62. Evaluation of in vitro activity of manogepix against multidrug-resistant and pan-resistant Candida auris from the New York outbreak

Yan Chun Zhu, MS; Shannon N. Kilburn, MPH, Epidemiology; Milu Kapoor, PhD; Sudha Chaturvedi, PhD; Karen J. Shaw, PhD; Vishnu Chaturvedi, PhD; 1NYSDOH Wadsworth Center, Albany, New York; 2New York State Department of Health, Delmar, New York; 3Amphly Pharmaceuticals, San Diego, California; 4New York State Department of Health Wadsworth Center, Albany, New York

Session: P-58. Novel Agents

Background. An ongoing Candida auris outbreak in the New York metropolitan area is the largest recorded to date in North America. NY C. auris isolates demonstrate resistance to fluconazole and variable resistance to other antifungals. Thus, there is an urgent need for new drugs with a novel mechanism of action to combat the resistance challenge. Manogepix (MGX) is a first-in-class agent that targets the fungal Gwt1 enzyme. The prodrug, fosmanogepix, is in clinical development for the treatment of invasive fungal infections.

Methods. The susceptibility of 58 non-consecutive, non-duplicate NTM isolates was determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) standard M24. Isolates included 20 rapidly-growing mycobacteria (10 M. abscessus/chelonae Group, 6 M. fortuitum Group, and 4 M. muenchien Group) and 38 slow-growing mycobacteria (28 MAC and 10 M. kansuissi). SPβ791 and comparators clarithromycin (CLA), amikacin (AMK), moxifloxacin (MXF), rifabutin (RFR), minocycline (MIN), and imipenem (IPM) were evaluated. Minimum bactericidal concentrations (MBC) for SPβ791, CLA, and AMK were determined in accordance with CLSI M26.

Results. The activity of SPβ791 and comparators by MIC range and MIC<sub>50</sub> (ug/ml) is summarized in the accompanying table. SPβ791 activity was not affected by resistance to CLA, AMK, or MXF. MBC/MIC ratios for SPβ791 and CLA were typically ~3 which indicates a bacteriostatic mode of action; AMK MBC/MIC ratios were typically ~4 5 fold more than the bactericidal of the comparator. These results highlight the potential of SPβ791 in the treatment of NTM pulmonary disease.

Disclosures. Nicole S. Cottonson, BS, Spero Therapeutics (Employee, Shareholder); Ian Critchley, PhD, Spero Therapeutics (Employee, Shareholder); Michael Pucci, PhD, Spero Therapeutics (Employee, Shareholder) Suzanne Stokes, PhD, Spero Therapeutics (Employee, Shareholder)

1275. Evaluation of in vitro activity of manogepix against multidrug-resistant and pan-resistant Candida auris from the New York outbreak

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Methods. We evaluated the susceptibility of 200 NY C. auris isolates (2017-2020) to MGX and 10 comparators. Testing was performed using TREK frozen broth microdilution panels for FLC, VRC, ETC, ISA, POS, AFG, CAs, and MFG. MGX MIC<sub>50</sub> against A/B/C 241 MIC were determined by Etest<sup>®</sup> and 40% of the drug was the fungicidal growth endpoint at 24 h. MICs were determined by Etest<sup>®</sup> at 24 h for AMK and FLC. We defined pan-resistant C. auris as isolates with resistance to two or more azoles, all echinocandins, and AMB. The epidemiological cutoff values (ECVs, ECOFVs) for MGX were estimated using the Microsoft Excel spreadsheet calculator ECOFinder.

Results. MGX demonstrated lower MICs than comparators (MIC<sub>50</sub> of 0.03 mg/l; range 0.004-0.06 mg/l). MGX was 8-32 fold more active that the echinocandins 16-64 fold more active than the azoles, and 64 fold more active than AMB. No differences were found in the MGX or comparators MIC<sub>50</sub>, MIC<sub>90</sub>, or GEOMEAN values when subsets of clinical, surveillance, and environmental isolates were evaluated. The range of MGX MIC values for six C. auris pan-resistant isolates was 0.008-0.015 mg/l, and the median and mode MIC values were 0.015 mg/l, demonstrating that MGX retains activity against these isolates. The MGX epidemiological cutoff value (ECV, 99% cutoff) was 0.06 mg/l.

Conclusion. MGX MICs were low against C. auris isolates including those with variable patterns of resistance to AMB, azoles, and echinocandins. In addition, MGX retained activity against six pan-resistant isolates. These data support the continued clinical evaluation of fosmanogepix for the treatment of C. auris infections, including highly resistant isolates.

Disclosures. Karen J. Shaw, PhD, Amplyx (Consultant)Forge Therapeutics (Consultant) Vishnu Chaturvedi, PhD, Amplyx (Grant/Research Support)
1279. In Vitro Activity of Nocabbactam (OP8995) Alone and in Combination with β-Lactams against β-Lactamase-Producing Enterobacteriales Isolated in Japan

Yu Nagira, MS; Keiko Yamada, BS; Meiji Seika Pharma Co., Ltd. (Employee) Hayato Okade, Ph.D.; Meiji Seika Pharma Co., Ltd. (Employee) Nami Senju, BS; Meiji Seika Pharma Co., Ltd. (Employee) Yoko Tsutsumi, MS; Meiji Seika Pharma Co., Ltd. (Employee) Yui Tataba, Ph.D.; Meiji Seika Pharma Co., Ltd. (Employee)

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 MICs of NAC alone against 112 IMP-producing Enterobacteriales and 154 ESBL-producing Enterobacteriales 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 MICs were 2 and 1 mg/L and the MIC ranges were 1/0.06 - 4 mg/L, respectively. The MICs of FEP/NAC and ATM/NAC against ESBL-producing isolates were 0.5 and 1 mg/L. These MICs 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 Enterobacteriales but also IMP-producing Enterobacteriales 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 anti-bacterial agent and also an enhancer when combined with β-lactams. Furthermore, these will be useful for selecting a partner β-lactam for NAC.

Disclosures. Yu Nagira, MS, Meiji Seika Pharma Co., Ltd. (Employee) Keiko Yamada, BS; Meiji Seika Pharma Co., Ltd. (Employee) Hayato Okade, Ph.D.; Meiji Seika Pharma Co., Ltd. (Employee) Nami Senju, BS; Meiji Seika Pharma Co., Ltd. (Employee) Yoko Tsutsumi, MS; Meiji Seika Pharma Co., Ltd. (Employee) Yui Tataba, Ph.D.; Meiji Seika Pharma Co., Ltd. (Employee)

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

Andrea Nuzzo, PHD; Stephanie Van Horn, BSc,1; Christopher Traini, PHD,1; Caroline R. Perry, PhD;1 Etienne Dumont, MD, PhD; Nicole Scangarella-Oman, MS;1 David Gardner, MD; James R. Brown, PhD;1 GlassmaksKline, Collegeville, Pennsylvania;2 GSK Pharmaceuticals, Collegeville, PA;1 GSK, Collegeville, PA;2 GlassmaksKline Pharmaceuticals, Collegeville, Pennsylvania

Methods. Gepotidacin (GSK2140944) is a first in class novel oral triazaace-naphthylene bacterial topoisomerase inhibitor. In this study, we evaluated the potential