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ARTICLE

Pharmacokinetics, safety, and tolerability of gepotidacin administered as single or repeat ascending doses, in healthy adults and elderly subjects

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Abstract

Gepotidacin, a novel, first-in-class triazaacenaphthylene antibiotic, inhibits bacterial DNA replication by a distinct mechanism of action. We report the pharmacokinetics (PKs), safety, and tolerability of gepotidacin following single or multiple ascending doses. Studies 1 and 2 were randomized, single-blind, placebo-controlled trials in healthy adults aged 18–60 years, who received single (study 1 [NCT02202187]; 100–3000 mg) or repeat (study 2 [NCT01706315]; 400 mg twice daily to 2000 mg thrice daily) ascending doses of gepotidacin. Study 3 (NCT02045849) was an open-label, three-part, study in healthy adults; here, we report on part 3, a two-period, repeat-dose, crossover study. Healthy elderly participants received repeat 1500 mg gepotidacin twice daily with or without a moderate-fat meal. Primary end points were PKs (studies 1 and 2) and safety (studies 1 and 3 part 3). Gepotidacin PK parameters were comparable across all ages and were dose proportional. In all studies, gepotidacin was readily absorbed with median time to maximum concentration observed ranging from 1.0 to 4.0 h across all doses. Median apparent terminal phase half-life was consistent across studies and doses (range: 5.97–19.2 h). Steady-state was achieved following repeated dosing for 3–5 days; gepotidacin PK parameters were time invariant after repeated oral dosing. A moderate-fat meal did not affect gepotidacin PK parameters. Gepotidacin was generally well-tolerated, with no drug-related serious adverse events reported. Collectively, these PK and safety data across a wide range of doses in healthy participants aged greater than or equal to 18 years support the development of gepotidacin in further clinical studies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Bacteria, such as *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, are frequently resistant to current antibiotics, including fluoroquinolones. New antibiotics with novel mechanisms of action can play a role in treating

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patients with uncomplicated urinary tract infections, urogenital gonorrhea, and other indications with bacteria resistant to currently available antibiotics.

WHAT QUESTION DID THIS STUDY ADDRESS?

These three phase I studies investigated the pharmacokinetics (PKs), safety, and tolerability of gepotidacin administered as a single or repeat dose in healthy participants aged 18–60 years and greater than or equal to 65 years.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study describes the PKs, safety, and tolerability of a new class of antibiotic, triazaacenaphthylene bacterial topoisomerase inhibitors, being developed for the treatment of uncomplicated urinary tract infections and urogenital gonorrhea.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These results support the further clinical development of gepotidacin, inform on dosing, and the safety and tolerability of gepotidacin for clinical trials in individuals with urinary tract infections and gonorrhea across a wide range of ages.

INTRODUCTION

Gepotidacin, a novel, first-in-class triazaacenaphthylene antibiotic, inhibits bacterial DNA replication by a distinct mechanism of action,[1] conferring activity against most strains of *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including those resistant to current antibiotics.[2–4]

Bacterial topoisomerase inhibitors (e.g., gepotidacin) bind to a similar region of the same target proteins as quinolone antibiotics.[5,6] However, they are structurally and pharmacologically distinct from quinolones[1,7,8]; they recognize different amino acids and inhibit different stages of the catalytic cycle of target proteins (Figure 1). Gepotidacin's novel mode of action confers activity in vitro against most strains of *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including target pathogens resistant to established antibiotics, such as fluoroquinolones.[2,3,9–11] Phase III clinical trials are ongoing to investigate gepotidacin for treatment of uncomplicated urinary tract infections (NCT04020341 and NCT04187144) and urogenital gonorrhea (NCT04010539).

Here, we present data from three phase I clinical trials evaluating the pharmacokinetics (PKs), safety, and tolerability of gepotidacin following single (study 1; NCT02202187) and repeat (study 2; NCT01706315) ascending oral doses in healthy adults aged 18–60 years, and following repeat oral doses in healthy adults aged greater than or equal to 65 years (study 3 part 3; NCT02045849).

METHODS

Study design

Studies 1 and 2 were randomized, single-blind, placebo-controlled trials in healthy adults aged 18–60 years (Figure 2). Study 3 was an open-label, three-part study. Here, we report on part 3: a two-period, repeat-dose, crossover study in healthy adults aged greater than or equal to 65 years (Figure 2).

Primary end points in studies 1 and 2 were to assess gepotidacin PKs, safety, and tolerability following single and repeat oral doses, respectively. The primary end point in study 3 part 3 was to assess repeat oral gepotidacin safety and tolerability in healthy elderly subjects in fasted and fed states. Secondary end points in studies 1 and 2 included, but were not limited to, assessment of dose proportionality. Study 3 part 3's secondary end point was to assess gepotidacin PKs.

All studies were performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. The institutional review board or independent ethics committee of each site approved the studies. All participants provided written informed consent.

Participants

Key inclusion criteria for all studies were that participants were determined "healthy" by a qualified physician, had body mass index (BMI) 19–31 kg/m^2, and had normal liver function. In studies 1 and 2, participants were aged 18–60 years; in study 3 part 3, participants were aged greater than or equal to 65 years. All studies excluded participants with a history of clinically significant organ conditions, smoking or use of nicotine-containing products within 3 months of screening, and history of drug and/or alcohol abuse. Studies 1 and 2 additionally excluded participants who used prescription drugs during the study. Full inclusion and exclusion criteria can be found in Methods S1.

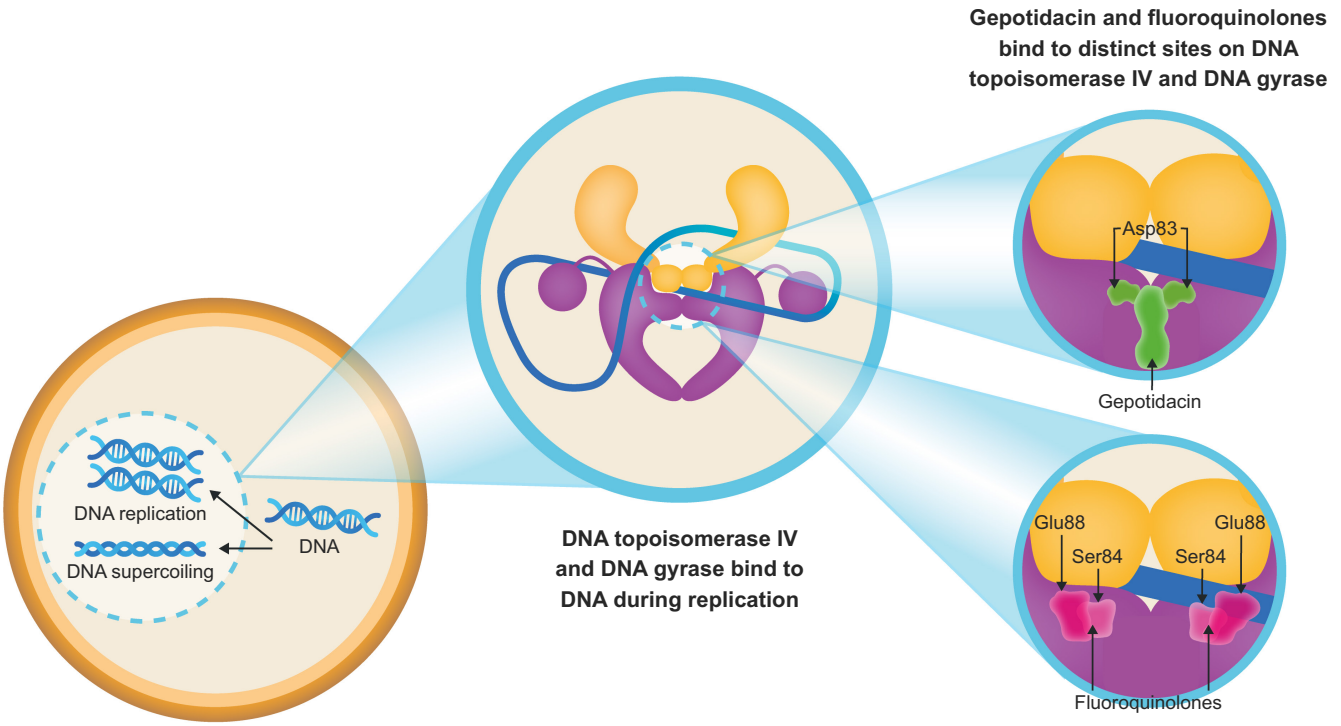

FIGURE 1 Simplistic representation showing fluoroquinolones and triazaacenaphthylene (e.g., gepotidacin) antibiotics bind to different sites on DNA gyrase/DNA topoisomerase IV bacterial targets. Two fluoroquinolone molecules can bind at the two separate sites of DNA cleavage on DNA gyrase (a type of topoisomerase) and DNA topoisomerase IV, by binding with the Ser84 and Glu88 residues (*Staphylococcus aureus* numbering of DNA gyrase) that also involve a divalent magnesium ion and water molecules. This results in stabilization of double-stranded DNA breaks that are lethal to the bacterial cell if they are not repaired. These quinolone binding residues are most commonly mutated in fluroquinolone-resistant clinical strains. In contrast, a single gepotidacin molecule binds to one site on DNA gyrase and topoisomerase IV through interactions with Asp83 of DNA gyrase or topoisomerase IV involving water molecule, resulting in enhancement of single-stranded DNA breaks, which can be lethal to the bacteria.[1]

Administration of study drug

In study 1, six cohorts of eight participants (6 participants received gepotidacin and 2 participants received placebo in each cohort; Figure 2) received single doses of gepotidacin or placebo at 100, 800, 1500, 2300, and 3000 mg in capsule formulation under fasted conditions, except for the 2300 mg dose level, which was also given with a moderate-fat meal. Doses were escalated in a sequential manner; sentinel dosing was used for all dose levels, except for the fed cohort. For sentinel dosing, the cohort was divided into two subgroups, in which three participants were dosed initially with gepotidacin and the remaining five participants were dosed if no acute safety issues were observed within 48 h in the first subgroup.

In study 2, seven cohorts of eight or 16 participants (multiples of 6 participants received gepotidacin and 2 participants received placebo; Figure 2) received repeat ascending doses of gepotidacin or placebo at 400, 800, 1500, or 2300 mg twice daily (b.i.d.), or 1500 or 2000 mg three times daily (t.i.d.) for 14 days; planned cohort enrollment was based on the use of a sequential panel. A single dose was administered on day 1 for characterization of single-dose PKs, followed by b.i.d. or t.i.d. dosing on days 3–16. All doses were given in capsule formulation with a moderate-fat meal, except the 1500 mg b.i.d. dose, which was given under fasted and fed conditions.

In study 3 part 3, two cohorts of eight participants received gepotidacin 1500 mg b.i.d. tablet formulation under fasted or fed conditions for 5 days, followed by a washout period of at least 7 days, then another 5-day treatment period of gepotidacin 1500 mg b.i.d. under the alternate condition (Figure 2).

Blood/urine collection and processing

PK sampling was performed through 72 h postdose in study 1, through 48 h after the first dose and to the dosing interval on day 16 in study 2, and predose on days 3 and 4, and postdose on day 5 in study 3 part 3. Blood and urine sampling schedules for each study can be found in Methods S1.

In study 1, blood concentrations of gepotidacin and its metabolites were conducted using high performance liquid chromatography tandem mass spectrometry (LC–MS/MS)

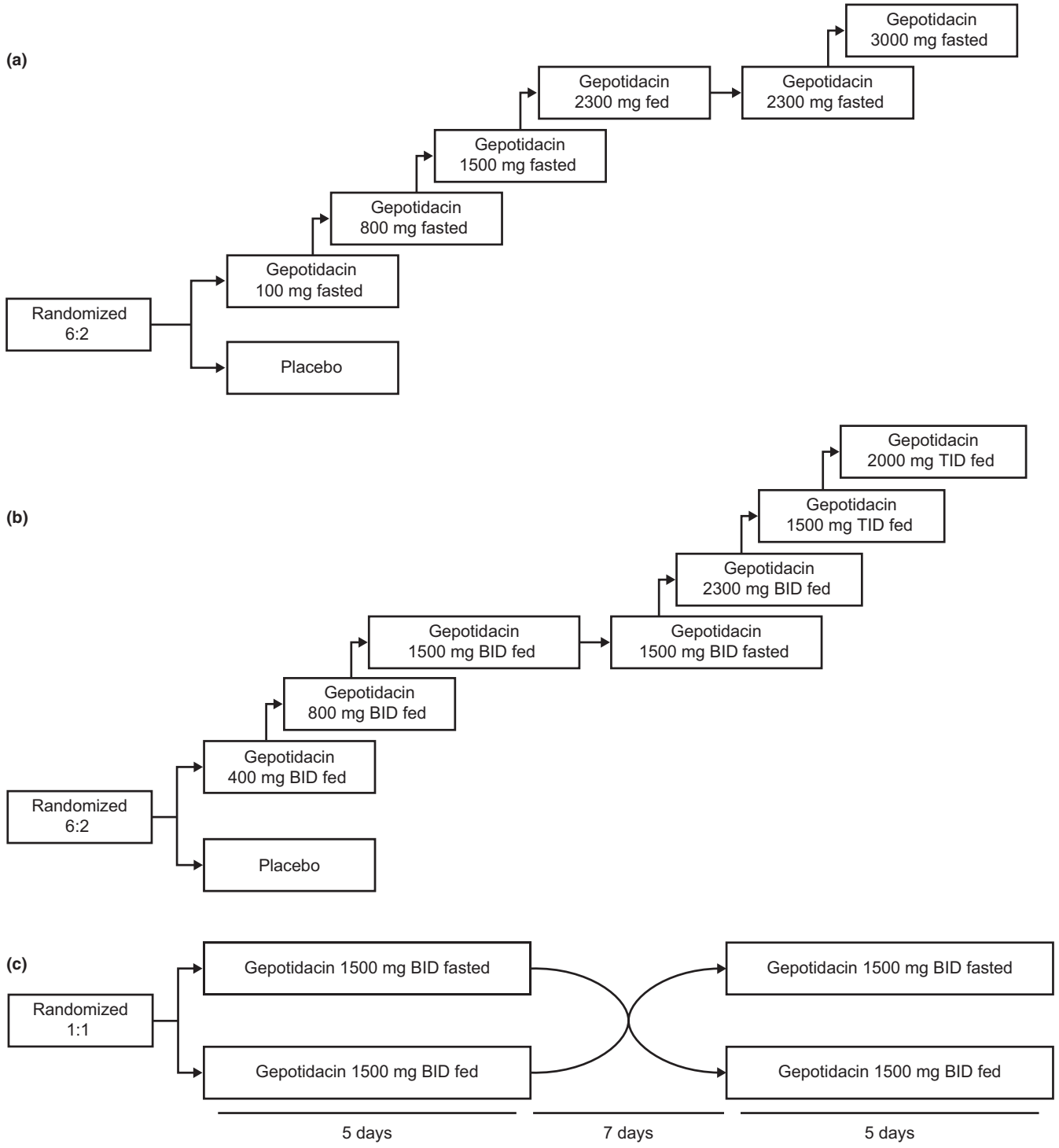

FIGURE 2 Study design of (a) study 1 (single ascending dose, aged 18–60 years), (b) study 2 (repeat ascending doses, aged 18–60 years), and (c) study 3 part 3 (repeat dose with or without food, aged ≥65 years).

validated over the concentration range of 10–5000 ng/mL. Urine concentrations were conducted using LC–MS/MS validated over the concentration range 100–50,000 ng/mL for gepotidacin. Plasma concentrations were conducted using LC–MS/MS validated over the range of 10–5000 ng/mL and 50–10,000 ng/mL for gepotidacin metabolites. All analytical methods were based on protein precipitation using acetonitrile, containing gepotidacin and its metabolites as internal standards, followed by LC–MS/MS.

In studies 2 and 3, gepotidacin plasma concentrations were conducted using LC–MS/MS validated over the range 10–5000 ng/mL based on protein precipitation extraction using acetonitrile followed by LC–MS/MS. Further information is available in Methods S1.

Safety assessments

Clinical safety assessments were performed at regular intervals for each treatment period throughout all studies and included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms, and physical examinations.

Statistical analyses

In study 1, a sample size of 36 participants was assumed to provide a precision of 5.4% and 8% for 20–30% coefficients of variation, respectively, for area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) based on the $\log_e$-scale with a type I error rate of 10%. In study 2, a sample size of 72 was largely based on feasibility; however, the precision of $AUC_{0-\infty}$, time of last quantifiable concentration (AUC_{0-t}), and maximum plasma concentration (C_{max}) based on the $\log_e$-scale with a type I error rate of 10% were considered. In study 3 part 3, a sample size of 12 participants was estimated to provide 85% power of observing greater than or equal to one gastrointestinal (GI) AE with an incidence rate of 15%.

The safety population included all participants who received a gepotidacin dose. The PK population included all participants in the safety population for whom evaluable and valid PK parameters were derived. The fasted/fed population included participants in study 3 part 3 that received gepotidacin in both fasted and fed states.

Blood and urine concentration-time data were analyzed using noncompartmental methods with Phoenix WinNonlin (versions 5.2, 6.2.1, and 6.3 for studies 1, 2, and 3, respectively). Calculations were based on recorded sampling times.

In study 1, the following PK parameters were determined from the blood concentration–time data: C_{max}; time to C_{max} (T_{max}); AUC_{0-t}; $AUC_{0-\infty}$; and apparent terminal phase half-life ($t_{½}$). $AUC_{0-\infty}$ and C_{max} were used for assessment of dose proportionality. The percentage of unchanged gepotidacin excreted in urine and renal clearance (creatinine concentration) were also calculated. Food-effect estimation was conducted based on gepotidacin 2300 mg in fasted/fed states.

In study 2, values for the following PK parameters were estimated following administration of a single gepotidacin dose of 400, 800, 1500 (fasted or fed), 2000, and 2300 mg on day 1, and following b.i.d. administration of 400, 800, 1500 (fasted or fed), and 2300 mg or t.i.d. administration of 1500 and 2000 mg on day 16, as appropriate: C_{max}; T_{max}; trough plasma concentration (C_{trough}; observed values at the predose time point on days 14, 15, and 16); AUC over the dosing interval ($AUC_{0-\tau}$), AUC_{0-24}, and $AUC_{0-\infty}$; accumulation ratio (Ro; $AUC_{0-\tau}$ on study day 16/$AUC_{0-\tau}$ on day 1); and apparent and effective terminal phase $t_{1/2}$. $AUC_{0-\infty}$ and C_{max} were used for assessment of dose proportionality after a single dose, and $AUC_{0-\tau}$ and C_{max} were used to assess dose proportionality after repeat doses. Steady-state was estimated based on C_{trough} slope (day 1 single dose and days 3–16 b.i.d.).

In study 3 part 3, the following PK parameters were determined from the plasma concentration-time data: C_{max}; T_{max}; $AUC_{0-\tau}$, AUC_{0-t}, and $AUC_{0-\infty}$; C_{trough}; and $t_{½}$. For food-effect analysis, T_{max} was analyzed nonparametrically using the Wilcoxon matched pairs method to compute the point estimate and 90% confidence intervals (CIs) for the median difference for each comparison of interest.

For all studies, AUC and C_{max} were log transformed. Food effect was assessed using a mixed-effects model and mean difference and 90% CIs were reverse log-transformed to obtain geometric mean ratios and CIs.

RESULTS

Study populations

In study 1 (single ascending dose study), 48 participants were enrolled between September 23, 2011 and February 15, 2012 (Table 1); 36 participants received gepotidacin and were included in the PK population. One participant experienced chest discomfort and was withdrawn from the study; this was classed as not related to the study drug (Figure S1). Most participants were White (79%) and men (79%); mean age (SD) was 37.5 years (12.7) and mean (SD) BMI was 25.6 kg/m^2 (3.3; Table 1).

In study 2, (repeat ascending dose study), 72 participants were enrolled between October 17, 2012 and December 13, 2013 (Table 1); 54 received gepotidacin and were included in the PK population. Five participants did not complete the study (2 withdrew consent, 2 withdrew due to AEs [1 event of treatment-related occult blood positive stool sample and 1 event of treatment-related abdominal tenderness], 1 reached protocol-defined stopping criteria; Figure S2). The majority of participants were White (53%) and men (82%); the mean age (SD) was 35.4 years (10.9) and mean BMI (SD) was 25.9 kg/m^2 (3.1).

In study 3 part 3, (2-period, repeat-dose food-effect study in elderly adults), 16 participants were enrolled between January 28, and August 21, 2014 (Table 1); 15 were included in the PK population and 13 were included in the fasted/fed population. Four participants did not complete the study (2 withdrew due to AEs [2 events of grade 1 treatment-related occult blood positive stool sample], 1 reached protocol-defined stopping criterion, 1 was withdrawn by the study physician because of increasing

TABLE 1 Baseline demographics across studies in the safety population

Characteristic	Study 1 (*N* = 48)	Study 2 (*N* = 72)	Study 3 part 3 (*N* = 16)
Age, years, mean (SD)	37.5 (12.7)	35.4 (10.9)	69.1 (4.1)
Male, *n* (%)	38 (79)	59 (82)	9 (56)
Body mass index, kg/m^2, mean (SD)	25.6 (3.3)	25.9 (3.1)	26.9 (2.2)
Height, cm, mean (SD)	175.2 (7.9)	173.8 (9.9)	170.0 (8.2)
Weight, kg, mean (SD)	78.9 (12.9)	78.4 (12.7)	78.4 (12.2)
Ethnicity, *n* (%)			
Hispanic/Latino	4 (8)	7 (10)	0
Not Hispanic/Latino	44 (92)	65 (90)	16 (100)
Race			
African American/African Heritage	9 (19)	28 (39)	0
American Indian/Alaska Native	1 (2)	3 (4)	0
Asian – East Asian Heritage	0	1 (1)	0
Asian – South East Asian Heritage	0	1 (1)	0
Native Hawaiian/other Pacific Islander	0	1 (1)	0
White/Caucasian/European Heritage	38 (79)	38 (53)	16 (100)

Notes: Study 1: Single ascending oral doses in healthy adults aged 18–60 years.
Study 2: Repeat ascending oral doses in healthy adults aged 18–60 years.
Study 3 part 3: Repeat oral doses in healthy adults aged greater than or equal to 65 years.

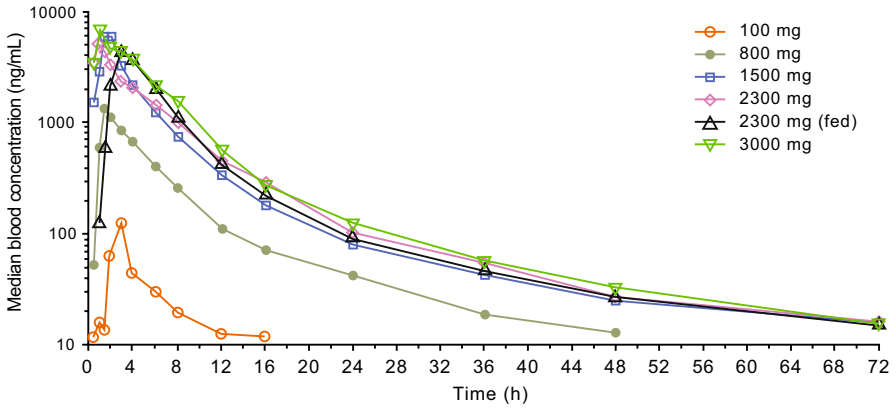

FIGURE 3 Median blood-concentration time profile (semi-log scale) for gepotidacin following single ascending oral doses in healthy adults aged 21–59 years (study 1) in the phamacokinetic population. Gepotidacin blood concentration-time profile displayed bi-phasic elimination. $n = 6$ per dose.

liver transaminases; Figure S3). All participants were White, the majority were men (56%), mean age (SD) was 69.1 years (4.1), and mean BMI (SD) was 26.9 kg/m^2 (2.2).

PK analyses

In healthy adults aged 21–59 years after single ascending doses of gepotidacin (study 1), gepotidacin blood concentration–time profile on a semi-logarithmic plot was biphasic (Figure 3). Gepotidacin was rapidly absorbed with a median T_{max} ranging between 1.0 and 3.5 h across all doses (Table 2). In study 1, a moderate-fat meal resulted in a 6%, 7%, and 16% decrease in mean $AUC_{0\text{-}t}$, (ratio: 0.94 [90% CI, 0.74–1.19]) $AUC_{0\text{-}\infty}$ (ratio: 0.93 [90% CI, 0.74–1.18]), and C_{max} (ratio: 0.84 [90% CI, 0.59–1.20]; Figure 4) respectively, and slightly delayed median T_{max} compared with fasted PK parameters (geometric mean ratio 2.3 [90% CI, 1.5, 3.5]). Except for the 100 mg dose, gepotidacin was eliminated with median terminal elimination $t_{½}$ ranging between 12.4 and 19.2 h; exposure increased dose-dependently and between-subject variability was low to moderate (15–32%). $AUC_{0-\tau}$, $AUC_{0-\infty}$, and C_{max} values increased in a greater than dose-proportional manner over the dose range of 100–3000 mg, but approached dose proportionality when the low dose of 100 mg was excluded. Blood partitioning of gepotidacin was similar between blood and plasma with geometric mean ratios of 0.86, 0.87, and 0.92 for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, respectively, and 90% CIs between 0.8 to 1.25. The main cleavage amine metabolite of gepotidacin readily appeared in whole

blood at higher doses of 1500–3000 mg, but exposure levels were low (<1%) when compared with the gepotidacin parent compound. Approximately 16 and 24% of the absorbed gepotidacin dose was excreted unchanged in urine within 72 h following 2300 and 3000 mg doses, respectively. Median renal clearance appeared to be dose independent (2300 mg: 15.4 L/h [range, 11.8–21.7]; 3000 mg: 16.7 L/h [range, 15.1–26.5]; Table S1).

In healthy adults aged 20–58 years following repeated ascending doses (study 2), gepotidacin was readily absorbed across all dose levels with a median T_{max} ranging between 1.25–2.5 h on day 1 and 1.5–2.0 h on day 16 (Table 2). After reaching C_{max} following a single dose, the mean terminal elimination $t_{½}$ ranged between 11.2 and 14.7 h across all dose levels; after 14 days of repeat b.i.d. or t.i.d. doses, the mean effective $t_{½}$ ranged from 6.12–8.96 h across all dose levels. C_{trough} samples collected on days 14, 15, and 16 indicated steady-state was achieved following repeat b.i.d. or t.i.d. dosing. Drug accumulation was low (27–52%) following b.i.d. oral dosing and moderate (67–70%) following t.i.d. oral dosing. A moderate-fat meal had a minimal effect on the AUC and C_{max} of gepotidacin following a single or repeat b.i.d. dose of 1500 mg in the fasted or fed state (Figure 4a,b). $AUC_{0-\tau}$, $AUC_{0-\infty}$, and C_{max} values increased in a greater than dose-proportional manner over the dose range of 400–2300 mg following single or repeat b.i.d. doses. As there were only two t.i.d. dose groups, dose proportionality could not be assessed for this regimen. The $AUC_{0-\infty}$ after a single dose was similar to the $AUC_{0-\tau}$ after repeat b.i.d. and t.i.d. dosing for 14 days, demonstrating linear gepotidacin clearance.

In healthy elderly adults following repeated doses of gepotidacin 1500 mg b.i.d. (study 3 part 3), median T_{max} was 1.5 h under fasted conditions and 4.0 h under fed conditions (Table 2). After reaching C_{max} (fasted: 4.9 μg/mL; fed: 5.3 μg/mL), gepotidacin concentrations declined, with mean apparent terminal phase $t_{½}$ values of 8.1 h under fasted conditions and 8.3 h under fed conditions. Geometric means of C_{max} (ratio: 1.07 [90% CI, 0.89–1.29]) and $AUC_{0-\tau}$ (ratio: 1.16 [90% CI, 1.05–1.27]) under fasted and fed conditions were comparable (Figure 4b). Geometric mean C_{trough} values for days 3–5 were consistent, with steady-state achieved following repeated b.i.d. dosing for 3–5 days.

Safety

After single ascending doses of gepotidacin in healthy adults aged 21–59 years (study 1; Table 3), 13 of 36 (36%) participants reported AEs. Drug-related AEs were reported by 11 participants, all considered mild or moderate in intensity; the most common drug-related AEs were nausea (5/36 [14%]), diarrhea (4/36 [11%]), and abdominal pain (3/36 [8%]). One serious AE (SAE) was reported in the 2300 mg fasted cohort, deemed unrelated to study drug; the participant was withdrawn from the study and hospitalized following chest discomfort that occurred ~4 h postdose on day 1. Electrocardiogram showed pronounced T inversion and ST (T/ST) depression, thought to be related to right bundle branch block. There were no drug-related SAEs and no clinically significant changes in laboratory values, vital signs, or electrocardiograms. Food appeared to improve tolerability of gepotidacin; incidence of GI AEs increased between 800 and 3000 mg in the fasted state, but no GI-related AEs were reported in the 2300 mg fed cohort.

After repeat ascending doses of gepotidacin in healthy adults aged 20–58 years (study 2; Table 3), 53 of 54 (98%) participants reported AEs; most AEs were mild to moderate in intensity and were more frequent at doses of 800 mg b.i.d. and higher; all AEs were considered drug-related. Six events of severe AEs were reported in three participants (proteinuria, increased alanine aminotransferase [ALT], increased aspartate aminotransferase [AST], *Clostridium difficile* [*C. difficile*] colitis, and infectious diarrhea). In all participants, the most frequent drug-related AEs were proteinuria (48/54 [89%]), diarrhea (24/54 [44%]), flatulence (18/54 [37%]), and increased ALT levels (11/54 [24%]). Most proteinuria events were trace or 1+ on urine dipstick. Increased liver transaminases were reported at higher doses of gepotidacin in study 2; all were asymptomatic and resolved. One participant had liver function test (LFT) results greater than or equal to three times the upper limit of normal after treatment stopped, which was related to hepatitis E. Tolerability appeared to be similar when dosing 1500 mg gepotidacin under fasted or fed conditions. At the highest dose level of 2000 mg t.i.d., three participants were withdrawn from treatment; two cases were due to mild/moderate GI AEs, and one case was due to acute hepatitis E. No SAEs were reported and no clinically significant changes in vital signs or electrocardiograms were observed.

After repeat doses of gepotidacin 1500 mg b.i.d. in healthy elderly adults (study 3 part 3; Table 3), the incidence of AEs was similar between the fasted (12/14 [86%]) and fed (13/15 [87%]) groups. Drug-related AEs were reported by 71% and 80% of participants in the fasted and fed groups, respectively. Diarrhea was the most commonly reported drug-related AE and was reported for a similar number of participants under fasted (4/14 [29%]) and fed (5/15 [33%]) conditions. All AEs were considered mild to moderate in intensity. GI AEs occurred in a numerically lower percentage of participants under fed conditions (60%) than under fasted conditions (71%); in addition, some participants under fasted conditions were provided with a snack ~1 h postdose to alleviate their GI symptoms.

TABLE 2 Summary of selected blood (study 1) or plasma (studies 2 and 3 part 3) pharmacokinetic parameters for gepotidacin across studies in the pharmacokinetic population

	Study 1						Study 2								Study 3 part 3	
Parameter	**100 mg –*fasted* ($n = 6$)**	**800 mg –*fasted* ($n = 6$)**	**1500 mg –*fasted* ($n = 6$)**	**2300 mg –*fasted* ($n = 6$)**	**2300 mg –*fed* ($n = 6$)**	**3000 mg –*fasted* ($n = 6$)**	**Visit[a]**	**400 mg b.i.d. –*fed* ($n = 6$)**	**800 mg b.i.d. –*fed* ($n = 12$)**	**1500 mg b.i.d. –*fed* ($n = 12$)**	**1500 mg b.i.d. –*fasted* ($n = 6$)**	**2300 mg b.i.d. –*fed* ($n = 6$)**	**1500 mg t.i.d. –*fed* ($n = 6$)**	**2000 mg t.i.d. –*fed* ($n = 6$)**	**1500 mg b.i.d. –*fasted* ($n = 13$)**	**1500 mg b.i.d. –*fed* ($n = 13$)**
C_{max}, μg/mL[b]	0.100 (70.2)	1.94 (41.8)	6.92 (14.0)	6.00 (30.0)	5.06 (38.9)	9.79 (45.5)	Day 1	0.60 (18.4)	1.86 (53.2)	4.08 (40.3)	5.07 (20.3)	6.73 (30.2)	4.80 (22.3)	5.49 (16.4)	4.89 (33.8)	5.25 (38.2)
							Day 16	0.87 (104.1)	2.28 (85.4)	5.41 (31.1)	6.50 (35.9)	7.85 (7.4)	6.04 (25.0)	8.64 (24.7)		
T_{max}, h[c]	3.0 (1.50–4.00)	1.75 (1.00–3.00)	1.50 (1.50–2.00)	1.00 (0.50–2.00)	3.50 (2.00–6.00)	1.25 (1.00–2.00)	Day 1	2.01 (1.50–4.00)	1.76 (1.00–4.00)	2.00 (1.50–4.02)	1.25 (1.00–1.50)	1.75 (1.50–6.00)	2.50 (1.98–4.00)	2.50 (1.50–3.07)	1.5 (1.0–3.0)	4.0 (1.5–6.0)
							Day 16	1.75 (1.50–4.02)	2.00 (1.50–4.05)	2.00 (1.50–4.00)	1.50 (1.50–2.00)	2.00 (1.50–4.00)	2.00 (2.00–3.00)[h]	1.50 (1.50–3.00)[i]		
C_{τ}, μg/mL[b]																
Day 3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.661 (24.7)	0.805 (39.6)[d]
Day 4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.722 (46.2)	0.632 (66.9)[d]
Day 5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.761 (49.1)	0.743 (47.7)[e]
AUC_{0-t}, μg·h/mL[b]	0.423 (31.3)	7.20 (15.0)	24.6 (15.3)	26.9 (25.1)[f]	25.3 (17.9)	37.9 (28.7)	Day 1	2.73 (21.6)	7.91 (36.4)	19.7 (21.9)	15.1 (25.8)	27.2 (22.1)	19.7 (23.6)	24.3 (13.5)	–	–
AUC_{0-24}, μg·h/mL[b]	–	–	–	–	–	–	Day 1	2.60 (21.5)	7.38 (38.0)	18.9 (22.6)	14.3 (25.2)	26.1 (22.2)	18.9 (23.9)	23.2 (14.6)	–	–
$AUC_{0-\tau}$, μg·h/mL[b,g]	–	–	–	–	–	–	Day 1	2.22 (23.3)	6.60 (40.5)	17.3 (23.7)	13.0 (24.9)	23.9 (21.5)	15.2 (21.6)	18.6 (14.2)	21.1 (28.8)	25.6 (35.5)
							Day 16	3.00 (43.0)	8.40 (40.1)	22.4 (29.6)	19.8 (31.5)	36.0 (11.7)	24.1 (29.4)[h]	30.3 (14.4)[i]		
$AUC_{0-\infty}$, μg·h/mL[b]	0.596 (27.6)[h]	7.44 (14.7)	25.0 (15.2)	27.5 (25.6)	25.7 (18.0)	38.3 (28.6)	Day 1	2.94 (19.6)	8.20 (37.0)[j]	20.1 (21.5)	15.5 (26.1)	27.5 (21.8)	20.0 (23.4)	24.8 (12.4)	–	–

TABLE 2 (Continued)

Parameter	Study 1						Study 2								Study 3 part 3	
	100 mg – *fasted* ($n = 6$)	800 mg – *fasted* ($n = 6$)	1500 mg – *fasted* ($n = 6$)	2300 mg – *fasted* ($n = 6$)	2300 mg – *fed* ($n = 6$)	3000 mg – *fasted* ($n = 6$)	Visit[a]	400 mg b.i.d. – *fed* ($n = 6$)	800 mg b.i.d. – *fed* ($n = 12$)	1500 mg b.i.d. – *fed* ($n = 12$)	1500 mg b.i.d. – *fasted* ($n = 6$)	2300 mg b.i.d. – *fed* ($n = 6$)	1500 mg t.i.d. – *fed* ($n = 6$)	2000 mg t.i.d. – *fed* ($n = 6$)	1500 mg b.i.d. – *fasted* ($n = 13$)	1500 mg b.i.d. – *fed* ($n = 13$)
Ro[b]	–	–	–	–	–	–	Day 16	1.35 (25.5)	1.27 (37.4)	1.30 (34.9)	1.52 (25.7)	1.50 (24.4)	1.69 (17.5)[h]	1.72 (8.8)[i]	–	–
$t_{1/2}$[k]	5.97 (3.45–8.64)[h]	12.4 (9.19–13.7)	16.1 (10.4–24.3)	19.2 (12.3–32.2)[f]	18.9 (9.5–22.4)	15.3 (8.1–23.2)	Day 1	11.2 (17.9)	14.7 (17.9)[j]	12.0 (17.9)	12.3 (25.3)	11.4 (14.5)	11.8 (13.8)	13.6 (21.5)	8.11 (15.7)	8.34 (12.8)[l]
$t_{1/2}$ (effective)[b]	–	–	–	–	–	–	Day 16	7.48 (11.0)[f]	7.20 (42.9)[m]	6.56 (56.4)[n]	8.96 (21.2)[f]	7.27 (42.3)	6.12 (28.9)[h]	6.37 (13.8)[i]	–	–

Notes: Study 1: Single ascending oral doses in healthy adults aged 21–59 years.

Study 2: Repeat ascending oral doses in healthy adults aged 20–58 years.

Study 3 part 3: Repeat oral doses in healthy adults aged greater than or equal to 64 years.

Abbreviations: AUC, area under the concentration-time curve from time 0 to the time point indicated; b.i.d., twice daily; C_{max}, maximum observed concentration; C_τ, trough plasma concentration; CVb, between-subject coefficient of variation; Ro, accumulation ratio ($AUC_{0-\tau}$ on day 16/$AUC_{0-\tau}$ on day 1); $t_{1/2}$, terminal phase half-life; t.i.d., three times daily; T_{max}, time to C_{max}.

[a]Visit on day 16 corresponded to steady-state pharmacokinetics on day 14.

[b]Geometric mean (CVb%).

[c]Median (range).

[d]$n = 15$.

[e]$n = 14$.

[f]$n = 5$.

[g]$\tau = 12$ h for b.i.d. dosing and $\tau = 8$ h for t.i.d. dosing.

[h]$n = 4$.

[i]$n = 3$.

[j]$n = 11$.

[k]Study 1, median (range); study 2, geometric mean (CVb%); study 3, arithmetic mean (CVb%) and $n = 13$ for fasted, $n = 12$ for fed.

[l]$n = 12$.

[m]$n = 9$.

[n]$n = 10$.

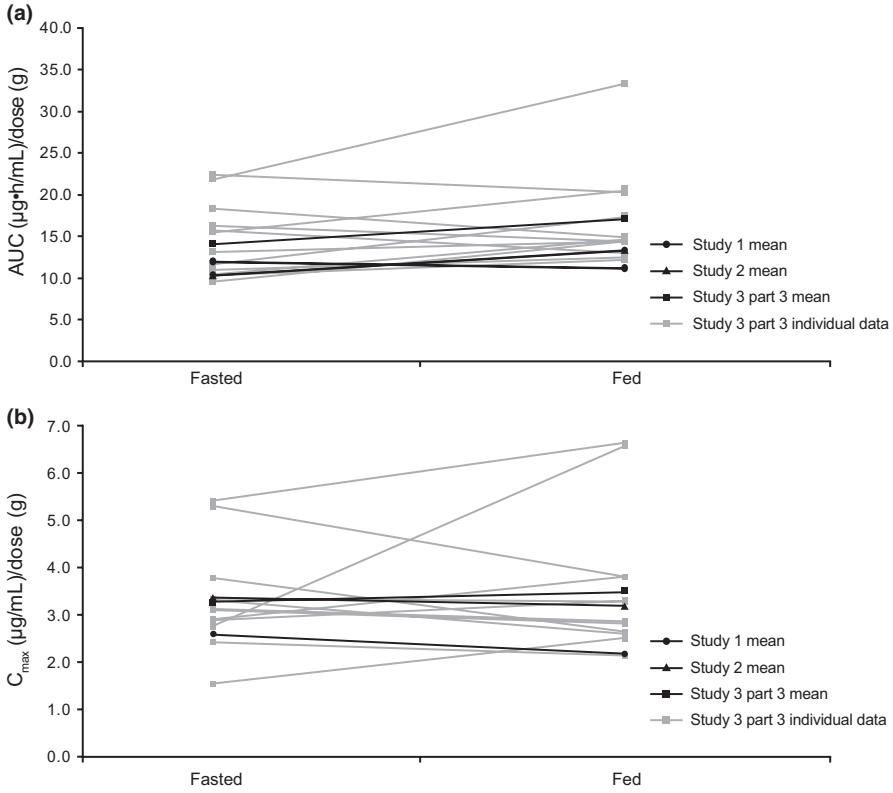

FIGURE 4 Geometric mean AUC (a) and C_{max} (b) concentrations for all studies and individual concentrations for participants form study 3 part 3 for C_{max}, normalized by dose in fasted and fed participants. Food had little effect on the rate and extent of absorption across all studies. $n = 6$ per dose for studies 1 and 2, and $n = 15$ per dose for study 3. Matched data were available for $n = 12$ in study 3 part 3. Study 1: single ascending dose, aged 18–60 years, 2300 mg fasted or fed; study 2: repeat ascending doses, aged 18–60 years, 1500 mg fasted or fed; study 3: repeat dose, aged ≥65 years, 1500 mg fasted or fed. In panel a, studies 1 and 2 are $AUC_{0-\infty}$, study 3 is $AUC_{0-\tau}$. AUC, area under the concentration-time curve from 0 to infinity; C_{max}, maximum observed concentration.

Four participants were withdrawn due to AEs: two participants experienced mild GI AEs (one fasted and one fed) and two participants experienced increased LFT results (one mild and one moderate case; both fed). No SAEs were reported.

DISCUSSION

The results presented here demonstrate gepotidacin was generally well-tolerated across a wide range of single and repeat doses (up to 3000 mg single dose and 2000 mg t.i.d. repeat dose) up to 14 days in a broad age range of adults, including elderly participants. Study 1 demonstrated single oral gepotidacin doses from 100–3000 mg were generally well-tolerated in healthy adults aged 21–59 years; food prolonged T_{max} but did not impact overall exposure (C_{max} or AUC). Study 2 demonstrated repeat oral gepotidacin doses from 400–2300 mg b.i.d. or 1500 mg t.i.d. for 14 days were generally well-tolerated in healthy adults aged 20–58 years; three participants withdrew from the study due to AEs at the highest dose level (2000 mg t.i.d.) studied (2 were drug-related AEs and one was due to hepatitis E, and were deemed unrelated to the study drug). The maximum tolerated dose was not met in study 2. Study 3 part 3 demonstrated repeat oral gepotidacin doses 1500 mg b.i.d. under fasted/fed conditions in healthy elderly adults aged greater than or equal to 64 years were generally well-tolerated; four participants withdrew due to AEs. Although results in healthy participants may not be representative of patient populations of interest (uncomplicated urinary tract infection and uncomplicated urogenital gonorrhea), our results are consistent with phase II results.[9,11]

PK parameters in elderly participants aged greater than or equal to 64 years (study 3 part 3) were comparable with those in adults aged 20–59 years (studies 1 and 2). In all three studies, gepotidacin was readily absorbed, with median T_{max} ranging from 1.0 to 4.0 h in studies 1 and 3, and day 1 of study 2 across all doses, whereas after 14 days of treatment in study 2, T_{max} was similar (1.5–2.0 h across all doses). These results are similar to previously published results, demonstrating median T_{max} was reached 1 h after oral administration of 2000 mg gepotidacin.[12] In studies 1 and 2, AUC and C_{max} values increased in a greater than

TABLE 3 Most common adverse events (i.e., ≥2 participants in any active treatment arm) in the safety population

Adverse event, *n* (%)		**Gepotidacin**						**Placebo**	**Total**
Study 1[a]		**100 mg – *fasted* (*n* = 6)**	**800 mg – *fasted* (*n* = 6)**	**1500 mg – *fasted* (*n* = 6)**	**2300 mg – *fasted* (*n* = 6)**	**2300 mg – *fed* (*n* = 6)**	**3000 mg – *fasted* (*n* = 6)**	**(*n* = 12)**	**(*N* = 48)**
Any		0	2 (33)	2 (33)	4 (67)	2 (33)	3 (50)	1 (8)	14 (29)
Nausea		0	0	2 (33)	0	0	3 (50)	0	5 (10)
Diarrhea		0	1 (17)	0	2 (33)	0	1 (17)	0	4 (8)
Abdominal pain		0	0	0	1 (17)	0	2 (33)	0	3 (6)
Study 2[b]	400 mg b.i.d. – *fed* (*n* = 6)	800 mg b.i.d. – *fed* (*n* = 12)	1500 mg b.i.d. – *fed* (*n* = 12)	1500 mg b.i.d. – *fasted* (*n* = 6)	2300 mg b.i.d. – *fed* (*n* = 6)	1500 mg t.i.d. – *fed* (*n* = 6)	2000 mg t.i.d. – *fed* (*n* = 6)	(*n* = 18)[c]	(*N* = 72)
Any	5 (83)	12 (100)	12 (100)	6 (100)	6 (100)	6 (100)	6 (100)	11 (61)	64 (89)
Proteinuria	4 (67)	9 (75)	12 (100)	6 (100)	6 (100)	6 (100)	5 (83)	4 (22)	48 (67)
Diarrhea	2 (33)	1 (8)	5 (42)	4 (67)	5 (83)	3 (50)	4 (67)	2 (11)	26 (36)
Flatulence	2 (33)	6 (50)	5 (42)	0	4 (67)	3 (50)	0	2 (11)	22 (31)
Increased ALT	0	0	1 (8)	4 (67)	3 (50)	2 (33)	3 (50)	0	13 (18)
Abdominal pain	1 (17)	0	2 (17)	1 (17)	0	0	5 (83)	1 (6)	10 (14)
Headache	1 (17)	0	1 (8)	1 (17)	0	1 (17)	2 (33)	2 (11)	8 (11)
Decreased appetite	1 (17)	0	1 (8)	0	0	1 (17)	3 (50)	0	6 (8)
Nausea	0	0	3 (25)	0	0	0	3 (50)	0	6 (8)
Hematuria	0	0	2 (17)	0	0	0	0	1 (6)	3 (4)
Chlamydial urethritis	0	2 (17)	0	0	0	0	0	0	2 (3)
Flank pain	0	0	0	0	0	2 (33)	0	0	2 (3)
Pyuria	0	0	2 (17)	0	0	0	0	0	2 (3)
Scleral hyperemia	0	0	0	0	2 (33)	0	0	0	2 (3)
Study 3 part 3[d]			1500 mg b.i.d. – *fasted* (*n* = 14)			1500 mg b.i.d. – *fed* (*n* = 15)			(*N* = 29)[e]
Any			12 (86)			13 (87)			25 (86)
Diarrhea			4 (29)			5 (33)			9 (31)
Flatulence			3 (21)			4 (27)			7 (24)
Abnormal feces			4 (29)			3 (20)			7 (24)
Increased blood urea			3 (21)			1 (7)			4 (14)
Nausea			3 (21)			1 (7)			4 (14)

(Continues)

TABLE 3 (Continued)

Study 3 part 3[d]	1500 mg b.i.d. – *fasted* ($n = 14$)	1500 mg b.i.d. – *fed* ($n = 15$)	($N = 29$)[e]
Positive fecal occult blood test	2 (14)	2 (13)	4 (14)
Proteinuria	3 (21)	1 (7)	4 (14)
Increased ALT	0	3 (20)	3 (10)
Dyspepsia	0	2 (13)	2 (7)
Increased AST	0	2 (13)	2 (7)
Increased GGT	0	2 (13)	2 (7)
Abdominal pain	2 (14)	0	2 (7)
Red blood cells in urine	2 (14)	0	2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; b.i.d., twice daily; CPK, creatine phosphokinase; GGT, gamma-glutamyl transferase; t.i.d., three times daily.

[a]After single ascending oral doses in healthy adults aged 18–60 years.

[b]After repeated ascending oral doses in healthy adults aged 18–60 years.

[c]Includes placebo administered b.i.d. ($n = 12$), t.i.d. ($n = 4$) and b.i.d. fasted ($n = 2$).

[d]After repeated dosing in healthy adults aged ≥65 years.

[e]Across both study periods.

dose-proportional manner across the dose range evaluated; the nonlinearity in the dose range could be explained by the possibility of saturation of gut metabolism and efflux transporters. However, despite gepotidacin being a known CYP3A4 substrate, the estimated fraction of drug escaping first-pass extraction through the gut wall is 100%.[12] In addition, PK studies using P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) knockout rats did not indicate any substantial changes to oral bioavailability or clearance compared with wild-type rats, indicating no consistent impact of P-gp and BCRP on gepotidacin absorption and clearance in vivo. In study 1, mean plasma gepotidacin C_{max} and AUC values were 8–14% lower than the mean C_{max} and AUC values observed in blood, indicating gepotidacin is moderately associated with red blood cells. Therefore, PK data derived from blood (study 1) were comparable to PK data derived from plasma (studies 2 and 3 part 3).

Across all studies, a moderate-fat meal had a minimal effect on the rate and extent of absorption following gepotidacin administration. Study 1 saw a slight decrease in AUC and C_{max} (6–16%), whereas in study 3 part 3, AUC and C_{max} increased (7–16%) slightly.

Median apparent terminal phase $t_{½}$ was consistent across studies 1, 2, and 3 part 3, and across all doses (5.97–19.2 h, 11.2–14.7 h, and 8.1–8.3 h, respectively). Given these results, steady-state would be expected to be reached in five half-lives, equal to 2.5 days. In studies 2 and 3 part 3, steady-state was achieved following repeated dosing for 3–5 days. Minimal-to-moderate accumulation was observed following b.i.d. and t.i.d. dosing in study 2. The 30–70% accumulation with b.i.d. and t.i.d. dosing, respectively, is in agreement with the effective $t_{½}$ of ~6 h. Gepotidacin PK parameters were unaltered after repeated oral dosing, with AUC similar after a single dose and at steady-state (i.e., time invariant PK). It should be noted that elderly participants in study 3 part 3 received gepotidacin in tablet form, whereas participants in studies 1 and 2 received a capsule formulation; however, the relative bioavailability of different gepotidacin formulations (tablet and capsule) are comparable.[13]

In study 1, ~16–24% of the absorbed gepotidacin dose was excreted unchanged in urine within 72 h. Median renal clearance appeared to be dose independent and exceeded the glomerular filtration rate, suggesting a significant role of tubular secretion in renal elimination. This is consistent with previous studies in healthy participants, which indicated 15–31% of the gepotidacin dose was excreted unchanged in urine.[9,12,14]

AEs reported across all three studies were mostly mild-to-moderate intensity. There were no drug-related SAEs reported in any of the studies; there was one SAE reported in study 1 (1 patient in the single dose 2300 mg gepotidacin – fasted conditions cohort who reported chest discomfort,

which was assessed by the investigator as not related to the study drug). One participant withdrew from study 2 due to significantly increased levels of ALT and AST meeting the protocol-defined stopping criteria; however, the individual was subsequently diagnosed with hepatitis E and the AE was deemed not related to the study drug. All LFTs returned to baseline levels. Consistent with previous studies, there were no other clinically important changes in laboratory parameters, or vital signs in these studies.[9,11,12,14–16]

The most common AEs among participants who received gepotidacin across all studies were GI (study 1, 10/36 [28%]; study 2, 35/54 [65%]; and study 3 part 3, 19/29 [66%]). Previous studies of gepotidacin have reported similar results, with the most common AEs of diarrhea, nausea, flatulence, and abdominal pain, which resolved by the end of the study and were not related to *C. difficile* infection.[9,11–14] Food effect was evaluated in studies 1, 2, and 3, to inform future studies regarding dosing in relation to meals. GI AEs occurred in a numerically lower percentage of participants under fed conditions than under fasted conditions. Phase III studies recommend gepotidacin dose administration in the fed state,[17,18] which may help optimize GI tolerability.[19] No clinically significant QT prolongations were noted in any of the three studies, consistent with previous data.[9,11,12,14–16]

In conclusion, the safety and PK profile of gepotidacin has been well-characterized across a wide range of doses in healthy participants aged greater than or equal to 18 years, with GI AEs (primarily mild-to-moderate nausea and diarrhea) commonly reported. These GI AEs are alleviated when oral gepotidacin is taken with food. Based on the present observations, combined with a lack of food effect on PK parameters (C_{max} and AUC), it is recommended that oral gepotidacin be taken with food in future studies.

AUTHOR CONTRIBUTIONS

C.T., E.F.D., M.H., M.S., and B.S. wrote the manuscript. C.T., E.F.D., and M.H. designed the research. C.T., E.F.D., M.H., M.S., and B.S. analyzed the data.

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CONFLICTS OF INTEREST STATEMENT

C.T., E.F.D. and M.H. are former employees of and past/current shareholders in GSK. B.S. and M.S. are employees of and shareholders in GSK.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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REFERENCES

1. Gibson EG, Bax B, Chan PF, Osheroff N. Mechanistic and structural basis for the actions of the antibacterial gepotidacin against Staphylococcus aureus gyrase. *ACS Infect Dis.* 2019;5:570-581.
2. Jacobsson S, Golparian D, Scangarella-Oman N, Unemo M. In vitro activity of the novel triazaacenaphthylene gepotidacin (GSK2140944) against MDR Neisseria gonorrhoeae. *J Antimicrob Chemother*. 2018;73:2072-2077.
3. Farrell DJ, Sader HS, Rhomberg PR, Scangarella-Oman NE, Flamm RK. In vitro activity of gepotidacin (GSK2140944) against Neisseria gonorrhoeae. *Antimicrob Agents Chemother*. 2017;61:e02047-16.
4. Mushtaq S, Vickers A, Sadouki Z, et al. In-vitro activities of gepotidacin, a novel triazaacenaphthylene and topoisomerase IV DNA gyrase inhibitor, against gram-negative bacteria and staphylococcus saprophyticus. *ECCMID*. 2019. abstract P1849.
5. Collin F, Karkare S, Maxwell A. Exploiting bacterial DNA gyrase as a drug target: current state and perspectives. *Appl Microbiol Biotechnol*. 2011;92:479-497.
6. Wohlkonig A, Chan PF, Fosberry AP, et al. Structural basis of quinolone inhibition of type IIA topoisomerases and target-mediated resistance. *Nat Struct Mol Biol*. 2010;17:1152-1153.
7. Bax BD, Chan PF, Eggleston DS, et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. *Nature*. 2010;466:935-940.
8. Biedenbach DJ, Bouchillon SK, Hackel M, et al. In vitro activity of gepotidacin, a novel triazaacenaphthylene bacterial topoisomerase inhibitor, against a broad spectrum of bacterial pathogens. *Antimicrob Agents Chemother*. 2016;60:1918-1923.
9. Overcash JS, Tiffany CA, Scangarella-Oman NE, et al. Phase 2a pharmacokinetic, safety, and exploratory efficacy evaluation of oral gepotidacin (GSK2140944) in female participants with uncomplicated urinary tract infection (acute uncomplicated cystitis). *Antimicrob Agents Chemother*. 2020;64:e00199-20.
10. O'Riordan W, Tiffany C, Scangarella-Oman N, et al. Efficacy, safety, and tolerability of gepotidacin (GSK2140944) in the treatment of patients with suspected or confirmed gram-positive acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother*. 2017;61:e02095-16.
11. Taylor SN, Morris DH, Avery AK, et al. Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a phase 2, randomized, dose-ranging, single-oral dose evaluation. *Clin Infect Dis*. 2018;67:504-512.
12. Negash K, Andonian C, Felgate C, et al. The metabolism and disposition of GSK2140944 in healthy human subjects. *Xenobiotica*. 2016;46:683-702.
13. Hossain M, Tiffany CA, McDonald M, Dumont EF. Bioavailability and drug–drug interaction profile of

GSK2140944, a novel bacterial topoisomerase inhibitor. *ICAAC*. 2015. abstract A-028.
14. Hossain M, Tiffany C, Raychaudhuri A, et al. Pharmacokinetics of gepotidacin in renal impairment. *Clin Pharmacol Drug Dev*. 2020;9:560-572.
15. Hossain M, Tiffany C, Tao Y, et al. Pharmacokinetics of gepotidacin in subjects with normal hepatic function and hepatic impairment. *Clin Pharmacol Drug Dev*. 2021;10:588-597.
16. Hossain M, Zhou M, Tiffany C, Dumont E, Darpo B. A phase I, randomized, double-blinded, placebo- and moxifloxacin-controlled, four-period crossover study to evaluate the effect of gepotidacin on cardiac conduction as assessed by 12-lead electrocardiogram in healthy volunteers. *Antimicrob Agents Chemother*. 2017;61:e02385-16.
17. ClinicalTrials.gov. NCT04010539: A study to evaluate efficacy and safety of gepotidacin compared with ceftriaxone plus azithromycin in the treatment of uncomplicated urogenital gonorrhea; 2019. Accessed January 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04010539
18. ClinicalTrials.gov. NCT04020341: A study to evaluate efficacy and safety of gepotidacin in the treatment of uncomplicated urinary tract infection (UTI); 2019. Accessed January 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04020341.
19. Tiffany CA, Hossain M, McDonald M, Dumont EF. Effect of food on safety, tolerability and pharmacokinetics in healthy volunteers >65 years following multiple doses of GSK2140944, a novel bacterial topoisomerase inhibitor. *ICAAC*. 2015. abstract A-030.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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