Background. Uncomplicated urinary tract infections (uUTIs) are very common, with approximately 11% of women >18 years of age experiencing at least 1 episode of acute cystitis per year [Foxman, 2000]. Multidrug resistance has now emerged at the community level and has made treatment approaches for UTIs more difficult [Hooton, 2012; Flamm, 2014; Sanchez, 2016]. Gepotidacin (GEP), a first-in-class, novel triazacanaphthene bacteriophage inhibitor, has demonstrated in vitro activity against uropathogens, including E. coli. With its unique ability to selectively inhibit bacterial DNA replication by a means not utilized by currently approved human therapeutic agent, GEP warrants further study as a potential opportunity to address unmet medical need by providing a new oral treatment option for acute cystitis.

Methods. All participants received oral GEP 1500 mg BID for 5 days (total of 10 doses) and PK sampling was performed on Days 1–5.

Results. GEP was rapidly absorbed with median Tmax values of 1.50 to 1.92 hours. Steady-state PK was achieved by Day 3 with moderate accumulation in plasma following BID dosing (1.4 fold), which is consistent with an effective elimination half-life of 6.6 hours. Steady-state trough levels were high and remained above an MIC of 4 µg/mL over 12 hours. Approximately 20% of the dose was excreted in urine over the 12-hour dosing interval on Day 1, which increased to 31% on Day 4. Urinary AUC24hr (11945 µg hours/mL) was higher than the free plasma AUC24hr (39.4 µg hours/mL). Slightly higher GEP plasma and urine exposures were observed in uUTI patients compared with Phase I healthy subjects.

Conclusion. Oral dosing of 1500 mg BID produces urine GEP exposures that exceed free plasma exposures by ~300-fold. Urine concentrations were also higher than the GEP MIC90 values for common UTI pathogens, such as E. coli (MIC90 = 4 µg/mL), suggesting that GEP warrants further clinical study for the treatment of uUTI.

Disclosures. All authors: No reported disclosures.

1482. Microbiological Analysis from a Phase II Study Evaluating Gepotidacin (GSK214904) in the Treatment of Uncomplicated Urinary Tract Infections Nicholas Scangarella-Omara, MD; Mohamed Hossain, PhD; Timothy Tiemeyer Jr., BS; Caroline R. Perry, PhD; Courtney Tiffany, BSc; Aparna Raychaudhuri, PhD; Etienne Dumont, MD; GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania; GlaxoSmithKline, Collegeville, Pennsylvania; PPD, Highland Heights, Kentucky

Background. Gepotidacin (GEP), a first in class novel triazacanaphthene bacterial topoisomerase inhibitor, inhibits bacterial replication and has in vitro activity against key pathogens, including drug-resistant strains, associated with a range of infections.

Methods. This phase IIa single-center study evaluated the safety, tolerability, pharmacokinetics, and efficacy of oral GEP 1,500 mg BID for 5 days in female subjects with acute cystitis. Clean catch mid-stream urine specimens were obtained for quantitative testing by standard methods. Susceptibility testing by CLSI broth microdilution and gradient diffusion (tobramycin) was conducted. Inclusion in the microbiological intent-to-treat population (micro-ITT) required growth of a qualifying baseline uropathogen from ≥ 0.06 to 4 µg/mL. Two E. coli isolates were multidrug-resistant (defined as resistance to ≥ 3 antibiotic classes) due to resistance to ampicillin, trimethoprim-sulfamethoxazole and ciprofloxacin/levofloxacin or cefazolin. One additional E. coli isolate was ampicillin-resistant. Of the 8 patients in the micro-ITT, 7 (88%), and 6 (75%) were microbiological successes at the Test of Cure (TOC) and Follow-up Visits, respectively. The one microbiological failure at TOC (E. coli) was due to an unreportable (out of stability) urine specimen. For the 4 participants with available steady-state PK, qualifying Enterobacteriaceae uropathogens and who were microbiological successes at TOC, plasma AUC24h/MICs ranged from 7 to 90.5 and urine AUC24h/MICs from 1292 to 121,698. The participant with the lowest plasma AUC/MIC (7) and urine AUC24h/MIC (1292) had a K. pneumoniae with a MIC of 4 µg/mL.

Conclusion. This first report of microbiological efficacy in the treatment of acute cystitis supports further clinical study of GEP as a first-in-class, novel mechanism of action antibacterial.

Disclosures. All authors: No reported disclosures.

1483. Comparison of Outcomes in Urinary Tract Infections Caused by SPICE Organisms Treated with Non-Carbapenem β-lactamants vs. Non-β-lactamant Agents Julia Sapochnikov, PharmD; Angela Huang, PharmD, BCIDP; Kelsey Powell, PharmD; Allison Gibble, PharmD; Froedtert and the Medical College of Wisconsin, Buffalo Grove, Illinois

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Background. The ‘SPICE organisms’ intrinsically produce low levels of a chromosomally encoded β-lactamase enzyme, AmpC. When SPICE organisms are exposed to certain antimicrobial agents, they can select for de-repressed mutants and induce the AmpC gene. No study to date has determined the optimal treatment of lower inoculum infections such as urinary tract infections (UTIs) caused by SPICE organisms.

Methods. This study is a single-center, retrospective observational review of adult hospitalized patients with a UTI caused by a SPICE organism from November 2012 to November 2015. The objective of this study was to compare outcomes amongst patients with UTIs caused by select SPICE organisms treated with drugs susceptible to AmpC hydrolysis (penicillins, cephalosporins except cefepime, and monobactams) vs. drugs stable against AmpC (carbapenems, cepfetine, and non-β-lactamant agents). The primary outcome was clinical response, defined as resolution of signs and symptoms of UTI without requiring escalation of antimicrobial therapy after 48 hours of therapy initiation. Secondary outcomes include 30 day infection-related readmission, 30 day infection recurrence rate, 30-day all-cause mortality, and length of hospital stay. Patients with resistance to ceftriaxone were reviewed for β-lactam exposure (27 days) within the last month.

Results. One hundred 56 patients were included. Clinical response, 30-day infection-related readmission, 30 day infection recurrence, 30 day all-cause mortality rates, and length of hospital stay were similar between the AmpC stable and AmpC susceptible groups (Table 1). Notably, 39.1% of patients with ceftriaxone resistance reported had recent β-lactam exposure vs only 11.6% of patients without ceftriaxone resistance (P = 0.0028).

Conclusion. Based on our data, there does not appear to be a difference in clinical response, 30-day related readmission, 30-day infection recurrence, 30-day all-cause mortality rates, or length of stay in patients with UTIs treated with AmpC stable and AmpC susceptible agents. AmpC induction can be seen with at least 7 days of β-lactam exposure vs. only 11.6% of patients without ceftriaxone resistance (P = 0.0028).