682. In Vivo Pharmacodynamics of VNRX-7145 in the Neutropenic Murine Thigh Infection Model When Administered in Combination with Humanized Exposures of Twice Daily Cefitobuten (CTB) Against Serine β-Lactamase-Producing Enterobacteriaceae (SBL-EB)

Lindsay M. Avery, PharmD; Kamila Abdelraouf, PhD; David P. Nicolau, PharmD; Hartford Hospital, Hartford, Connecticut

**Session:** 68. Novel Antimicrobials and Approaches Against Resistant Bugs

**Thursday, October 3, 2019: 12:15 PM**

**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 reduce in vitro susceptibility to (CTB), an oral cephalosporin, among CTRB-susceptible SBL-EB.

**Methods.** CTB-resistant SBL-EB (N = 21) with CTB MICs n = 10^4 µg/mL and CTB/VNRX-5236 MIC range 0.12–2 µg/mL (VNRX-5236 fixed at 4 µg/mL) were evaluated. Carbapenemases 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 cefitobuten (CTB HSR) equivalent to a 400 µg 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-5263 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_0-24/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 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 21/21 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 an AUC_0-24/MIC of 9.0 (R^2 = 0.70) was associated with stasis.

**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_0-24/MIC target associated with bacterial stasis should be considered when selecting VNRX-7145 doses for clinical studies.

**Disclosures.** All authors: No reported disclosures.

683. Assessment of Biofilm Eradication and Cytotoxicity of a Novel Polylactogalacturonic Acid + Caprylic Acid Wound Ointment Compared with Antisepctic Wound Ointments

Bahgat Gerges, PhD; Ruth A. Reitzel, PhD; Joel Rosenblatt, PhD; Ray Y. Hachem, MD; Isam I. Raad, MD; UT MD Anderson Cancer Center, Houston, Texas; MD Anderson Cancer Center, Houston, Texas; The University of Texas MD Anderson Cancer Center, Houston, Texas

**Session:** 68. Novel Antimicrobials and Approaches Against Resistant Bugs

**Thursday, October 3, 2019: 12:15 PM**

**Background.** Antisepctic wound ointments are increasing importance from safety, microbiological and public health points of view. Previously, Rosenblatt et al. (2017) has assessed polygalacturonic acid (PG) + caprylic acid (CAP) solution for biofilm eradication and cytotoxicity and compared with KPC-producing strains, VNRX-5236 potentiated the in vivo activity of the CTB human-simulated exposure. The identified AUC_0-24/MIC target associated with bacterial stasis should be considered when selecting VNRX-7145 doses for clinical studies.

**Disclosures.** All authors: No reported disclosures.

684. Cardiac Safety in Adults with Community-Acquired Bacterial Pneumonia (CABP) Treated with Lefamulin (LEF) or Moxifloxacin (MOX): Analysis of Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Study Results

Björn Darpo, MD, PhD; Anita E. Das, PhD; Daniel Stein, MD, PhD; Jennifer Schranz, MD; Steven P. Gelone, PharmD; Jennifer Schranz, MD; Steven P. Gelone, PharmD; CardioCare, ERT, Rochester, New York; Das Consulting, Guerneville, California; Nahbra Therapeutics US Inc., King of Prussia, Pennsylvania

**Session:** 68. Novel Antimicrobials and Approaches Against Resistant Bugs

**Thursday, October 3, 2019: 12:15 PM**

**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, and MOX 400mg IV q24h for 7 days, with optional IV-to-oral switch (600mg LEF q12h or 400 mg MOX q24h). In LEAP 2, PORT III–IV patients received oral LEF 400q12h for 7 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 analysis.

**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 5 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-IV 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

| LEAP 1 | LEAP 2 |
|--------|--------|
| Any postbaseline increase ≥30 msec | Any postbaseline increase ≥50 msec |
| LEF (n=641) | MOX (n=638) |
| LEF (n=641) | MOX (n=638) |
| Any postbaseline increase ≥50 msec | Any postbaseline increase ≥405 msec |
| LEF (n=641) | MOX (n=638) |
| LEF (n=641) | MOX (n=638) |

**Disclosures.** All authors: No reported disclosures.

685. An In Vitro Investigation of WCK 5222 (Cefetim/Zipdebactam) and Currently Available Combination Antibiotic Regimens Against Enterobacteriaceae That Co-express Serine–β-Lactamase (SBL) and Metallo-β-Lactamase (MBL) Enzymes

M. Avery, PharmD; Elias M. Mullane; David P. Nicolau, PharmD; Hartford Hospital, Hartford, Connecticut

**Session:** 68. Novel Antimicrobials and Approaches Against Resistant Bugs

**Thursday, October 3, 2019: 12:15 PM**

**Background.** Carbapenem-resistant Enterobacteriaceae (CRE) that simultaneously harbor SBLs and MBLs may demonstrate pan-drug resistance. Current