Phase 2a Pharmacokinetic, Safety, and Exploratory Efficacy Evaluation of Oral Gepotidacin (GSK2140944) in Female Participants With Uncomplicated Urinary Tract Infection (Acute Uncomplicated Cystitis)

Running Title: PK and Safety of Gepotidacin in uUTI

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ABSTRACT Gepotidacin, a triazaacenaphthylene bacterial type II topoisomerase inhibitor, is in development for treatment of uncomplicated urinary tract infection (uUTI). This Phase 2a study in female participants with uUTI evaluated the pharmacokinetics (primary objective), safety, and exploratory efficacy of gepotidacin. Eligible participants (N = 22) were confined to the clinic at baseline, received oral gepotidacin 1,500 mg twice daily for 5 days (on-therapy; Days 1 to 5), and returned to the clinic for test-of-cure (Days 10 to 13) and follow-up (Day 28±3).

Pharmacokinetic, safety, clinical, and microbiological assessments were performed. Maximum plasma concentrations were observed approximately 1.5 to 2 hours postdose. Steady state was attained by Day 3. Urinary exposure over the dosing interval increased from 3,742 µg.h/ml (Day 1) to 5,973 µg.h/ml (Day 4), with trough concentrations of 322 to 352 µg/ml from Day 3 onward. Gepotidacin had an acceptable safety-risk profile with no treatment-limiting adverse events and no clinically relevant safety trends. Clinical success was achieved in 19 (86%) and 18 (82%) of 22 participants at test-of-cure and follow-up, respectively. Eight participants had a qualifying baseline uropathogen (growth; ≥10⁵ CFU/ml). A therapeutic (combined clinical and microbiological [no growth; <10³ CFU/ml]) successful response was achieved in 6 (75%) and 5 (63%) of 8 participants at test-of-cure and follow-up, respectively. Plasma area under the free-drug concentration-time curve over 24 hours at steady state divided by the MIC (fAUC₀₋₂₄/MIC) and urine AUC₀₋₂₄/MIC ranged from 6.99 to 90.5 and 1,292 to 121,698, respectively. Further evaluation of gepotidacin in uUTI is warranted. (NCT03568942)

KEYWORDS gepotidacin, uncomplicated urinary tract infection, acute cystitis, pharmacokinetics, safety
INTRODUCTION

Predominant uropathogens in uncomplicated urinary tract infections (uUTIs; acute uncomplicated cystitis) are *Escherichia coli* (75% to 90%), *Staphylococcus saprophyticus* (5% to 15%), and *Klebsiella*, *Enterobacter*, *Proteus*, and enterococci uropathogens (5% to 10%) (1–3). Multidrug-resistant (MDR) uropathogens, commonly associated with nosocomial infections, have emerged at the community level and treatment for uUTIs has become more difficult (4–6). Health authorities recognize extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* as a serious threat (7) and drug-resistant *Enterobacteriaceae* as a critical priority pathogen (8). The MDR *E. coli* sequence type 131 clone has emerged as a cause of urinary tract infections and bacteremia worldwide (9–11). The availability of oral antimicrobials effective against ESBLs is limited and, for some outpatient infections, no oral options remain.

Gepotidacin (GSK2140944) is a triazaacenaphylene bacterial type II topoisomerase inhibitor with a novel mode of action with *in vitro* activity against most target pathogens resistant to established antibacterials (12–15). Phase 2 studies have demonstrated the efficacy of gepotidacin in acute bacterial skin and skin structure infections and uncomplicated urogenital gonorrhea (16–18). The microbiological activity of gepotidacin includes *E. coli*, the key causative uropathogen of uUTI, and *S. saprophyticus* and *Enterococcus faecalis*. In addition, the efficacy of gepotidacin against *E. coli* was evaluated in a rat pyelonephritis model, which indicated potential efficacy in uUTI and supported clinical dose selection (19). The pharmacokinetics (PK) of gepotidacin have been well defined in healthy participants and demonstrated urine exposures that may support uUTI treatment (20–23). A Phase 2a evaluation of oral gepotidacin in female participants with uUTI was conducted with the main objectives of...
evaluating plasma and urinary gepotidacin exposures and safety in this population. In addition, exploratory efficacy and PK/pharmacodynamic (PD) endpoints were assessed.

RESULTS

Participant disposition

A total of 22 female participants with uUTI were enrolled and evaluated for PK, safety, and clinical efficacy in this Phase 2a, single-center, single-arm, open-label study in the United States from July 2018 to January 2019 (Fig. S1). Participants were confined to the clinic from baseline (Days −1 to 1 predose) through on-therapy (Days 1 to 5) and returned as outpatients for test-of-cure (TOC; Days 10 to 13) and follow-up (Day 28±3). Participants received oral gepotidacin 1,500 mg twice daily (BID) for 5 days. Two participants (9%) withdrew from the study due to lost to follow-up and family reasons; there were no discontinuations due to adverse events (AEs) (Figure 1).

Participant baseline characteristics

The majority of participants were white, age ranged from 19 to 60 years, and body mass index ranged from 20.9 to 37.9 kg/m² (Table 1). The number of past uUTI episodes ranged from 0 to 10 over the past 12 months across participants; the majority of participants reported ≤2 episodes.

The mean total clinical symptom score at baseline was 7.9 (range: 4 to 12). All participants reported frequency and urgency, and all but 1 participant (5%) reported dysuria.

In the 22 intent-to-treat (ITT) participants, 19 baseline uropathogens were recovered, 8 uropathogens from 8 participants (36%) met the qualifying uropathogen definition and
inclusion in the microbiological intent-to-treat (micro-ITT) population (Figure 1). This subset of 8 participants underwent both clinical and microbiological efficacy assessments.

84 Pharmacokinetics
85 Median gepotidacin plasma concentrations peaked rapidly with median maximum observed concentrations ($T_{\text{max}}$) observed at 1.50 and 1.92 hours postdose on Days 1 and 4, respectively (Figure 2). Concentrations declined in a multiphasic manner. Plasma exposure (maximum observed concentration [$C_{\text{max}}$] and area under the concentration-time curve from time 0 to the 12-hour dosing interval [AUC$_{0-\tau}$]) was approximately 1.4-fold higher on Day 4 versus Day 1 (Table 2). The accumulation was consistent with an effective elimination half-life of 6.6 hours. The between-participant variability in plasma exposures was moderate with a higher coefficient-of-variation range for $C_{\text{max}}$ (38% to 47%) compared with AUC$_{0-\tau}$ (29% to 32%) across Days 1 and 4. Based on observed plasma predose concentrations ($C_t$) and statistical analysis, steady state was achieved by Day 3 (Fig. S2 and Table S1).

84 Median urine gepotidacin concentrations were generally higher on Day 4 compared to Day 1 (Figure 3). On Day 1, approximately 20% of the dose was excreted in urine over the dosing interval, increasing to 31% on Day 4 (Table 3). Overall exposure in urine (AUC$_{0-\tau}$) also increased from Day 1 to 4, with urine $C_t$ ranging from 322 to 352 µg/ml from Day 3 onward. The renal clearance was similar on Days 1 and 4. Approximately 460 mg of unchanged gepotidacin was excreted in urine over the steady-state dosing interval, with a minimum steady-state AUC$_{0-\tau}$ of 2,256 µg.h/ml. Gepotidacin was measurable in cervical, rectal, and pharyngeal swabs on Day 4 with the highest concentrations in rectal swabs (Table S2).
Safety

Twenty-one participants (95%) experienced AEs; gastrointestinal-related disorders had the highest prevalence (Table 4). Gastrointestinal AEs reported in >10% of participants were diarrhea, nausea, and vomiting, and were the most prevalent drug-related events. Other drug-related AEs were vulvovaginal mycotic infection (2 participants, 9%), headache (1 participant, 5%), and chest discomfort (1 participant, 5%, noncardiac in nature).

All AEs were mild (4 participants, 18%) or moderate (16 participants, 73%), except for a nonfatal serious AE of major depression with voluntary psychiatric hospitalization in 1 participant (5%) that occurred 9 days after the last dose and was considered not related to gepotidacin by the investigator. No participant experienced a drug-related AE of an intensity greater than moderate.

No clinically relevant laboratory changes were observed. Baseline and repeat urine dipstick results were consistent with the uUTI under study.

There were no clinically significant electrocardiogram (ECG) findings or changes from baseline. No participants had a QT interval corrected for heart rate according to Fridericia (QTcF) value ≥480 msec or an increase >30 msec (Figure 4). Mean QTcF (minimum, maximum) change from baseline to Day 4 at 2 hours postdose was 3.4 (–89, 27) msec. No clinically relevant changes in vital signs were observed.
**Exploratory efficacy**

**Clinical**

In the ITT population, at TOC, clinical success was observed for 19 of 22 participants (86%, Clopper-Pearson 95% confidence interval [CI] 65%-97%) and clinical failure for 3 of 22 participants (14%, Clopper-Pearson 95% CI 3%-35%) (Table 5). Clinical success was achieved in 12 of 14 participants (86%) who did not have a qualifying baseline uropathogen, indicating complete resolution of clinical symptoms in these participants. Clinical response results were similar between TOC and follow-up (Table S3); however, per sponsor-determined clinical response, there was an additional clinical failure at follow-up.

The mean baseline total clinical symptom score (7.9) decreased to 0.1 and 0 at TOC and follow-up, respectively, with a similar trend for each symptom category (Figure 5). All participants who completed the full course of gepotidacin and presented at TOC (n = 19) had complete symptom resolution; 1 participant who received only 6 doses of gepotidacin had a score of 2. All 20 participants with clinical scores reported at follow-up had a score of 0.

Clinical cure in most uropathogen groups was observed by approximately Day 4 with an increase through TOC and follow-up.

**Microbiological**

The 8 qualifying baseline isolates consisted of 5 *E. coli* isolates and 1 isolate each of *Citrobacter koseri*, *Klebsiella pneumoniae*, and *S. saprophyticus* (Table 6). Of the 5 qualifying *E. coli* uropathogens, 2 were MDR and 1 of those was both MDR and quinolone-resistant.

Most qualifying baseline uropathogens were resistant to ampicillin (5 of 8 isolates, 63%); none were resistant to nitrofurantoin, meropenem, or fosfomycin. No phenotypic
ESBL-producing uropathogens were recovered. Against the 8 qualifying baseline uropathogens in the micro-ITT population, gepotidacin MIC values ranged from 0.06 to 4 µg/ml (Table S4).

For 7 of 8 participants (88%) in the micro-ITT population, no growth (eradication) was observed starting on Day 2. At TOC, microbiological success was achieved in 7 of 8 participants (88%), including a participant with *K. pneumoniae* (Table 7 and Table S5). At TOC, there was 1 microbiological failure (13%) due to an indeterminant laboratory result (i.e., out-of-stability specimen); however, the participant was a clinical success. Microbiological response results were similar between TOC (Table S5) and follow-up (Table S6) except there was an additional microbiological failure at follow-up. One participant had regrowth of *C. koseri*, with no change in gepotidacin MIC or susceptibility.

Growth was observed for 2 isolates posttreatment (1 *E. coli* isolate on Day 3 and 1 *C. koseri* isolate at follow-up); both were resistant to ampicillin at baseline and the posttreatment timepoint; there was no change in gepotidacin MIC (Table S4).

No participants had a baseline uropathogen that demonstrated a reduction in susceptibility to gepotidacin (i.e., ≥4-fold increase in gepotidacin MIC for baseline uropathogens versus postbaseline uropathogens of the same species and from the same participant) at any timepoint in the ITT population.

Therapeutic response

The overall participant-level therapeutic response in the micro-ITT population was success for 6 of 8 participants (75%) and was failure for 2 of 8 participants (25%) at TOC (Table 7 and Table S7). Details on clinical and microbiological failures leading to therapeutic response failures are described in previous text (Table 7). Therapeutic response results were comparable
between TOC and follow-up (Table 7 and Table S8); however, there was an additional microbiological failure at follow-up. No clinical or microbiological failures required an alternative antibiotic for treatment of uUTI throughout the study.

Pharmacokinetic/pharmacodynamic

Four out of the 5 participants with a qualifying *E. coli* uropathogen at baseline had evaluable PK/PD parameters (Table 7). Other qualifying baseline uropathogens were observed but data were limited. Similar to the *E. coli* data, the PK parameter/MIC ratios were higher for the urine parameters compared to the free-plasma parameters.

For the 4 participants with qualifying *Enterobacteriaceae* uropathogens and who were microbiological successes at TOC, area under the free-drug concentration-time curve over 24 hours at steady state divided by the MIC plasma (fAUC\(_{0-24}/\text{MIC}\)) ranged from 6.99 to 90.5 and urine AUC\(_{0-24}/\text{MICs}\) from 1,292 to 121,698 (Table 7). The participant with the lowest plasma fAUC\(_{0-24}/\text{MIC}\) (6.99) and urine AUC\(_{0-24}/\text{MIC}\) (1,292) had *K. pneumoniae* with a gepotidacin MIC of 4 µg/ml and was a microbiological success.

**DISCUSSION**

These results suggest gepotidacin may provide a new oral treatment option for uUTI (acute uncomplicated cystitis) with further evaluation. The novel mechanism of action of gepotidacin could help meet the current need for oral antibacterial agents with activity against drug-resistant uropathogens (12–15).

The gepotidacin dose regimen in this population provided >600-fold higher concentrations in urine versus free plasma at steady state, which is the target site of action for the
treatment of uUTIs. The minimum gepotidacin urine concentrations remained above the
gepotidacin MIC value of 4 µg/ml throughout the dosing interval. Of note, fluid intake was not
standardized during the study; thus, any impact hydration status had on gepotidacin urinary
exposures is unknown. The gepotidacin renal excretion for female participants with uUTI was
higher compared to healthy participants with normal renal function or mild renal impairment
(20% versus 7.5% of the dose) and Day 1 plasma exposures in this study appeared to be higher
than in previous Phase 1 studies (mean C max, 5.89 µg/ml versus 3.20 µg/ml) (unpublished data).
Furthermore, gepotidacin concentrations were measurable in cervical, rectal, and pharyngeal
swabs, supporting the evaluation of gepotidacin for gonorrhea (NCT04010539).

An acceptable safety-risk profile was demonstrated after gepotidacin administration with
no treatment-limiting AEs and no discontinuations due to AEs. The safety profile of gepotidacin
was similar to that observed in previous studies. A high prevalence of gastrointestinal AEs was
expected (16, 17, 20–23); however, the prevalence of gastrointestinal AEs in the current study
(95%) was higher than observed previously. This was the first study in all female participants
and in uUTI. The investigator observed that most nausea AEs had an acute onset within the first
few doses and tolerance was observed with repeat dosing.

Based on a previous gepotidacin QTc evaluation (24), this study strategically included an
on-treatment ECG assessment at the maximum steady-state gepotidacin exposures (i.e., Day 4 at
2 hours postdose); however, there were no cardiac AEs reported and no clinically significant
ECG findings. In addition, there were no clinically relevant trends in the safety parameters.

In the ITT population (N = 22), symptom resolution (i.e., clinical score of 0) was
achieved in 19 participants at TOC and in 20 participants at follow-up. The only participant
without symptom resolution at TOC withdrew from study treatment, did not receive the full
5-day course of gepotidacin, but underwent TOC and follow-up assessments. All participants had clinical efficacy observations consistent with expectations for a UTI antibacterial. All participants had 219 clinical efficacy observations consistent with expectations for a UTI antibacterial.

The gepotidacin PK parameters were well defined in this female uUTI population. Oral

PK/PD hollow-fiber infection model (26) by approximately 4-fold, and 100% target attainment is expected in participants with uropathogens with gepotidacin MICs ≤4 µg/ml.

This was a single-center evaluation in the United States, which led to very few drug-resistant isolates for evaluation. The study was open-label and did not include a comparator antibacterial. Global, multicenter, noninferiority gepotidacin Phase 3 studies (NCT04020341 and NCT04187144) should address these limitations.

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METHODS AND MATERIALS

Study population

The study recruited nonpregnant females who were ≥18 to ≤65 years of age. Participants were required to have 2 or more of the following clinical signs and symptoms with onset ≤72 hours at Screening: dysuria, frequency, urgency, or lower abdominal pain; and to have pyuria (≥10 white blood cells/mm³ or the presence of leukocyte esterase) and/or nitrite from a pretreatment urine sample. Participants who had any pre-existing condition that may have impacted gepotidacin absorption, distribution, metabolism, or excretion were excluded. Full inclusion and exclusion criteria are provided in the Supplemental Materials.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Protocol and procedures were reviewed and approved by an institutional review board. Written informed consent was obtained from participants before any study procedures were performed.

Study design

This was a Phase 2a, single-center, single-arm, open-label study. Participants were confined to the clinic from baseline (Days –1 to 1 predose) through on-therapy (Days 1 to 5). Participants returned for outpatient visits at TOC (Days 10 to 13) and follow-up (Day 28±3). Gepotidacin (1,500 mg; 2 × 750 mg tablets) was administered orally BID for 5 days under site supervision. The target sample size was approximately 20 participants based on PK requirements.
Pharmacokinetic assessments

Serial blood and urine samples were collected from predose to 12 hours postdose on Day 1 (first dose) and Day 4 (time-matched to the first dose on Day 1) (collection timepoints are denoted in Fig. S1). For steady-state assessment, predose blood (single collection) and urine (0 to 2-hour interval) samples were collected before each time-matched dose on Days 1 through 5.

For each plasma PK sample, 3 ml of whole blood was collected via an indwelling catheter and/or direct venipuncture into tubes containing EDTA anticoagulant. Each tube was inverted approximately 5 to 10 times immediately after the sample was drawn. The whole blood sample may have been stored at room temperature for up to 60 minutes prior to centrifugation. The sample was centrifuged under refrigerated conditions (2°C to 8°C) at approximately 650 to 1,450 × g. Approximately 1.5 ml of plasma was transferred via a pipette into a 2-ml Cryovial® tube and kept frozen until analysis. Batched samples were shipped on dry ice to the bioanalytical laboratory for validated analysis.

For predose urine PK samples, a urine cup was used for collection. For all postdose urine PK samples, a urine jug was used for each collection interval. For each interval, approximately 1 ml of urine was transferred via a pipette into a 2-ml Cryovial tube and kept frozen until analysis. Batched samples were shipped on dry ice to the bioanalytical laboratory for validated analysis.

Exploratory PK assessment included the collection of cervical, rectal, and pharyngeal swab specimens on Day 4 (predose and 2 hours postdose).
All PK samples were analyzed using validated ultra- or high-performance liquid chromatography with tandem mass spectroscopy methods by PPD Bioanalytical Laboratory (Middleton, WI).

Safety assessments

Adverse event monitoring, vital sign measurements, clinical laboratory evaluations, and ECGs, including on-treatment ECGs on Days 1 and 4 matched with the 2-hour PK collection, were performed.

Exploratory efficacy assessments

Clinical signs and symptoms of uUTI were recorded based on participant interview at baseline (pretreatment), Days 2 through 5, TOC, and follow-up using a 0- to 3-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) for the categories of dysuria, frequency, urgency, and lower abdominal or suprapubic pain (Fig. S3). At each on-therapy assessment, clinical success included both resolution of or improvement in signs and symptoms. Clinical success at TOC and follow-up was defined as resolution of signs and symptoms present at baseline (and no new signs and symptoms) and no use of other antimicrobial therapy for the current uUTI. At TOC, a score of zero was required for a participant to be deemed a clinical success. At follow-up, the participant must have had a score of zero at TOC that persisted from TOC to follow-up for a response of clinical success.
Microbiological

A urine sample was collected at baseline (pretreatment), predose Days 2 through 5, TOC, and follow-up for Gram stain, quantitative bacteriology culture, and *in vitro* antimicrobial susceptibility testing using standard methods at a central laboratory (PPD Laboratories Central Lab, Highland Heights, KY). Susceptibility testing was conducted for all uropathogens by broth microdilution and gradient diffusion (fosfomycin only) according to Clinical and Laboratory Standards Institute guidelines (27, 28). Inclusion in the micro-ITT population required growth of a qualifying baseline uropathogen (≥10^5 CFU/ml) (29, 30) (Fig. S4). Microbiological success was defined as culture-confirmed eradication (no growth; <10^3 CFU/ml) of the qualifying baseline uropathogen. Multidrug-resistance was defined as a baseline uropathogen that was resistant to ≥3 relevant antibiotic classes.

Statistical analysis

Analysis populations

Analysis populations are defined in Table S9.

Pharmacokinetic

Noncompartmental PK analyses were performed using Phoenix WinNonlin version 6.4 (Certara USA, Inc., Princeton, NJ) and SAS version 9.3 (SAS Institute, Inc, Cary, NC) with actual sampling times. As total gepotidacin concentrations were measured in plasma, unbound values were derived by multiplying total concentrations by 0.67 to correct for the plasma protein binding of gepotidacin (33%) (unpublished data). Steady-state achievement was assessed using a linear mixed model with Helmert transformation.
Safety

Adverse events, change from baseline values for clinical chemistry, hematology, vital signs, and ECG findings were summarized using SAS version 9.3. Posthoc QTcF plots were generated using SAS version 9.4.

Exploratory efficacy

Efficacy data were summarized by qualifying baseline uropathogen using counts and percentages, with the 95% Clopper-Pearson CI presented at TOC and follow-up using SAS version 9.3.

Clinical outcome (investigator- and sponsor-determined) and response were summarized for the ITT and micro-ITT populations. Mean clinical symptom scores were summarized for the ITT population. Clinical cure was summarized for qualifying baseline uropathogens.

Microbiological outcome and response were summarized by predefined uropathogen groups or species. Urine quantitative bacteriology culture results were summarized. Results and interpretations of susceptibility testing for all uropathogens against gepotidacin and other antimicrobials were summarized.

Therapeutic response (success/failure), determined by statistical programming, was a measure of the overall efficacy response. Therapeutic success required both clinical success and microbiological success or the participant was deemed therapeutic failure. Therapeutic success was summarized by per-participant microbiological response and clinical response.
The plasma $fAUC_{0-24}/MIC$ and the urine $AUC_{0-24}/MIC$ ratio were determined using the Day 4 PK parameters and the qualifying baseline uropathogen (Day 1) MIC.
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All authors, with the exception of A.B., contributed to the study concept/design. Only J.S.O contributed to the acquisition of study data. All authors, with the exception of J.S.O., contributed to the data analysis/interpretation. All authors provided manuscript review and approval.
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FIG 1 Participant disposition$^a$

$^a$ITT, intent-to-treat; micro, microbiological; PD, pharmacodynamic; PK, pharmacokinetic.

FIG 2 Median gepotidacin plasma concentration-time plot (pharmacokinetic population)

The lower limit of quantification (LLOQ) was 0.10 µg/ml. The dashed line represents LLOQ.

Day 1 plasma pharmacokinetic data after the 0.5-hour collection for 2 participants were excluded due to vomiting. The 12-hour pharmacokinetic data for 1 participant on Day 1 and 1 participant on Day 4 were excluded because the samples were collected after the second daily dose.

FIG 3 Median gepotidacin urine concentration-time plot (pharmacokinetic population)

The lower limit of quantification (LLOQ) was 1.00 µg/ml. The dashed line represents LLOQ.

Data are plotted by the planned relative midpoint time for each interval.

FIG 4 Boxplot of change from baseline in QTcF over time (safety population)

The triangle symbol inside the box represents the mean value; the circle symbol represents individual change from baseline; the top, middle, and bottom line of the box represent the 75th, 50th (median), and 25th percentiles, respectively. The interquartile range (IQR) is the distance between the 25th and 25th percentiles. The top and bottom whiskers represent maximum and minimum, which are within 1.5× IQR from the edge of the box, respectively. Any points outside of the whiskers are deemed outliers. QTcF, QT interval corrected for heart rate according to Fridericia.
FIG 5 Individual clinical symptom score and boxplot of total score over time (ITT population)
(N = 22)

The box represents the 25% to 75% percentiles. Within the box, the horizontal line is the median and the square dot is the mean. The upper and lower whiskers represent 1.5× the interquartile range. The open circles represent individual participant outlier scores.
TABLE 1 Baseline demographics (ITT population)

| Demographics                  | Total  |
|-------------------------------|--------|
|                              | N = 22 |
| Age (years)                   | 37.1 (12.26) |
| Reproductive status, n (%)    |        |
| Postmenopausal                | 3 (14) |
| Sterile (of childbearing age) | 1 (5)  |
| Potentially able to bear children | 18 (82) |
| Body mass index (kg/m²)       | 26.96 (5.366) |
| Height (cm)                   | 163.22 (6.033) |
| Weight (kg)                   | 72.01 (16.015) |
| Ethnicity, n (%)              |        |
| Hispanic or Latino            | 6 (27) |
| Not Hispanic or Latino        | 16 (73) |
| Race, n (%)                   |        |
| Black or African American     | 4 (18) |
| White – White/Caucasian/European Heritage | 18 (82) |

*Mean (standard deviation).
| PK parameter | Summary statistic | Day 1       | Day 2       | Day 3       | Day 4       | Day 5       |
|--------------|------------------|-------------|-------------|-------------|-------------|-------------|
| C<sub>max</sub> (μg/ml) | Geo mean (%CVb) | 5.89 (47.3) | –           | –           | 8.44 (38.0) | –           |
|              | Min–max          | 1.82–12.8   | –           | –           | 3.82–16.8   | –           |
| T<sub>max</sub> (h) | Median           | 1.50        | –           | –           | 1.92        | –           |
|              | Min–max          | 0.470–3.07  | –           | –           | 0.450–4.12  | –           |
| AUC<sub>0→t</sub> (μg·h/ml) | Geo mean (%CVb) | 20.2 (28.6) | –           | –           | 29.3 (31.8) | –           |
|              | Min–max          | 11.0–31.0   | –           | –           | 15.2–49.5   | –           |
| CL/F (L/h)   | Geo mean (%CVb) | –           | –           | –           | 51.2 (31.8) | –           |
|              | Min–max          | –           | –           | –           | 30.3–98.7   | –           |
| R<sub>o</sub> | Geo mean (%CVb) | –           | –           | –           | 1.40 (20.4)<sup>a</sup> | –           |
|              | Min–max          | –           | –           | –           | 1.09–2.20   | –           |
| C<sub>i</sub> (μg/ml) | Geo mean (%CVb) | –           | 0.621 (62.3) | 0.789 (37.4) | 0.851 (41.4) | 0.819 (46.4) |
|              | Min–max          | –           | 0.122–1.84  | 0.371–1.60  | 0.460–1.99  | 0.327–1.93  |

<sup>a</sup>%CVb, between-participant geometric coefficient of variation; geo, geometric; max, maximum; min, minimum; N, number of participants in the treatment; n, number of participants with evaluable PK parameter data.

<sup>a</sup>AUC<sub>0→t</sub>; area under the concentration-time curve from time 0 to the 12-hour dosing interval; C<sub>i</sub>, predose concentration; CL/F, apparent steady-state clearance; C<sub>max</sub>, maximum observed concentration; R<sub>o</sub>, accumulation ratio based on AUC<sub>0→t</sub>; T<sub>max</sub>, time of occurrence of C<sub>max</sub>.

<sup>a</sup>n = 19.
TABLE 3 Summary of gepotidacin urine PK parameters (PK parameter population) (N = 22)\(^a\)

| PK parameter, Summary statistic | Day 1\(^c\) n = 20 | Day 2 n = 20 | Day 3 n = 21 | Day 4 n = 21 | Day 5 n = 21 |
|---------------------------------|-----------------------|--------------|--------------|--------------|--------------|
| **Ae\(_{12}\) (mg)** Geo mean (%CVb) | 299 (107.6)          | –            | –            | 460 (55.8)   | –            |
| **Ae\(_{12}\) (mg)** Min-max | 9.55–578              | –            | –            | 135–1,100    | –            |
| **AUC\(_o\) (\mu g.h/ml)** Geo mean (%CVb) | 3,742 (93.9)\(^d\) | –            | –            | 5,973 (87.2)\(^e\) | –            |
| **AUC\(_{0-24}\) (\mu g.h/ml)** Min-max | 1,034–24,858         | –            | –            | 2,256–30,425 | –            |
| **fe\(\%\) (%)** Geo mean (%CVb) | 19.9 (107.6)         | –            | –            | 30.7 (55.8)  | –            |
| **fe\(\%\) (%)** Min-max | 0.637–38.5            | –            | –            | 9.03–73.5    | –            |
| **CLR (L/h)** Geo mean (%CVb) | 14.8 (118.2)         | –            | –            | 15.7 (45.2)  | –            |
| **CLR (L/h)** Min-max | 0.420–41.5            | –            | –            | 8.31–41.6    | –            |
| **C\(_i\) (\mu g/ml)** Geo mean (%CVb) | –               | 279 (154.7) | 322 (138.8) | 327 (248.7) | 352 (146.5) |
| **C\(_i\) (\mu g/ml)** Min-max | –               | 26.8–1,800 | 42.1–3,670 | 32.8–4,540 | 68.2–4,010 |

\(^{ac}\)CVb, between-participant geometric coefficient of variation; geo, geometric; max, maximum; min, minimum; N, number of participants in the treatment; n, number of participants with evaluable values.

\(^d\)Ae\(_{12}\), total unchanged drug excreted over 12 hours; AUC\(_o\), area under the concentration-time curve from time 0 to the 12-hour dosing interval; AUC\(_{0-24}\), area under the concentration-time curve from time 0 to 24 hours; C\(_i\), predose concentration; CLR, renal clearance; fe\(\%\), percentage of the given dose of drug excreted in urine.

\(^e\)Day 1 urine PK parameter data for 2 participants were excluded from the summary statistics analysis due to vomiting.

\(^c\)n = 16.

\(^d\)n = 18.
**TABLE 4** Summary of adverse events (safety population)

| System organ class                  | Total               |
|-------------------------------------|---------------------|
| Preferred term                      | N = 22              |
| Any adverse event                   | 21 (95)             |
| Gastrointestinal disorders          | 21 (95)             |
| Diarrhoea                           | 18 (82)             |
| Nausea                              | 17 (77)             |
| Vomiting                            | 5 (23)              |
| Anal pruritus                       | 1 (5)               |
| Colitis                             | 1 (5)               |
| Dyspepsia                           | 1 (5)               |
| Eructation                          | 1 (5)               |
| Faeces soft                         | 1 (5)               |
| Flatulence                          | 1 (5)               |
| Infections and infestations         | 6 (27)              |
| Viral upper respiratory tract infection | 2 (9)              |
| Vulvovaginal mycotic infection      | 2 (9)               |
| Gastroenteritis                     | 1 (5)               |
| Upper respiratory tract             | 1 (5)               |
| Nervous system disorders            | 5 (23)              |
| Headache                            | 5 (23)              |
| Musculoskeletal and connective tissue disorders | 3 (14) |
| Back pain                           | 2 (9)               |
| Muscle spasms                       | 1 (5)               |
| Myalgia                             | 1 (5)               |
| System organ class                                      | Total |
|--------------------------------------------------------|-------|
| Preferred term                                         | N = 22|
| General disorders and administration site conditions   | n (%) |
| Chest discomfort                                       | 2 (9) |
| Psychiatric disorders                                  | 1 (5) |
| Major depression                                       | 1 (5) |
| Respiratory, thoracic, and mediastinal disorders        | 1 (5) |
| Oropharyngeal pain                                     | 1 (5) |
**TABLE 5** Summary of investigator-determined and sponsor-determined clinical outcome and response at test-of-cure by qualifying uropathogen isolated at baseline

| Qualifying uropathogen | Intent-to-Treat population N = 22 | Microbiological Intent-to-Treat population N = 8 |
|------------------------|----------------------------------|-----------------------------------------------|
| Clinical response, n (%) (95% CI) | Investigator-Determined | Sponsor-Determined | Investigator-Determined | Sponsor-Determined |
| Clinical outcome | | | | |
| All qualifying uropathogens | 8 | 8 | 8 | 8 |
| Success | 7 (88) (47 - 99) | 7 (88) (47 - 99) | 7 (88) (47 - 99) | 7 (88) (47 - 99) |
| Clinical success, n (%) | 7 (88) | 7 (88) | 7 (88) | 7 (88) |
| Failure | 1 (13) (<1 - 53) | 1 (13) (<1 - 53) | 1 (13) (<1 - 53) | 1 (13) (<1 - 53) |
| Clinical failure, n (%) | 1 (13) | 1 (13) | 1 (13) | 1 (13) |
| Unable to determine, n (%) | 0 | 0 | 0 | 0 |
| No qualifying uropathogen | 14 | 14 | – | – |
| Success | 12 (86) (57 - 98) | 12 (86) (57 - 98) | – | – |
| Clinical success, n (%) | 12 (86) | 12 (86) | – | – |
| Failure | 2 (14) (2 - 43) | 2 (14) (2 - 43) | – | – |
| Clinical failure, n (%) | 0 | 0 | – | – |
| Unable to determine, n (%) | 2 (14) | 2 (14) | – | – |
Qualifying uropathogen | Clinical response, n (%) (95% CI) | Clinical outcome | Intent-to-Treat population N = 22 | Microbiological Intent-to-Treat population N = 8
---|---|---|---|---
| Investigator-Determined | Sponsor-Determined | Investigator-Determined | Sponsor-Determined |

| Clinical outcome | All participants | Success | Failure<sup>a</sup> | Success | Failure<sup>a</sup> | Success | Failure<sup>a</sup> |
|---|---|---|---|---|---|---|---|

<sup>a</sup>A participant was counted more than once under a uropathogen category if multiple qualifying uropathogens within that uropathogen category were isolated at baseline for the participant. Other gram-negative bacilli consisted of Citrobacter koseri (1) and Klebsiella pneumoniae (1). CI, confidence interval.

<sup>b</sup>Clopper-Pearson CI.

<sup>c</sup>No failures required an alternative antibiotic for treatment of uncomplicated urinary tract infection throughout the study.
### TABLE 6 Uropathogens recovered at baseline (ITT population)\(^a\)

| Baseline uropathogens recovered | Total |
|---------------------------------|-------|
| **N = 22**                      |       |
| Total number of uropathogens recovered | 19     |
| Acinetobacter pittii            | 1 (5) |
| *Citrobacter freundii* complex  | 1 (5) |
| C. koseri                       | 1 (5) |
| *Escherichia coli*              | 14 (74)|
| Multidrug-resistant *E. coli*   | 2 (11)|
| Quinolone-resistant *E. coli*   | 1 (5)\(^b\) |
| *Klebsiella pneumoniae*         | 1 (5) |
| *Staphylococcus saprophyticus*  | 1 (5) |
| Total number of qualifying uropathogens recovered (≥10^5 CFU/ml) | 8      |
| C. koseri                       | 1 (13)|
| *E. coli*                       | 5 (63)|
| Multidrug-resistant *E. coli*   | 2 (25)|
| Quinolone-resistant *E. coli*   | 1 (13)\(^b\) |
| *K. pneumoniae*                 | 1 (13)|
| *S. saprophyticus*              | 1 (13)|

\(^a\) Multidrug-resistant (MDR) refers to a uropathogen that was resistant to ≥3 relevant antibiotic classes. The denominator for the percentage calculations was the number of pathogens.

\(^b\) Of the *E. coli* uropathogens, 2 were MDR and 1 of those was both MDR and quinolone-resistant.
TABLE 7 Summary of plasma and urine PK/PD, microbiological response, clinical response, and therapeutic response at TOC and follow-up by qualifying uropathogen isolated at baseline (micro-ITT population)*

| Participant No. | uropathogen                | MIC (µg/ml) | Gepotidacin AUC0-24/MIC | Gepotidacin AUC2-24/MIC | Plasma AUC0-24/MIC | Plasma AUC2-24/MIC | Microbiological response | Clinical response | Therapeutic response |
|-----------------|----------------------------|-------------|-------------------------|-------------------------|-------------------|-------------------|-------------------------|-------------------|-------------------|
| 1               | Citrobacter koseri         | 0.5         | 79.6                    | NA                      | Success           | Failure           | Success                 | Success           | Success           |
| 2               | Escherichia coli           | 2           | 22.1                    | 7,379                   | Success           | Success           | Success                 | Success           | Success           |
| 3               | E. coli                   | 0.5         | 90.5                    | 121,680                 | Success           | Success           | Success                 | Success           | Success           |
| 4               | E. coli                   | 2           | 30.6                    | 9,011                   | Success           | Success           | Success                 | Success           | Success           |
| 5               | E. coli                   | 1           | 30.6                    | 7,926                   | Failure0          | Failure1          | Success                 | Success           | Failure           |
| 6               | E. coli                   | 2           | NA                      | NA                      | Success           | Success           | Failure                 | Failure           | Failure           |
| 7               | Klebsiella pneumoniae     | 4           | 6.99                    | 1,292                   | Success           | Success           | Success                 | Success           | Success           |
| 8               | Staphylococcus saprophyticus | 0.06       | 1,040                   | 543,252                 | Success           | Success           | Success                 | Success           | Success           |

*AUC0-24, area under the concentration-time curve from time 0 to 24 hours; AUC2-24, area under the free-drug concentration-time curve; NA, not available (steady-state pharmacokinetic data not available); PD, pharmacodynamic; PK, pharmacokinetic; TOC, test-of-cure.

*Isolate was multidrug-resistant (e.g., resistant to ≥3 relevant antibiotic classes) and quinolone-resistant.

Microbiological failure due to an out-of-stability urine specimen.

Microbiological failures at TOC were also considered microbiological failures at follow-up.

*Isolate was multidrug-resistant.

Participant received only 6 doses of gepotidacin due to withdrawal by the participant. The participant had a baseline total clinical score of 10.
that decreased to 2 at TOC; however, that was not complete symptom resolution and the clinical response was clinical failure. At follow-up, the total clinical symptom score was 5, which was a sponsor-determined clinical outcome of delayed clinical success; however, the clinical response remained a clinical failure per the analysis plan.
Enrolled (n = 22), received at least 1 dose of gepotidacin, and had evaluable PK concentration and parameter data

ITT, PK, PK Parameter, and Safety Populations

Participants with a qualifying baseline uropathogen (n = 8)
Micro-ITT and PKPD Populations

Participants withdrawn from the study (n = 2)
Reasons:
- Lost to follow-up (n = 1)
- Other (n = 1)

Completed study (n = 20)
