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.

Disclosures. Andrea Nuzzo, PHD, GlaxoSmithKline (Employee) Stephanie Van Horn, B.Sc., GlaxoSmithKline (Employee) Christopher Traini, PHD, GlaxoSmithKline (Employee) Caroline R. Perry, PhD, GlaxoSmithKline (Employee) Etienne Dumont, MD, GlaxoSmithKline (Employee) Nicole Scangarella-Oman, MS, GlaxoSmithKline plc. (Employee, Shareholder) David Gardiner, MD, GlaxoSmithKline (Employee) James R. Brown, PhD, GlaxoSmithKline (Employee)

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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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.

Disclosures. Ashraf S. Ibrahim, PhD, Astellas Pharma (Research Grant or Support) Karen J. Shaw, PhD, Amplyx (Consultant)Forge Therapeutics (Consultant) Nathan P. Wiederhold, PharmD, Astellas (Grant/Research Support)BioMerieux (Grant/Research Support)Cepheid (Grant/Research Support)Covance (Grant/Research Support)F2G (Grant/Research Support)Gilead (Speaker's Bureau)Mayne Pharma (Advisor or Review Panel member)Sfunga (Grant/Research Support)

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.