682. In Vivo Pharmacodynamics of VNRX-7145 in the Neutropenic Murine Thigh Infection Model When Administered in Combination with Humanized Exposures of Twice Daily Cefditoren (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 reduce in vivo susceptibility to (CTB), an oral cephalosporin, among CTRB-resistant SBL-EB.

Methods. CTB-resistant SBL-EB (N = 21) with CTB MICs ≥232 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 (∼10^9 CFU/mL) were used to inoculate the thighs of neutropenic mice. A human-simulated regimen of cefditoren (CTB HSR) equivalent to a 400 mg q12h dosage was developed in infected mice. In does 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 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 CFU/thigh, 5.7 ± 0.3), the bacterial load for all isolates increased in saline-dosed controls and CTB HSR groups by 3.1 ± 0.8 and 2.5 ± 0.8 log 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 CFU/thigh. A composite assessment of exposure-responses indicated a [AUC/MIC/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/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 Polylactogluconuronic Acid + Caprylic Acid Wound Ointment Compared withAntiseptic Wound Ointments

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Background. Antiseptic wound ointments are increasing importance from safety, microbiological and public health points of view. Previously, Rosenblatt et al. (2017) has assessed polylactogluconuronic acid (PG + caprylic acid (CAP) solution for biofilm eradication efficacy and cytotoxicity. In this study, we assessed 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 and exposed wound ointments for 2 hours. Discs were then sonicated and cultured to quantitate any remaining viable biofilm. To assess cytotoxic effects of wound ointments, L-929 fibroblasts were exposed to 2% extracts of each ointment. The trypan blue exclusion test was used to access cell viability and Alamar blue was used to assess metabolic function. Ointments tested include, PG+CAP formulated in an inert ointment base, benzalkonium chloride quaternary ammonia antiseptic ointment (BZK), polyhexamethylene biguanide (PHMB) antiseptic ointment, and 2-hydroxyethylcellulose + glycerol inert ointment base. Untreated fibroblast cells were used as controls.

Results. Within 2 hours of exposure, 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 86.66% 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 toxicity 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 or 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-V patients received oral LEF 150q12h 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 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 | 58 (2.1) | 27 (2.3) | 56 (1.4) | 10 (1.9) | 113 (17.9) | 38 (2.2) |
| Any postbaseline increase >50 msec | 7 (2.6) | 9 (3.3) | 4 (1.1) | 7 (1.9) | 11 (1.7) | 16 (2.5) |
| Any postbaseline increase >400 msecs | 13 (4.8) | 12 (4.4) | 7 (1.9) | 9 (2.5) | 20 (3.1) | 21 (3.3) |

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685. An In Vivo Investigation of WCK 5222 (Cefepime/Zidobactam) 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