subgroups were defined by any medical history of diabetes (type 1, type 2, or unspecified), or no medical history of diabetes. Efficacy outcomes were early clinical response (ECR) and investigator’s assessment of clinical response at post-treatment evaluation (PTE), as defined for each indication. Safety was assessed by treatment-emergent adverse events (TEAEs) and laboratory measures, and data were pooled across the three studies.

Results. A total of 2,136 patients were included, of whom 238 (11.1%) had any history of diabetes (n = 105 for ABSSSI, n = 113 for CABB). In the pooled ABSSSI studies and the CABB study, clinical success at ECR and PTE was similar between patients with or without diabetes, and between OMC and the respective comparator (figure). TEAEs and serious TEAEs, respectively, were reported in similar numbers of OMC, L2D-, and MOX-treated patients with diabetes (41.8–49.3%, 4.5–7.0%) and without (41.2–48.3%, 1.6–6.9%). Rates of nausea and vomiting, respectively, in patients with diabetes were similar across treatment arms: OMC (5.0%, 5.9%), L2D (7.5%, 6.0%), MOX (7.0%, 2.8%).

Conclusions. Efficacy and safety were similar and consistent in patients with or without diabetes.

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701. Comparison of MIC Results for Gepotidacin by Agar Dilution and Broth Microdilution Methods

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Methods. MIC results for 130 clinical isolates of Gram-positive and Gram-negative organisms were determined by μ dilution of the reference method divided by the total number of results. Equivalency was defined using the 95% criteria from the FDA’s class II controls document.

Results. Equivalency (EA >95%) was established between AD and BMD for each of these species/groups; OMC, L2D-, and MOX-treated patients with diabetes (41.8–49.3%, 4.5–7.0%) and without (41.2–48.3%, 1.6–6.9%). Rates of nausea and vomiting, respectively, in patients with diabetes were similar across treatment arms: OMC (5.0%, 5.9%), L2D (7.5%, 6.0%), MOX (7.0%, 2.8%).

Conclusions. Efficacy and safety were similar and consistent in patients with or without diabetes.

Disclosures. All authors: No reported disclosures.

702. Hepatic Safety Among Patients Treated with Anti-Fungal Triazole Agent Posaconazole: Characterization of Adverse Events in a Manufacturer’s Safety Database

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
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Background. Second-generation triazoles including posaconazole are highly efficacious for the prophylaxis and salvage treatment of life-threatening invasive fungal infections. All triazoles have been associated with hepatic adverse events (AEs), which may affect their clinical use; however, risk factors for these AEs are poorly defined.

Methods. Reports of hepatobiliary AEs for posaconazole from clinical trials and post-market use in our company’s global safety database were reviewed to characterize concomitant medical conditions and drug exposure.

Results. As of 2018, 444 cases of hepatic AEs were reported; 139 (31%) led to discontinuation of posaconazole. Most hepatic AEs had a time onset >20 days (55.5%). The most frequent AEs reported (per Medical Dictionary for Regulatory Activities) were: Hyperbilirubinemia (17%); Hepatotoxicity (13.5%); Hepatic function abnormal (11.5%); and Hepatocellular injury (11.3%). Most patients were adults (18–64 years old) (65%). Hematological malignancy (128 cases, 29%) and hematopoietic stem cell transplant (91 cases, 20%) were leading concurrent medical conditions. Notably, 75% of the cases reported exposure to other drugs (often multiple ones) with known risks for drug-induced liver injury (DILI, e.g., acetaminophen, cyclosporine). Among 139 cases in which posaconazole treatment was discontinued due to hepatic AEs, 6 of the 20 most frequently used co-medications (used by >4.5% of the cases) were classified by the FDA in its DILIRank as “Most-DILI-Concern” (resulting in drug withdrawal, or prominent labeling for severe DILI risk in boxed warning or warnings and precautions), and 7 were “Less-DILI-concern” drugs (DILI risk language in warnings or precautions or adverse reactions). Similarly, of the top 35 concomitant medications for the entire group, 9 are classified as “Most-DILI-Concern” and 12 are “Less-DILI-Concern” drugs.

Conclusion. The use of concomitant medications with known risks for hepatic injury appears to be an important contributor to the development of hepatotoxicity in patients treated with posaconazole. Co-administration of these drugs with anti-fungal triazole agents such as posaconazole, when needed, will continue to be carefully monitored.

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703. In Vitro Activity of Lefamulin Against Bacterial Pathogens Causing Community-Acquired Bacterial Pneumonia (CABP): SENTRY Surveillance 2017–2018 Results from the United States (US)

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Background. Lefamulin (LEF), a novel pleuromutilin protein synthesis inhibitor in development for use as an empiric IV and oral monotherapy for CABP, recently demonstrated safety and efficacy in two phase 3 trials in adults with CABP (PORT II–V). LEF IV or IV/oral (5–7 days) or 10 days for meticillin-resistant Staphylococcus aureus (MRSA) and LEF oral (5 days) were noninferior to MOX IV or IV/oral (7 days; 10 days for MRSA) and MOX oral (7 days) in patients with CABP caused by the most prevalent typical and atypical bacterial pathogens. This study investigated the in vitro activity of LEF and comparators against bacterial respiratory pathogens collected in the United States in 2017 and 2018.

Methods. As part of the SENTRY Surveillance Programme, isolates (n = 2299, 1 patient) were collected from 39 medical centers in the United States from patients with community-acquired respiratory tract infections (1812/2299 [78.8%]) and pneumonia in hospitalized patients (457/2299 [21.2%]). LEF and comparators were tested by broth microdilution and CLSI (2019) breakpoints were applied.

Results. LEF demonstrated potent antibacterial activity against all pathogens tested and was unaffected by resistance to other antibiotic classes (table). Streplococcus pneumoniae isolates were largely susceptible (~98%) to most comparators; however, 45.6% and 20.4% were resistant (R) to macrolides and tetracycline, respectively. LEF exhibited a MIC90 of 0.12/0.25 mg/L for S. pneumoniae, including all R subsets. Among S. aureus isolates, and particularly MRSA, resistance to macrolides was high (48.5% and 81.2% R, respectively). LEF showed a MIC90 of 0.06/0.12 mg/L for S. aureus, including all R subsets. Haemophilus influenzae isolates were susceptible to all comparators except for ampicillin (31.4% R) and trimethoprim-sulfamethoxazole (35.3% R). LEF displayed a MIC90 of 0.52/2 mg/L for H. influenzae isolates. Moraxella catarrhalis isolates, which were largely β-lactamase positive (98%), were susceptible to LEF and all comparators.

Conclusion. LEF displayed potent in vitro activity against contemporary CABP pathogens collected in the United States. LEF activity was unaffected by resistance to other antibiotic classes, including fluoroquinolones, macrolides, β-lactams, and tetracyclines.
704. Incidence and Patient Outcomes of S. aureus Isolates from Acute Bacterial Skin and Skin Structure Infections (ABSSSI) with High Iclaprim MIC values in Phase 3 REVIVE Trials

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Methods. REVIVE-1 and REVIVE-2 studies were 600-patient, double-blinded, randomized, (1:1), active-controlled trials among patients with ABSSSI that compared the safety and efficacy of iclaprim 80 mg fixed dose with vancomycin 15 mg/kg (adjusted for renal function), both administered intravenously over 2 hours every 12 hours (on-dialysis treatment periods for the HD group). Subjects in the Normal and Severe groups received a single 1-hour 150 mg iclaprim infusion. Subjects in the HD group started HD within 1 hour after iclaprim infusion.

Results. The incidence of culture confirmed S. aureus isolates among patients with an iclaprim MIC ≥8 µg/mL, a concentration that is not systemically achievable, were determined among patients from two Phase 3 studies for the treatment of ABSSSI, REVIVE-1 and -2.

Conclusion. No dosage adjustment is required for LEF when treating subjects with severe renal impairment, and LEF can be administered without regard to HD timing. LEF was generally well tolerated in all subjects regardless of renal function status.

Disclosures. All authors: no reported disclosures.

705. Pharmacokinetics (PK) and Safety of Lefamulin (LEF) After Single Intravenous Dose Administration in Subjects With Impaired Renal Function and in Those Requiring Hemodialysis

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Methods. In the open-label study, subjects were allocated to 1 of 3 groups based on renal function level. Severe subjects (estimated glomerular filtration rate <30 mL/min/1.73 m², not on HD, Severe) were matched (gender, age, and weight) to subjects with normal renal function (estimated creatinine clearance ≥90 mL/minute, Normal). Subjects in the Normal and Severe groups received a single 1-hour 150 mg LEF infusion. Subjects in the HD group started HD within 1 hour after LEF infusion ("On-dialysis") and on a nondialysis day ("Off-dialysis"). Blood and urine samples were collected predose and over a 36-hour period postdose for PK analysis. LEF and BC-8041 were assayed in plasma and urine with validated methods. Safety assessments included treatment-emergent adverse events (TEAEs), labs, vital signs, and electrocardiograms.

Conclusion. 23 subjects enrolled in and completed the study (n = 7, Normal; n = 8, Severe; n = 8, HD). LEF and BC-8041 pharmacokinetic parameters (table) were comparable between the Normal and Severe groups and between the On-dialysis and Off-dialysis treatment periods for the HD group. The majority of LEF and BC-8041 were excrated primarily in the filtered and fecal routes with no apparent recycle after filtration into dialyse. TEAEs were reported in 2 (28.6%) subjects in the Normal group, 4 (50%) in the Severe group, and 4 (50%) in the HD group. None of the TEAEs were serious or led to study drug discontinuation. Within 4 h post-dose, the maximum mean change from baseline in the QTcF interval was 8.9, 6.6, 15.9, and 17.6 msec in the normal, severe, on-dialysis, and off-dialysis groups, respectively.

Disclosures. All authors: no reported disclosures.

706. In Vitro Activity of Ceftazidime–Avibactam and Comparator Agents Against MDR Enterobacteriaceae and Pseudomonas aeruginosa Collected in Latin America During the ATLAS Global Surveillance Program 2016–2017

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Methods. Nonduplicate clinical isolates were collected in 2016–2017 in 6 countries in Latin America. Susceptibility testing was performed using CLSI broth microdilution and interpreted using CLSI 2019 and FDA (tigecycline) breakpoints. MDR was defined as nonsusceptible (NS) (intermediate or resistant) to ≥3 classes and ≥2 MDR classes. Resistance caused by these β-lactamases often results in multidrug-resistance (MDR). This study evaluated the in vitro activity of CAZ-AVI and comparators against MDR Enterobacteriaceae and Pseudomonas aeruginosa isolates collected from patients in Latin America.

Results. The activity of CAZ-AVI and comparators against all isolates and MDR subsets is shown in the table. The MDR rates ranged from 28.4% among E. cloacae to 41.5% among K. pneumoniae. CAZ-AVI was active against >97% of Enterobacteriaceae isolates and maintained activity against >92% of MDR isolates of the examined species. No other tested drug consistently exceeded this activity. Among P. aeruginosa, CAZ-AVI was active against 87% of all isolates and 63% of MDR isolates; only colistin was more active. The two most common MDR phenotypes among Enterobacteriaceae were (1) NS to aztreonam, cefepime, levofloxacin, colistin, meropenem, and piperacillin-tazobactam and (2) NS to aztreonam, cefepime, levofloxacin, colistin, meropenem, and piperacillin-tazobactam (n = 301, 21% of all MDR isolates; 99.7% susceptible to CAZ-AVI). The two most common MDR phenotypes among P. aeruginosa were (1) NS to all sentinel drugs except colistin (n = 154, 33% of all MDR isolates;