MIC range and MIC50/90 summary table

Organism (N)		SPR719	CLA	AMK	MXF	RFB	MIN	IPM
MAC (28)	Range	0.25-4	0.25->32	4->256	0.25-8	≤0.008-2	2->32	2-128
	$MIC_{50/90}$	1/2	2/8	16/32	1/4	0.25/1	16/>32	32/128
M. kansasii (10)	Range	0.03-0.06	0.12-0.5	2-8	0.06-2	≤0.008-0.06	0.5-8	1-64
	$MIC_{50/90}$	0.03/0.06	0.5/0.5	8/8	0.25/0.5	≤0.008/0.06	4/8	16/64
M. abscessus/ chelonae Group (10)	Range	1-16	0.12->32	2->256	1->8	0.12-4	8->32	8-64
	$MIC_{50/90}$	2/4	0.5/1	4/16	8/>8	2/4	32/>32	8/16
M. fortuitum Group (6)	Range	0.5-2	1-16	0.5-2	0.03-0.5	0.5-2	0.05-8	0.015-4
	$MIC_{50/90}$	0.5/-	4/-	0.5/-	0.06/-	0.5/-	0.5/-	2/-
M. mucogenicum Group (4)	Range	0.12-2	≤0.03-0.25	≤0.25-1	0.25-1	0.5-1	≤0.03-4	0.25-2
	$MIC_{50/90}$	-/-	-/-	-/-	-/-	-/-	-/-	-/-

Methods: The susceptibility of 58 non-consecutive, non-duplicate clinical 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. mucogenicum* Group) and 38 slow-growing mycobacteria (28 MAC and 10 *M. kansasii*). SPR719 and comparators clarithromycin (CLA), amikacin (AMK), moxifloxacin (MXF), rifabutin (RFB), minocycline (MIN), and imipenem (IPM) were evaluated. Minimum bactericidal concentrations (MBC) for SPR719, CLA, and AMK were determined in accordance with CLSI M26.

Results. The activity of SPR719 and comparators by MIC range and $MIC_{50/90}$ (µg/mL) is summarized in the accompanying table. SPR719 activity was not affected by resistance to CLA, AMK, or MXF. MBC:MIC ratios for SPR719 and CLA were typically >8 which indicates a bacteriostatic mode of action; AMK MBC:MIC ratios were typically ≤ 4 indicative of bactericidal activity.

Conclusion. SPR719 had potent activity by both $MIC_{50/90}$ and MIC range across the evaluated NTM species. The SPR719 activity against clinically relevant MAC and *M. abcessus/chelonae* Group isolates was comparable or superior to the evaluated comparators, and SPR719 was active against isolates resistant to currently utilized agents. These results highlight the potential of SPR719 in the treatment of NTM pulmonary disease.

Disclosures. Nicole S. Cotroneo, 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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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. 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, ITC, ISA, POS, AFG, CAS, and MFG. MGX MICs were evaluated (CLSI M27-A3 guidelines) using a 50% reduction in fungal growth endpoint at 24 h. MICs were determined by ETEST® at 24 h for AMB and FLC. We defined pan-resistant *C. auris* as isolates with *in vitro* resistance to two or more azoles, all echinocandins, and AMB. The epidemiological cutoff values (ECVs, ECOFFs) for MGX were estimated using the Microsoft Excel spreadsheet calculator ECOFFinder.

Results. MGX demonstrated lower MICs than comparators (MIC_{50} and MIC_{90} 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_{50}, MIC_{90}, 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 potent 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)

1276. Evaluation of CD377, a Novel Antiviral Fc-Conjugate (AVC), In Vitro Activity and In Vivo Efficacy in Immune-Competent and -Deficient (SCID) Lethal Mouse Models

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Session: P-58. Novel Agents

Background. Cidara's AVCs are novel, potent, antiviral agents conjugated with the Fc domain of human IgG1. CD377 is an AVC development candidate being evaluated for prevention and treatment of seasonal and pandemic influenza, including in immune-deficient populations unable to benefit from vaccination. We evaluated CD377 in vitro and in SCID mice to determine the impact of compromised immune status on efficacy.

Methods. CD377 and comparators (oseltamivir [OS], zanamivir [ZA], baloxavir marboxil [BM]) were evaluated in vitro by neuraminidase inhibition (NAI), and cytopathic effect (CPE) assays. The pharmacokinetics (PK) and efficacy of CD377 were determined in immune-competent (IC; BALB/c) and immune-deficient (ID; BALB/c SCID) mice. Efficacy was assessed by intranasal challenge at 3x the LD_{95} of influenza A/Puerto Rico/8/1934 (H1N1), followed by a single subcutaneous (SC) dose of CD377, 2 hours post-challenge. The SCID study also evaluated the efficacy of BM at 3 mg/kg (BID x 1 day). Body weights (BW) were monitored for 21 days, with 20% BW loss recorded as mortality.

Results. In vitro evaluation by NAI showed CD377, OS, and ZA to be approximately equipotent, with IC_{50} values between 0.5 and 1.7 nM. However, by CPE, CD377 was ~4.5-fold more active than BM and >1,000-fold more active than OS and ZA.

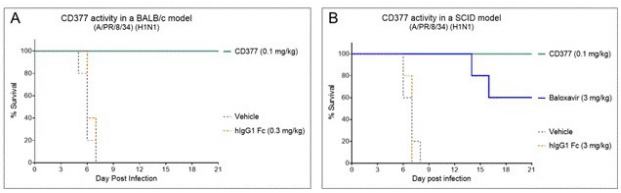
In vivo, the PK of CD377 was found to be comparable in IC and ID mice. In subsequent efficacy studies, CD377 was protective at 0.1 mg/kg in IC mice (P=0.0020 vs. vehicle), while control groups fully succumbed to infection by Day 7 (Fig. 1A).

In a similar study with ID mice, CD377 dosed at 0.1 mg/kg was also fully protective (P=0.0020). In contrast, mice treated with 6 mg/kg (total dose) of BM were only partially protected until day 13 (40% mortality by study end) (Fig. 1B). The potency of CD377 was further supported by BW data, which mirrored the survival data in both studies.

Conclusion. CD377 exhibited potent in vitro activity and had similar PK in IC and ID mice. In efficacy studies, CD377 demonstrated robust potency in both IC and ID mouse models at equivalent doses (0.1 mg/kg, SC, single dose). These results support further development of CD377 as a novel antiviral for the prevention and treatment of influenza infection, including in people with immune deficiencies and higher risk of infection.

Balb/c and Balb/c SCID

Figure 1. Activity of CD377 in lethal mouse models. (A) Immune competent; (B) Immune deficient



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1278. Impact of Different Breakpoint Criteria on the Susceptibility Rates of Enterobacterales resistant Subsets to the Aminoglycosides

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Session: P-58. Novel Agents

Background. Plazomicin (PLZ) is an aminoglycoside recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections, including pyelonephritis. We evaluated the susceptibility (S) rates of PLZ, amikacin (AMK), gentamicin (GEN) and tobramycin (TOB) by applying current breakpoints published by different organizations.

Methods. A total of 9,303 *Enterobacterales* (ENT) isolates (1/patient) were collected in 2018-2019 from medical centers located in the US (n=3,899; 33 centers), Europe (n=3,782; 39 centers in 19 nations), Asia-Pacific (n=795; 13 centers in 7 nations [2018 only]), and Latin America (n=827; 10 centers in 6 nations [2018 only]). PLZ and