comparator agents were S tested by reference broth microdilution methods at a central laboratory. Breakpoints for the following organizations were applied when available: CLSI, EUCAST, USCAST, and US FDA.

Results. PLZ was active against 95.5% and 98.0% of isolates as per US FDA (≤2 mg/L) and USCAST (≤4 mg/L) criteria, respectively. S rates as per US FDA and USCAST criteria were 97.4% and 90.2% for AMK, 86.4% and 85.6% for GEN, and 83.8% and 81.1% for TOB, respectively (Table). CLSI and US FDA breakpoints were identical for these three older aminoglycosides, and EUCAST breakpoints were identical for GEN and TOB and one doubling dilution higher for AMK when compared with USCAST. Per US FDA criteria, carbapenem-resistant ENT (CRE) S rates to PLZ and AMK were 71.5% and 58.3%, respectively. Differences in S rates between PLZ and AMK were higher when applying USCAST for resistant subsets, such as CRE (72.2% versus 38.5%, respectively), ESBL-phenotype (92.7% versus 72.4%, respectively), and multidrug-resistant isolates (n=1,348; 88.6% versus 59.6%, respectively). GEN and TOB exhibited limited activity against ENT resistant subsets.

Conclusion. PLZ retained potent activity against ENT, including resistant subsets. The discrepancies among the S rates for aminoglycosides were greater when applying breakpoints generated using the same stringent contemporary methods applied to determine PLZ breakpoints.

Table 1

Breakpoint setting organization/ organism group (number tested)	% Susceptible			
	Plazomicin	Amikacin	Gentamicin	Tobramycin
All *Enterobacterales* (9,303)				
CLSI	NA[a]	97.4	86.4	83.8
EUCAST	NA	95.5	85.6	81.1
USCAST	98.0	90.2	85.6	81.1
US FDA	95.5	97.4	86.4	83.8
CRE (403)				
CLSI	NA	58.3	42.2	17.4
EUCAST	NA	45.7	40.4	14.6
USCAST	72.2	38.5	40.4	14.6
US FDA	71.5	58.3	42.2	17.4
ESBL-phenotype (1,907)				
CLSI	NA	88.7	52.7	38.7
EUCAST	NA	82.6	51.8	35.0
USCAST	92.7	72.4	81.8	35.0
US FDA	91.7	88.7	52.7	38.7

[a] NA, not available.

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1279. In Vitro Activity of Nacubactam (OP0595) Alone and in Combination with β-Lactams against β-Lactamase-Producing Enterobacterales Isolated in Japan

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Session: P-58. Novel Agents

Background. Nacubactam (NAC) is a novel serine β-lactamase inhibitor in clinical development, and inhibits Ambler class A, class C, and some class D β-lactamases. In addition, it has penicillin-binding protein (PBP) 2-dependent antibacterial activity and an 'enhancer' effect when combined with β-lactams bound to PBP3. This study assessed the in vitro activity of NAC alone and in combination with β-lactams against IMP-type metallo-β-lactamase-producing and ESBL-producing Enterobacterales isolated in Japan.

Methods. The MICs for the clinical isolates in Japan were determined and time kill studies were performed. IMP and ESBL genes were detected by PCR. The MICs were determined by broth microdilution method following CLSI methodology. β-lactams and NAC were tested as a ratio of 1:1. Time kill profiles were also studied according to CLSI methodology.

Results. The MIC_{50}/MIC_{90}s of NAC alone against 112 IMP-producing Enterobacterales and 154 ESBL-producing Enterobacterales were 2/ >32 and 2/8 mg/L, respectively. Regarding the MICs of cefepime (FEP)/NAC and aztreonam (ATM)/NAC against IMP-producing isolates, the MIC_{90}s were 2 and 1 mg/L and the MIC ranges were 0.06 - 32 and 0.06 - 4 mg/L, respectively. The MIC_{90}s of FEP/NAC and ATM/NAC against ESBL-producing isolates were 0.5 and 1 mg/L. These MIC_{90}s of β-lactam/NAC against IMP-producing and ESBL-producing isolates were significantly lower than those of β-lactam alone (>128 mg/L). The highest MIC of ATM/NAC against IMP-producing isolates was lower than that of FEP/NAC. In addition, bactericidal activities of β-lactam/NAC were observed at the lower concentration of β-lactam compared to that of β-lactam alone.

Conclusion. NAC in combination with β-lactams showed excellent in vitro activities against not only ESBL-producing Enterobacterales but also IMP-producing Enterobacterales isolated in Japan. ATM/NAC tended to show higher antimicrobial effect against IMP-producing isolates by the enzyme stability of ATM. These results support the complex activities of NAC which works as a β-lactamase inhibitor, an antibacterial agent and also an enhancer when combined with β-lactams. Furthermore, these will be useful for selecting a partner β-lactam for NAC.

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1280. In-Vitro Activity of Cefiderocol, Imipenem/Relebactam, & Ceftazidime/Avibactam in Ceftolozane/Tazobactam Resistant Strains of Multidrug Resistant Pseudomonas aeruginosa

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Session: P-58. Novel Agents

Background. The activity of imipenem/relebactam (I/R), ceftazidime/avibactam (CZA) and cefiderocol (FDC) were evaluated against clinical isolates of multidrug resistant (MDR) strains of *P. aeruginosa* which was resistant to ceftolozane/tazobactam (C/T). The recent increase of MDR *P. aeruginosa* strains isolated from clinical samples has prompted research and development of new antimicrobials that can withstand its multiple resistance mechanisms. C/T is an effective option for treatment of MDR *P. aeruginosa* in our facility with only 10% of resistance in MDR strains, but the emergence of resistance may occur due to the presence of a carbapenemase gene or an ampC mutation.

Methods. Antimicrobial susceptibility testing for C/T Etest® (bioMérieux, Inc.) were performed on all MDR strains initially screened by the VITEK2® (bioMérieux, Inc.). 10% (n=20) of all MDR isolates were resistant to C/T by the CLSI 2019 breakpoints. These resistant isolates were tested for presence of a carbapenemase gene using the GeneXpert CARBA-R (Cepheid®) PCR and against CZA Etest® (bioMérieux, Inc.) I/R gradient strips (Liofilchem®) and FDC broth microdilution (Thermo Scientific™ Sensititre™).

Results. A total of 20 clinical isolates of MDR *P. aeruginosa* resistant to C/T were tested following standardized CLSI protocols and techniques. All 20 isolates were screened for the presence of a carbapenemase gene (*bla*VIM, *bla*NDM, *bla*KPC, *bla*OXA-48, *bla*IMP). A *bla*VIM gene was detected in 6 (30%) out of 20 isolates. FDC demonstrated the greatest activity with 85% (n=17) of susceptible isolates (CLSI MIC <4μg/dL). CZA (CLSI MIC <8μg/dL) and I/R (FDA MIC <2μg/dL) showed 15% (n=3) and 10% (n=2) of susceptible isolates respectively. FDC was active against all 6 *bla*VIM isolates, where all 6 strains were resistant to CZA and I/R as expected. 3 isolates tested non-susceptible against FDC; additional characterization was not performed at this time.

Conclusion. Based on these results, FDC demonstrated the greatest in-vitro activity against C/T resistant strains of MDR *P. aeruginosa*. FDC also demonstrated activity against all 6 MDR *P. aeruginosa* carrying *bla*VIM gene. FDC is a strong option to consider on MDR *P. aeruginosa* strains based on a resistance testing algorithm and a cost/effective protocol.

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1281. Longitudinal and Spatial Variation in the Human Microbiome in a Phase 2a Clinical Study of Gepotidacin in Adult Females with Uncomplicated Urinary Tract Infection

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Session: P-58. Novel Agents

Background. Gepotidacin (GSK2140944) is a first in class novel oral triazaacenaphthylene bacterial topoisomerase inhibitor. In this study, we evaluated the potential

impact of orally administered gepotidacin on the human microbiome, across three body-sites and at three specific time-points, as an exploratory endpoint in a Phase 2a clinical trial for the treatment of uncomplicated Urinary Tract Infection (uUTI) (ClinicalTrials.gov: NCT03568942).

Methods. Through DNA sequencing of the 16S rRNA variable region 4, we analyzed samples collected with consent from study subjects from the gastrointestinal tract or GIT (stool), pharyngeal cavity (saliva swabs) and vagina (vaginal swabs). Samples were taken at three time points which were pre-dosing (Day 1), end of dosing (Day 5) and follow-up visit (Day 28 ±3 days). A total of 156 samples were collected and 141 samples passed quality control criteria for DNA sequence analyses. Using a rigorous computational work-flow, changes in microbiome diversity and relative abundances of microbial species were quantified.

Results. Time series analyses showed that microbiota alpha diversity dropped, relative to pre-dose, by the end of gepotidacin dosing but trended a return trajectory to original pre-dose levels by the follow-up visit, for all body sites (Figure). However, the character and extent of the microbiota changes varied by location. The relative ordering from least to greatest changes in microbiota diversity of body sites is vaginal, pharyngeal and GIT. We found no statistically significant occurrences of pathogen related taxa, such as *Clostridioides* or *Enterobacterales* spp., at the final timepoints.

Conclusion. Since gepotidacin is both orally dosed and elimination includes the biliary route, it was predicted to affect the GIT microbiome, however changes in the distal pharyngeal and vaginal microbiota were also observed. Gepotidacin alteration of the endogenous microbial community appears to be temporary and reversible as microbiota diversity rebounded to near pre-dosing status within a period of several weeks. Our study illustrates how microbiome analyses in antibiotic clinical studies can quantify patterns of microbiota disruption and recovery.

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1282. Manogepix, the Active Moiety of the Investigational Agent Fosmanogepix, Demonstrates In vitro Activity Against Members of the Fusarium oxysporum and Fusarium solani Species Complexes

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Session: P-58. Novel Agents

Background. Invasive fusariosis is associated with marked morbidity and mortality in immunocompromised hosts, and treatment options are limited. Common etiologic agents include members of the *F. oxysporum* and *F. solani* species complexes (FOSC and FSSC, respectively). Manogepix (MGX), the active moiety of fosmanogepix, is a novel GWT1 inhibitor with broad antifungal activity. Fosmanogepix has previously shown *in vivo* efficacy in an immunocompromised murine model of invasive fusariosis. Our objective was to evaluate the *in vitro* activity of MGX against FOSC and FSSC isolates.

Methods. Clinical isolates of FOSC (n=49) and FSSC (19) were identified by combined phenotypic characteristics and DNA sequence analysis of the translation elongation factor 1-alpha (*TEF1α*) and RNA polymerase II second largest subunit (*RPB2*). Antifungal susceptibility testing was performed by CLSI M38 broth microdilution. Minimum effective concentrations (MEC) and minimum inhibitory concentrations (MIC) were read after 48 hours of incubation at 50% and 100% inhibition of growth for MGX, and MIC values were read for amphotericin B, posaconazole, isavuconazole, and voriconazole at 100% inhibition of growth.

Results. MGX demonstrated potent *in vitro* activity against both FOSC and FSSC isolates. Against the 49 FOSC isolates, the MGX MECs ranged from <0.015-0.03 mg/mL, and MICs at the 50% inhibition of growth endpoint ranged from <0.015-0.12 mg/mL (Table). MIC values were higher when read at 100% inhibition of growth. Similar results were observed against FSSC isolates (MEC and MIC ranges <0.015 and <0.015-0.25 mg/mL, respectively). MGX MEC and MIC 50% inhibition values were in close agreement for both FOSC and FSSC isolates. Of the other antifungals tested, amphotericin B demonstrated *in vitro* good activity (MIC ranges 1-4 and 0.25-4 mg/mL against FOSC and FSSC, respectively). In contrast, the azoles demonstrated reduced susceptibility (MIC range 1- >16 mg/mL).

MIC/MEC values (mcg/mL) for manogepix and other antifungals against FOSC and FSSC isolates

Antifungal	Manogepix			Amphotericin	Posaconazole	Isavuconazole	Voriconazole
Endpoint read	MEC	MIC 50%	MIC 100%	MIC 100%	MIC 100%	MIC 100%	MIC 100%
Fusarium oxysporum species complex (n = 49)							
Range	≤0.015-0.03	≤0.015-0.12	>8	1-4	1->16	>16	4-16
MEC/MIC_{50}	≤0.015	≤0.015	>8	2	4	16	8
MEC/MIC_{90}	≤0.015	0.080	>8	2	>16	>16	8
GM MEC/MIC	≤0.015	0.021	>8	1.59	6.11	>16	6.94
Fusarium solani species complex (n = 19)							
Range	≤0.015	≤0.015-0.25	≤0.015->8	0.25-4	4->16	>16	2->16
MEC/MIC_{50}	≤0.015	≤0.015	>8	1	>16	>16	>16
MEC/MIC_{90}	≤0.015	≤0.015	>8	2	>16	>16	>16
GM MEC/MIC	≤0.015	0.017	5.95	1.08	>16	>16	16

Conclusion. MGX demonstrated *in vitro* activity against FOSC and FSSC clinical isolates. Both changes in fungal morphology (MEC) and reductions in growth (MIC 50% inhibition) were observed. Clinical studies are ongoing to determine the efficacy of fosmanogepix in patients with invasive fungal infections.

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1283. New Generation Antiviral Conjugate (AVC): Stable, Safe, and Single

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Session: P-58. Novel Agents

Background. CD377 is a novel antiviral Fc-conjugate (AVC) development candidate for influenza prevention and treatment, comprising multiple copies of a novel potent small-molecule antiviral and the Fc domain of human IgG1. CD377 was designed as a stable, long-acting molecule for treatment and prevention of influenza A and B. Studies were conducted to characterize CD377 stability/pharmacokinetics (PK), single-dose efficacy in influenza models, and safety/toxicology.

Methods. PK in the mouse (1-100 mg/kg), rat (5-50 mg/kg), ferret (3 mg/kg), and monkey (5-20 mg/kg) were studied by sampling plasma over a 1-2 week interval. Plasma levels of intact molecule and total Fc were measured by neuraminidase (NA)-capture and Fc-capture with Fc-detection ELISA, respectively. Two-week safety/toxicology (bodyweight, coagulation, clinical signs, chemistries, hematology, cytokines, urinalsis, histopathology) was evaluated in monkeys (5-20 mg/kg on days 1 and 8). Prophylaxis efficacy was studied in a lethal influenza mouse model using a single dose of CD377 (0.3–3 mg/kg) 28 days prior to intranasal (IN) challenge with 3x the LD_{95} of A/California/07/2009 (H1N1)pdm, A/Hong Kong/1/68 (H3N2), or B/Malaysia (Victoria lineage). Treatment efficacy was studied in a similar mouse model using a single dose of CD377 (0.3–3 mg/kg) administered 2 hours after IN challenge with A/CA/12/2012 (H1N1)pdm.

Results. Plasma concentrations measured by Fc-capture/Fc-detection and NA-capture/Fc-detection were comparable, indicating that CD377 remained intact in vivo. In species tested, CD377 $t_{1/2}$ was 3–10 days. Dose proportional increases in exposure were observed, notably from 1–100 mg/kg in mouse. High bioavailability (77%) was observed after subcutaneous (SC) or intramuscular (IM) administration. A single SC dose of 1 mg/kg administered 28 days prior to infection provided 100% protection against H1N1, B, and H3N2 subtypes in mouse (Fig. 1). Treatment efficacy was observed with a single 0.3 mg/kg IM dose. The 2-week monkey toxicology study showed no adverse effects.