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

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs

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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 ≥232 µg/mL and CTB/VNRX-5236 MIC range 0.02–2 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 ceftibuten (CTB HSR) equivalent to a 400 mg q12h dosing 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_{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 in 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_{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 Polygalacturonic Acid + Caprylic Acid Wound Ointment Compared with Antibiotic Wound Ointments

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Background. Antibiotic wound ointments are increasing importance from prevention and treatment of biofilm-related infections. The need for therapeutic agents that specifically target biofilm is highlighted by the difficulties associated with bacterial biofilm eradication. The present study evaluated the biofilm eradication and cytotoxicity of PG+CAP wound ointment compared with commercially available wound ointment comparators.

Methods. Assessment of antimicrobial efficacy was conducted using a well-established biofilm model. Twenty-four-hour biofilm was formed on silicone discs (2017) has assessed polygalacturonic acid (PG) + caprylic acid (CAP) solution for biofilm eradication and cytotoxicity. In this study, we assessed biofilm eradication and cytotoxicity of PG+CAP wound ointment with commercially available wound ointment comparators.

Results. In 24-hour exposure of PG+CAP ointment able to completely eradicate C. albicans (CA), MDR Pseudomonas aeruginosa (PS), and MRSA. Additionally, PG+CAP was significantly more efficacious than BZK for MRSA (P = 0.002) and PS (P = 0.015) and PHMB for MRSA (P = 0.002).

In the trypan blue exclusion test PG+CAP yielded 96.29% viable cells compared with 77.83% and 83.25%, for the QUAT and PHMB ointments, respectively. Fibroblasts treated with 2% PG+CAP retained 86.6% of metabolic activity compared with untreated cells while the QUAT and PHMB ointments retained 37.5% and 44.5% metabolic activity, respectively.

Conclusion. PG+CAP has enhanced effects on eradication of biofilm in vitro as well as less cytotoxicity in vitro relative to the antiseptic wound ointments. Further in vivo studies are warranted.

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

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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, 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 II–IV patients received oral LEF 400q12h 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 ±13 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 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 MedDTA query of Torso 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 | P = 0.02 | P = 0.96 |
| Any postbaseline increase >50 msec | P = 0.02 | P = 0.96 |

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685. An In Vitro Investigation of WCK 5222 (Cefepime/Zidovudine) 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