In Vitro Activity of Gepotidacin and Comparators Against a Collection of *E. coli* and

– Gepotidacin is a novel, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action, which confers activity against most strains of target pathogens, such as *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including those resistant to current antibiotics. This study reports on results of the *in vitro* activity of gepotidacin when tested against contemporary *E. coli* and *S. saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin global surveillance study as part of the SENTRY Antimicrobial Surveillance G1n(23o-3(robim)21.ml)31(Surv)13(e)30 960 540 reW BT0.953 0.4 0.2 rg0.95

In Vitro Activity of Gepotidacin and Comparators Against a Collection of *E. coli* and *S. saprophyticus* Urine Isolates Collected Worldwide During 2019-2021

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Introduction

Gepotidacin is a novel, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action, which confers activity against most strains of target pathogens, such as *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including those resistant to current antibiotics.

Gepotidacin (GSK2140944) is in Phase 3 clinical development for the treatment of gonorrhea and uncomplicated urinary tract infections (UTIs).

This study reports on results of the in vitro activity of gepotidacin and comparator agents when tested against contemporary *E. coli* and *S. saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin global surveillance study as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

A total of 4,664 *E. coli* and 433 *S. saprophyticus* isolates were collected from 96 medical centres located in 25 countries.

- Europe (EU), 17 countries, United States (US), Latin America (LATAM) 6 countries, and Japan (JPN).
- All isolates were recovered from patients with UTIs, 68.1% percent from ambulatory, emergency, family practice, and outpatient services.

Susceptibility tested by CLSI methods in a central laboratory (JMI Laboratories).

MIC results for all comparators except amoxicillin-clavulanic acid were interpreted per EUCAST guidelines.

Amoxicillin-clavulanic acid was tested at a 2:1 ratio and MICs were interpreted using CLSI breakpoints.

Susceptibility to fosfomycin and mecillinam was determined by agar dilution.

Fosfomycin testing was supplemented with glucose-6-phosphate (25 mg/L).

The extended-spectrum β-lactamase (ESBL) phenotype in *E. coli* was characterized by isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 mg/L.

Gepotidacin demonstrated potent *in vitro* activity against contemporary *E. coli*, including ESBL-producing isolates, and *S. saprophyticus*.

Gepotidacin activity showed little variability across regions.

Table 1 Activity of gepotidacin and comparators against *E. coli* isolates collected from urinary tract infections stratified by region

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Results

Gepotidacin activity against all *E. coli* isolates was similar across all 4 regions (Table 1).

- MIC_{50} values were 2 mg/L.
- MIC_{90} values ranged from 2 to 4 mg/L.

Among *E. coli* isolates, lower susceptibilities and larger variation were observed for some comparators while other comparators remained active.

- Amoxicillin-clavulanic acid ($MIC_{50/90}$, 4-8/16 mg/L, 74.1-88.6%S).
- Ciprofloxacin ($MIC_{50/90}$, 0.015-0.25/>4 mg/L, 54.4-76.1%S).
- Trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.12-1/>4 mg/L, 50.7-79.8%S).
- Fosfomycin ($MIC_{50/90}$, 0.5/1-2 mg/L; 94.5

Table 2 Activity of gepotidacin and comparators against 433 *S. saprophyticus* isolates collected from urinary tract infections stratified by region