionation studies indicating the free area under the VNRX-5236 concentration–time curve to MIC ratio (AUC/MIC) as the PK/PD driver of efficacy, the Hill equation was used to estimate the magnitude required to achieve a static endpoint.

Results. Compared with 0 hour controls (mean log_10 CFU/thigh, 5.7 ± 0.3), the bacterial burden was identical for all isolates increased in saline-dosed controls and CTB HSR groups by 3.1 ± 0.8 and 2.5 ± 0.8 log_10 CFU/thigh, respectively. The addition of VNRX-5236 resulted in bacterial stasis at 20/21 strains; the mean reduction in bacterial burden with the 1:1 CTB/VNRX-5236 dose ratio was 0.2 ± 0.7 log_10 CFU/thigh. A composite assessment of exposure-responses indicated a AUC/MIC target associated with bacterial stasis should be considered when selecting VNRX-7145 doses for clinical studies.

Conclusion. Against CTB-resistant SBL-EB, inclusive of OXA-48- and KPC-producing strains, VNRX-5236 potentiated the in vivo activity of the CTB human-simulated exposure. The identified AUC/MIC target associated with bacterial stasis should be considered when selecting VNRX-7145 doses for clinical studies.

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684. Cardiac Safety in Adults with Community-Acquired Bacterial Pneumonia (CABP) Treated with Leflumadin (LEF) or Moxifloxacin (MOX): Analysis of Leflumadin Evaluation Against Pneumonia (LEAP! 1) and LEAP 2 Study Results
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Background. Preclinical data suggest potential effects of LEF on cardiac interval parameters. We therefore assessed LEF cardiac safety from the LEAP 1/2 trials.

Methods. In LEAP 1, PORT III–V patients received LEF 150mg IV q12h for 5 days or MOX 400mg IV q24h for 7 days, with optional IV-to-oral switch (680mg LEF q12h or 400 mg MOX q24h). In LEAP 2, PORT II–IV patients received oral LEF 400g q12h for 5 days or oral MOX 400mg q24h for 7 days. Patients with known QT prolongation or on medication with potential to prolong the QT interval were excluded as per MOX label. After 5 minutes of rest in the supine position, triplicate 12-lead ECGs were obtained within a 5-minute interval at Screening in both studies, on Days 1/3 in LEAP 1 (predose and ≤15 minutes after first IV dose), and on Days 1/4 in LEAP 2 (predose and 1–3 hours after first oral dose), and sent to a central ECG reader for adjudication.

Results. Of 1,282 randomized/treated patients (n = 641/group), 1,274 had baseline (BL) and post-BL ECG data (n = 636 LEF, n = 638 MOX). Consistent with the resolution of infection, ECGs revealed mean reductions of 7–8 beats/minute for both groups in all studies. The largest mean change in QTcF from BL to post-BL was on Day 3 in LEAP 1 (13.6 and 16.4 msec with IV LEF and MOX, respectively) and on Day 4 in LEAP 2 (9.3 and 11.6 msec with oral LEF and MOX, respectively). The proportion of patients meeting potentially important post-BL QTcF values/changes was comparable between treatment groups (table). In the standardized MedDRA query of Torsade de points/QT prolongation (broad), the most common treatment-emergent adverse event was ECG QT prolongation (n = 4 LEF; n = 5 MOX). All events were nonserious and mild or moderate in severity. 6 events were considered study drug related (n = 4 LEF; n = 2 MOX). 5 events led to study drug discontinuation (n = 2 LEF; n = 3 MOX). In 2 patients with cardiovascular disease, 1 had ventricular arrhythmia on Day 20 (18 days after last LEF dose) and 1 had cardiac arrest on Day 18 (9 days after last MOX dose); both events were fatal and considered unrelated to study drug by investigator.

Conclusion. Mild prolongation of the QTcF interval was seen with LEF and MOX, with somewhat smaller effects seen with LEF. Given the small effect, LEF is unlikely to pose a clinically significant risk of ventricular proarrhythmia with appropriate precautions and use.

Table. Summary of Postbaseline QTcF Changes From Baseline and Values

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685. An In Vivo Investigation of WCK 5222 (Cefepime/Zidebactam) and Currently Available Combination Antibiotic Regimens Against Enterobacteriaceae That Co-express Serine–β-Lactamase (SBL) and Metallo-β-Lactamase (MBL) Enzymes
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Background. Carbapenem-resistant Enterobacteriaceae (CRE) that simultaneously harbor SBLs and MBLs may demonstrate pan-drug resistance. Current
therapeutic options include combinations of aztreonam (ATM), which is resistant to hydrolysis by MBLs, plus cefazidime/avibactam (CZA) or meropenem/vaborbactam (M/V) for coverage of relevant SRLs. However, these selections add a level of complexity to clinical management compared with administration of a single antibiotic as a monotherapy.

Methods. Minimum inhibitory concentrations (MICs) of WCK 5222 (cefpimezidebactam), ATM, CZA, and M/V were determined with Liofilchem MIC Test Strips against SBL- and MBL-positive CRE (N = 15). The gradient diffusion strip (GDS) cross method was used to assess the activities of CZA+ATM and M/V+ATM. Additive interactions as defined by fractional inhibitory concentration indices ≤ 1 would be predicted based upon the known genotypic profiles; thus, the relative activities of the combination regimens were compared with the “zone of hope” (ZOH) test. The size of the ZOH (the zone of inhibited growth) was quantitated by multiplying the observed length of inhibited growth (in mm) adjacent to each GDS from the point of intersection. The Mann–Whitney rank-sum test was used to assess differences.

Results. All isolates (N = 15) contained one MBL and one non-β-lactam, were resistant to ATM, CZA, and M/V with the exception of one isolate intermediate to M/V (MIC = 0.5 μg/mL). WCK 5222 MIC (range) was 0.19–2 μg/mL. The median (interquartile range) ZOH product for CZA+ATM and M/V+ATM was 75.4 (62.8–93.7) and 23.5 (14.1–60.4), respectively (P = 0.002). In strains that produced OXA-type carbapenemases (n = 6), the median ZOH product for CZA+ATM and M/V+ATM was 78.1 and 23.5 (P = 0.002), respectively. In one isolate with SBL and one with β-lactamase (i.e., the MBL), the median ZOH product for CZA+ATM and M/V+ATM was 73.8 and 25.6, respectively (P = 0.052).

Conclusion. WCK 5222 displayed potent in vitro activity against SBL- and MBL-positive CRE, warranting further pre-clinical to clinical evaluation as a monotherapy option. When considering the co-expression of SBL and MBL, CZA+ATM appears to offer enhanced coverage compared with M/V+ATM.

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686. Evaluation of Contezolid Activity to Anaerobic and Gram-positive-cocci Isolates from a Phase 3 Acute Bacterial Skin and Skin Structure Infection Clinical Trial (MRX-I-06)

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Background. Contezolid (MRX-I) is an oxazolidinone in development for the treatment of acute bacterial skin and skin structure infections (ABSSSI). In this study, in vitro susceptibility (S) for Contezolid and comparator agents for Gram-negative (GP) and anaerobic isolates from Phase 3 ABSSSI clinical trials were determined.

Methods. 313 isolates were collected from 65 participated sites and sent to a central laboratory for MIC testing. Clinical isolates included 34 anaerobes (15 Finegoldia magna, 8 Actinomyces spp., 4 Prevotella spp., 3 Propionibacterium avidum, 2 Peptonstreptococcus spp., 1 Veillonella spp. and 1 Bacteroides fragilis), 187 S. aureus (59.7%), 12 S. pyogenes, 5 Enterococcus, and 75 other Gram-positive organisms. Broth microdilution was used to determine MICs of Contezolid, ATM, CZA, and other comparators to facultative isolates. Agar dilution was carried out for the anaerobes.

Results. For both 33 MSSA and 154 MSSA MIC₅₀ values of cefoxitin and linezolid were 2 μg/mL. One E. faecalis showed decreased susceptibility to oxazolidinones (both MIC = 4). 1 mg/L of linezolid and cefoxitin could inhibit 12 S. pyogenes. 2 mg/L of linezolid and cefoxitin could inhibit 15 Finegoldia magna. 0.5 mg/L of linezolid and cefoxitin could inhibit 8 Actinomyces spp. To one Bacteroides fragilis, two Prevotella bivia (including Lecanomonaiva [Intrinsically resistant to vancomycin]) the MIC of cefoxitin or 4 or 8 μg/mL. In general, Contezolid had lower or equal MIC₅₀ values against both GP and ANA species compared with linezolid for all organisms.

Conclusion. Contezolid demonstrated potent in vitro antibacterial activity against Gram-positive and anaerobic isolates tested. These data suggest that cefoxitin might be a beneficial supplement to the arena against MDR Gram-positive infection.

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687. In vitro Activity of a New Generation Oxyprazole Antibiotic Against Acinetobacter spp.

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Background. Acinetobacter spp. resistant to common antibiotics have become a worrying cause of hospital-acquired infections and represent a critical need for innovative new agents in development. New copy was ingesting targeting penicillin-binding proteins (PBPs) based on a non-β-lactam core and incorporating a siderophore moiety (figure) which facilitates transport to the periplasm are being developed which show promise against Gram-negative organisms including Acinetobacter spp.

Methods. YU255911, an example of this new class of antibacterials, was characterized in vitro. Minimum inhibitory concentrations (MICs) were determined by broth microdilution against a collection of 200 previously described (whole-genome sequencing) Acinetobacter isolates including 98 carbapenem-resistant A. baumannii strains. YU255911 antimicrobial activity was also evaluated in combination with currently PBP agents and β-lactamase inhibitors by MIC and disc diffusion testing. All studies were performed according to current Clinical and Laboratory Standards Institute (CLSI) guidelines using iron-depleted media. Breakpoints for ceftazidime were arbitrarily chosen as reference.

Results. Using ceftazidime (breakpoint 58 μg/mL) as a comparator, 175 of the 200 Acinetobacter isolates were susceptible to YU255911, which possessed an MIC₅₀ of 0.5 μg/mL and an MIC₉₀ of 16 μg/mL. This compared favorably to all previously tested β-lactams including penicillins, cephalosporins, monobactams and carbapenems (MIC₅₀ ≥ 16 μg/mL). Against the subset of carbapenem-resistant A. baumannii isolates, YU255911’s potency was similar with an MIC₅₀ of 1 μg/mL. Genetic analysis showed β-lactamase genes, including OXA-23 and other carbapenemases, were common in both YU255911-resistant and susceptible strains.

Conclusion. YU255911 demonstrates promising in vitro potency against a collection of Acinetobacter isolates and compares favorably to β-lactam antibiotics. Understanding interactions with PBP agents and β-lactamase inhibitors is being explored as well as further studies on the mechanism of resistance.

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688. In vitro Activity of Eravacycline, a New Tetracycline Analog, and Comparators Against the Six Most Commonly Isolated Ribotypes of Clostridioides difficile

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Background. Eravacycline is a novel, tetracycline class antibacterial indicated for the treatment of complicated intra-abdominal infections in adults. In clinical trials, patients given eravacycline had a low likelihood of developing Clostridioides difficile infection (CDI). We hypothesized this was likely due, in part, to the in vitro susceptibility of eravacycline vs. comparators on contemporary clinical isolates representing common ribotypes, including isolates with decreased susceptibility to metronidazole and vancomycin.

Methods. Two hundred and thirty-four isolates from our biobank were selected from the six most common ribotypes (F001, F002, F014-020, F027, F106, and F255). Minimum inhibitory concentrations (MIC) at 24 hours were measured according to CLSI guidelines for eravacycline, vancomycin, metronidazole and fidaxomicin. MICs results were tabulated and are presented as the geometric mean by ribotype.

Results. Geometric MIC results are shown in Table 1. Eravacycline was the most potent antimicrobial tested followed by fidaxomicin, metronidazole, and vancomycin. Results were consistent amongst all ribotypes, including isolates with reduced susceptibility to vancomycin and metronidazole.

Conclusion. Eravacycline displayed potent in vitro activity against a large collection of Clostridioides difficile isolates. These data provide insight into why patients given eravacycline had a low likelihood of developing CDI and support further research to better understand the use of eravacycline to prevent or potentially treat patients with CDI.