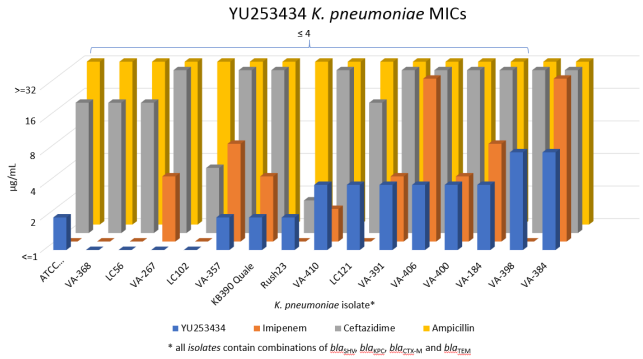

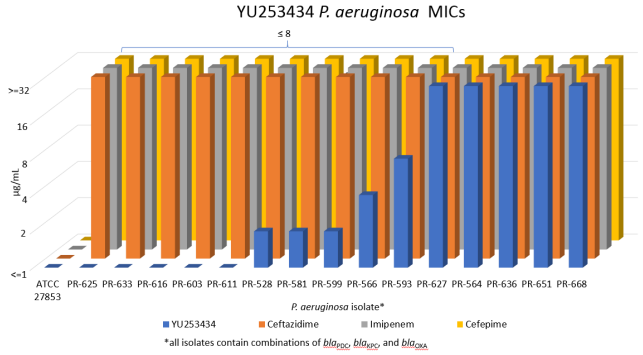

Disclosures. **All authors:** No reported disclosures.

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

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. LEF efficacy and safety were shown in 2 noninferiority trials (LEAP 1/2) vs. MOX in adults with CABP. We assessed the hepatobiliary safety of LEF based on pooled analyses of LEAP 1/2 data.

Methods. In LEAP 1, PORT III–V patients received LEF 150 mg IV q12h for 5–7 days or MOX 400 mg IV q24h for 7 days, with optional IV-to-oral switch (600 mg LEF q12h or 400 mg MOX q24h). In LEAP 2, PORT II–IV patients received oral LEF 600 mg q12h for 5 days or oral MOX 400mg q24h for 7 days. Exclusion criteria included infection with HBV/HCV, acute hepatitis, cirrhosis, AST or ALT >5xULN, total bilirubin >3xULN (unless Gilbert's disease), AST or ALT >3xULN and total bilirubin >2xULN, and manifestation of end-stage liver disease. Hepatic safety was assessed from baseline (BL) and multiple post-BL blood samples using a central laboratory, TEAEs, and expert consultant adjudication. Pooled analyses included all randomized/treated patients (safety population).

Results. Of 1282 randomized/treated patients, 1251 had BL and post-BL hepatobiliary data (table). Post-BL distribution of ALT/AST was generally similar for both groups, although ALT >AST in the absence of muscle injury or alcohol use. Overall, rates of patients experiencing an increase in ALT/AST >3xULN, ALP >2xULN, or total bilirubin >1.5xULN were low (table). Patients with elevated vs. normal BL transaminases (TAs) were more likely to have post-BL elevations >3xULN, but the vast majority remained <5xULN. Among patients with ALT >5xULN, peak increases were generally seen in the first week after the first LEF dose and declined to within/near normal levels by late follow-up (day 28); for MOX, time to peak ALT was less consistent (figure). No LEF pt and 1 MOX pt met laboratory criteria for Hy's Law. Elevations in TAs were reversible, with no evidence of chronic injury. The LEF injury pattern was predominantly hepatocellular (50.0%)/mixed (40.0%), with no apparent gender, age, or ethnic predominance. TEAEs in the hepatobiliary disorders system organ class were reported in 6 (0.9%) LEF patients and 6 (0.9%) MOX patients, with similar levels seen in patients with elevated BL TAs. There were no symptomatic patients, severe disease, or evidence of hypersensitivity.

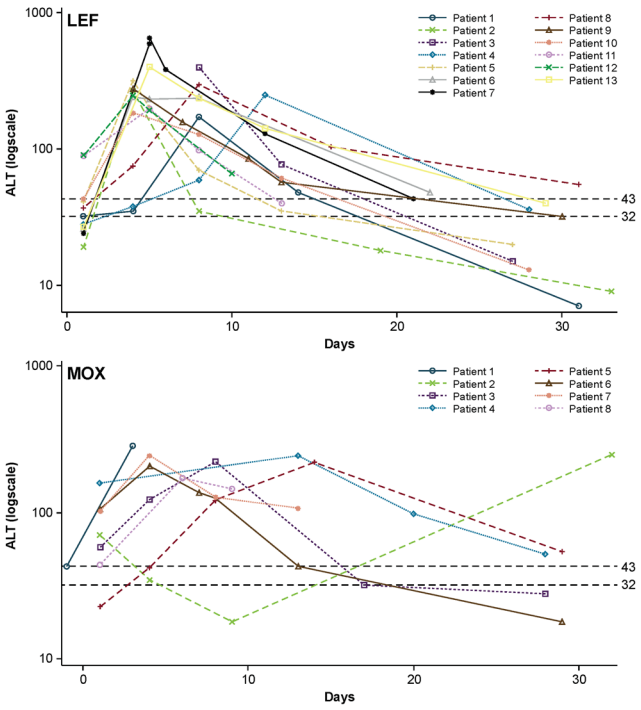
Conclusion. Low incidences of hepatobiliary parameter elevations and TEAEs were observed, with no apparent differences between LEF and MOX.

Table. Maximum Postbaseline Increases in Hepatobiliary Parameters

	LEAP 1		LEAP 2		Pooled	
n (%)	LEF (n=268)	MOX (n=267)	LEF (n=355)	MOX (n=361)	LEF* (n=623)	MOX† (n=628)
ALT >3×ULN	19 (7.1)	17 (6.4)	15 (4.2)	17 (4.7)	34 (5.5)	34 (5.4)
ALT >5×ULN	6 (2.2)	5 (1.9)	7 (2.0)	3 (0.8)	13 (2.1)	8 (1.3)
ALT >10×ULN	1 (0.4)	0	1 (0.3)	0	2 (0.3)	0
AST >3×ULN	11 (4.1)	7 (2.6)	12 (3.4)	8 (2.2)	23 (3.7)	15 (2.4)
AST >5×ULN	2 (0.7)	2 (0.7)	6 (1.7)	5 (1.4)	8 (1.3)	7 (1.1)
AST >10×ULN	1 (0.4)	0	1 (0.3)	0	2 (0.3)	0
ALP >2×ULN	5 (1.9)	5 (1.9)	14 (3.9)‡	6 (1.7)‡	19 (3.0)‡	11 (1.7)‡
Total bilirubin >1.5×ULN	3 (1.1)	3 (1.1)	3 (0.8)	3 (0.8)	6 (1.0)	6 (1.0)
Total bilirubin >2×ULN	0	2 (0.7)	2 (0.6)	0	2 (0.3)	2 (0.3)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LEF=lefamulin; MOX= moxifloxacin; ULN=upper limit of normal.
*Lefamulin 150 mg IV / 600 mg oral.
†Moxifloxacin 400 mg IV / 400 mg oral.
‡For LEAP 2: LEF, n=357; MOX, n=362. For pooled analysis: LEF, n=625; MOX, n=629.

Figure. Individual ALT Values for Patients With Postbaseline ALT >5xULN



ALT=alanine aminotransferase; LEF=lefamulin; MOX=moxifloxacin; ULN=upper limit of normal.
Note: The ALT ULN range for the central laboratory is 32-43 U/L, depending on age and sex.

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700. Safety and Efficacy of Omadacycline in Patients with Diabetes in Phase 3 Clinical Studies

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

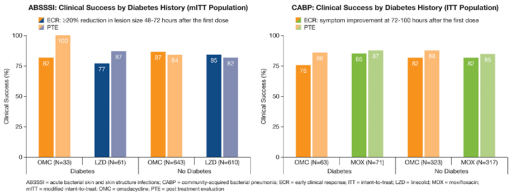
Background. The risk of serious infections and poor treatment outcomes is reported to be higher in patients with diabetes compared with the general population. Omadacycline (OMC) is an intravenous (IV) and oral aminomethylcycline antibiotic approved in the US to treat acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adults. Here we assessed safety and efficacy results from OMC Phase 3 studies (ABSSSI: Omadacycline in Acute Skin and skin structure Infections Study [OASIS]-1 and OASIS-2; CABP: Omadacycline for Pneumonia Treatment In the Community study [OPTIC]), by diabetes history.

Methods. In OASIS-1 (IV to optional oral medication) and OASIS-2 (oral only), patients were randomized to OMC or linezolid (LZD) for 7–14 days. In OPTIC, patients were randomized to IV OMC or moxifloxacin (MOX) for 7–14 days, with optional transition to oral medication. Data from OASIS-1 and OASIS-2 were pooled, and patient

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 2,150 patients were included, of whom 238 (11.1%) had any history of diabetes (n = 105 for ABSSSI, n = 133 for CABP). In the pooled ABSSSI studies and the CABP 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-, LZD-, 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%, 5.0%), LZD (7.5%, 6.0%), MOX (7.0%, 2.8%).

Conclusion. Omadacycline efficacy and safety were similar and consistent in patients with or without diabetes.



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

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

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in clinical development for the treatment of gonorrhea and uncomplicated UTI (acute cystitis). Gepotidacin selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism not utilized by any currently approved therapeutic agent and demonstrates *in vitro* activity against most target pathogens resistant to established antibacterials, including fluoroquinolones. This study tested the equivalency of minimal inhibitory concentrations (MICs) obtained by 2 reference susceptibility testing methods, agar dilution (AD) and broth microdilution (BMD), for gepotidacin against Gram-positive and Gram-negative organisms.

Methods. Susceptibility testing for both methods was performed on a total of 733 clinical isolates recovered largely in 2016 from over 120 medical centers worldwide. For *N. gonorrhoeae*, only the AD method is recommended by CLSI, therefore BMD was performed using Fastidious Broth for comparison purposes. Essential agreement (EA) based on evaluable results was calculated as the number of isolates with MICs within one 2-fold 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. The EA observed for gepotidacin with these 2 methods was 85.8% overall and 98.3% when *H. influenzae* and *N. gonorrhoeae* isolates were excluded. Slightly higher gepotidacin MICs were observed when tested by BMD for each of these species/groups; this trend was especially prominent for *E. coli* and *S. pyogenes*. Gepotidacin tested against *H. influenzae* (73.1%) or *N. gonorrhoeae* (28.6%) species had much lower EAs.

Conclusion. Equivalency (EA >95%) was established between AD and BMD methods for determining gepotidacin susceptibility results against *Staphylococcus* spp., *Streptococcus* spp. and *E. coli*. However, for *N. gonorrhoeae* and *H. influenzae*, equivalency between the 2 methods was not established; therefore, future antimicrobial susceptibility testing for gepotidacin against these organisms should adhere to the methods for which quality control ranges and breakpoints are approved.

Organism / organism group (number of organisms)	% essential agreement[b]	No. of isolates (log_2 difference[a]) Higher agar ← dilution MIC				Higher broth microdilution MIC →		
		≤ -3	-2	-1	0	1	2	≥ 3
Gepotidacin								
All isolates (718)	85.8	16	80	97	318	201	5	1
Isolates excluding *H. influenzae* and *N. gonorrhoeae* (523)	98.3	1	2	14	302	198	5	1
E. coli (102)	97.1				48	51	3	
Staphylococcus spp. (110)	98.2			3	71	34	2	
S. aureus (80)	97.5			2	53	23	2	
S. saprophyticus (30)	100.0			1	18	11		
Streptococcus spp. (311)	98.7	1	2	11	183	113		1
S. pneumoniae (101)	100.0			4	79	18		
β-hemolytic streptococci (105)	100.0				45	60		
S. pyogenes (77)	100.0				27	50		
S. agalactiae (28)	100.0				18	10		
Viridans group streptococci (105)	96.2	1	2	7	59	35		1
H. influenzae (104)	73.1	2	26	64	12			
N. gonorrhoeae (91)	28.6	13	52	19	4	3		

[a] The log_2 dilution difference calculated as the log_2 difference between the broth microdilution and agar dilution MIC value.

[b] Essential agreement calculated as the number of broth microdilution and agar dilution MIC values for each isolate that are ±1 log_2 dilution (shaded values), divided by the total number of isolates.

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
Thursday, October 3, 2019: 12:15 PM

Background. Second-generation triazoles including posaconazole are highly efficacious for the prophylaxis and salvage treatment of life-threatening invasive fungal diseases. All triazoles have been associated with hepatic adverse events (AEs), which may affect their clinical use; however, risk factors for those 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 to onset >20 days (55.5%). The most frequent AEs reported (per Medical Dictionary for Regulatory Activities) were: Hyperbilirubinaemia (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, cytarabine, 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 and 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.

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

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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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

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; 10 days for methicillin-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 (487/2299 [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). *Streptococcus pneumoniae* isolates were largely susceptible (>80%) to most comparators; however, 45.6% and 20.4% were resistant (R) to macrolides and tetracycline, respectively. LEF exhibited a $MIC_{50/90}$ 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 $MIC_{50/90}$ 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 $MIC_{50/90}$ of 0.5/2 mg/L for *H. influenzae* isolates. *Moraxella catarrhalis* isolates, which were largely β-lactamase positive (98%), were susceptible to 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.