Integrated Review

Table 1. Application Information

Application type	NDA
Application number	218230
Priority or standard	PRIORITY
Submit date	7/26/2024
Received date	7/26/2024
PDUFA goal date	3/26/2025
Division/office	Division of Anti-Infectives (DAI)
Review completion date	3/17/2025
Established/proper name	Gepotidacin
(Proposed) proprietary name	Blujepa
Pharmacologic class	Triazaacenaphthylene bacterial type II topoisomerase inhibitor
Other product name(s)	GSK 2140944
Applicant	GLAXOSMITHKLINE LLC
Dosage form(s)/formulation(s)	Tablet
Dosing regimen	1500 mg orally, twice daily for 5 days
Applicant-proposed indication(s)/ population(s)	For treatment of uncomplicated urinary tract infections (uUTI) in female adults and adolescents from 12 years of age, both weighing at least 40 kilograms (kg).
SNOMED CT code for proposed indication disease term(s)[1]	68226007 | Acute cystitis (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	1500 mg orally, twice daily for 5 days
Approved indication(s)/ population(s) (if applicable)	For the treatment of female adult and pediatric patients 12 years of age and older weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTIs) caused by the following susceptible microorganisms: Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii complex, Staphylococcus saprophyticus, and Enterococcus faecalis.
SNOMED CT code for approved indication disease term(s)1	68226007 | Acute cystitis (disorder)

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AAG	alpha-1-glycoprotein
ABSSSI	acute bacterial skin and skin structure infections
AChE-I	acetylcholinesterase inhibition
AESI	adverse event of special interest
AI	Acceptable Intake
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
	(b) (4)
BID	twice daily
BMD	broth microdilution
BMI	body mass index
CDI	*Clostridioides difficile* infection
CFU	colony-forming unit
CI	confidence interval
CIP	ciprofloxacin
CLnr	non renal clearance
CLr	renal clearance
CLSI	Clinical & Laboratory Standards Institute
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	clinical response
CrCl	creatinine clearance
CYP	cytochrome P450
DDI	drug-drug interaction
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECV	epidemiological cutoff value
eGFR	estimated glomerular filtration rate
ESBL	extended-spectrum beta-lactamase
ESRD	end stage renal disease
*f*AUC	area under the free-drug concentration-time curve
$fAUC_{0-24}$	area under the free-drug concentration-time curve from 0 to 24 hours
*f*AUC/MIC	area under the free-drug concentration-time curve to minimum inhibitory concentration ratio
FDA	Food and Drug Administration
F_{oral}	oral bioavailability
FQ-R	fluoroquinolone-resistance
FU	follow-up
GC	gonorrhea

GI	gastrointestinal
GLP	good laboratory practice
GOF	goodness of fit
hCES	human carboxylesterase enzymes
hERG	human ether-a-go-go related gene
HFIM	hollow-fiber infection model
HI	hepatic impairment
HLM	human liver microsomes
HSWG	high shear wet granulation
IA	interim analysis
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IHD	intermittent hemodialysis
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
IR	Information Request
ITT	intent-to-treat
IV	intravenous
KO	knock out
LLC	limited liability company
LoQ	level of quantification
LVX	levofloxacin
MATE	multidrug and toxin extrusion protein
MDRD	Modification of Diet in Renal Disease
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
micro-ITT	microbiological intent-to-treat
MLST	multilocus sequence typing
MR	microbiological response
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NDA	new drug application
	(b) (4)
NOAEL	no observed adverse effect level
NTF-NS	not susceptible to nitrofurantoin
NTF-S	nitrofurantoin susceptible
OCT	organic cation transporter
OT	on therapy
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
PFGE	pulsed-field gel electrophoresis
P-gp	P-glycoprotein
PI	Prescribing Information
PIND	Pre-Investigational New Drug
PK	pharmacokinetic
PK-PD	pharmacokinetic-pharmacodynamic

PMQR	Plasmid-mediated Quinolone Resistance Genes
PO	orally
PT	preferred term
PTA	probability of target attainment
QC	quality control
QD	once daily
QIDP	Qualified Infectious Disease Product
QRDR	quinolone-resistance determining region
(Q)SAR	quantitative structure-activity relationship
QT	interval from the start of the Q wave to the end of the T wave
QTc	QT interval corrected for heart rate
RC	roller compacted
RI	renal impairment
SAE	serious adverse event
SEE	substantial evidence of effectiveness
TEAE	treatment-emergent adverse event
TID	three times daily
TK	toxicokinetic
T_{max}	time to maximum concentration
TOC	test-of-cure
TR	therapeutic response
ULN	upper limit of normal
UTD	unable to determine
UTI	urinary tract infections
uUTI	uncomplicated urinary tract infections
UV	ultraviolet
WBC	white blood cell

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On July 26, 2024, GlaxoSmithKline limited liability company (LLC), (the Applicant) submitted a 505(b)(1) new drug application (NDA) for gepotidacin 750 mg tablets, a triazaacenaphthylene bacterial type II topoisomerase inhibitor antibacterial drug intended to treat uncomplicated urinary tract infections (uUTI) in female adult and pediatric patients 12 years of age and older, weighing at least 40 kg. Gepotidacin has Qualified Infectious Disease Product (QIDP) designation qualifying for Priority Review. The Prescription Drug User Free Act goal date is March 26, 2025.

Gepotidacin is a new molecular entity that inhibits bacterial deoxyribonucleic acid (DNA) gyrase and topoisomerase IV (type II topoisomerases). Gepotidacin demonstrated in vitro and clinical activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, *Enterococcus faecalis*, and *Staphylococcus saprophyticus.*

Clinical efficacy data were provided from two phase 3, randomized, multicenter, double-blind, active-controlled noninferiority clinical studies, EAGLE-2 and EAGLE-3, in which five days of twice daily oral gepotidacin 1500 mg was compared to five days of twice daily oral nitrofurantoin 100 mg for the treatment of uUTI. The primary analysis population in both trials was the microbiologic intent-to-treat nitrofurantoin-susceptible (micro-ITT NTF-S) population. The primary efficacy endpoint in both studies was a composite endpoint assessing clinical and microbiological response. Each trial met the prespecified -10% margin for the primary efficacy endpoint of overall success (composite of clinical cure and microbiologic eradication) at Test of Cure in the micro-ITT NTF-S population. Compared to nitrofurantoin, the treatment difference was 4.3% (-3.6%, 12.1%) in EAGLE-2 and 14.6% (6.4%, 22.8%) in EAGLE-3, in the micro-ITT NTF-S population.

The safety database was composed of 1570 study subjects enrolled in the phase 3 clinical studies who received at least one dose of gepotidacin. The available data indicate that gepotidacin's safety profile is acceptable for its intended use and gepotidacin's known and potential safety risks can be mitigated through labeling and pharmacovigilance. Overall, as delineated in the Benefit/Risk Framework below, the review team and signatory authority have concluded that the benefits of gepotidacin outweigh its associated risks for the treatment of uUTI in female adult and pediatric patients 12 years of age and older, weighing at least 40 kg.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

SEE was provided by data from two randomized, active-controlled phase 3 clinical studies in subjects with uUTI titled EAGLE-2 and EAGLE-3. Both clinical studies met the primary endpoint showing that gepotidacin was non-inferior to nitrofurantoin for the treatment of uUTI.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Uncomplicated urinary tract infections (uUTI) occur in women with normal urinary tract anatomy and are characterized by symptoms such as lower abdominal discomfort, urinary urgency, urinary frequency, and dysuria (Ferry et al. 2007; Gupta et al. 2011; Hooton 2012; Vik et al. 2018; FDA 2019; Kaye et al. 2021). • Urinary tract infections are the most common bacterial infections encountered in the ambulatory care setting in the United States, accounting for 8.6 million visits (84% by women) in 2007 (Hooton 2012). uUTI is among the most common indications for antimicrobial therapy in healthy women. • uUTI may have early resolution of symptoms (25 to 42%) (Ferry et al. 2007) but can rarely progress to cUTI in the absence of antimicrobial therapy (Vik et al. 2018). • *E. coli* is the most frequent pathogen associated with uUTI. Other Enterobacterales, such as *K. pneumoniae* and *P. mirabilis*, and other bacteria such as *S. saprophyticus* are also commonly identified as causitive pathogens. (Gupta et al. 2011).	uUTI are common bacterial infections in adult women, with *E.coli* being the most common causative pathogen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• uUTI is often treated empirically without identification of the causitive pathogen. (Kaye et al. 2021) • The Infectious Diseases Society of America recommends the following antibacterial drugs for the treatment of uUTI: nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX) (if local resistance rates of uropathogens causing uUTI do not exceed 20%), fosfomycin, or pivmecillinam. • Fluoroquinolones (including ciprofloxacin) and β-lactams (including amoxicillin/clavulanate) are considered alternative antibacterials for uUTI (Gupta et al. 2011). • Antimicrobial resistance may complicate selection of appropriate antibacterial treatment for uUTI and limit available oral options.	Effective antimicrobial therapies alleviate the symptoms of uUTI, shorten the course of illness, and may prevent progression to complicated UTI, which may require intravenous antibacterial treatment. Available treatment options for uUTIs can be limited by development of resistance and adverse reactions.
Benefit	• Clinical efficacy of gepotidacin was demonstrated in two adaquate and well-controlled studies (EAGLE-2 and EAGLE-3) • The primary efficacy endpoint in both studies was a composite endpoint assessing clinical and microbiological response using a prespecified noninferiority margin of -10% in the microbiologic intent-to-treat nitrofurantoin-susceptible (micro-ITT NTF-S) population. • In EAGLE-2, gepotidacin met the prespecified -10% margin for the primary efficacy endpoint at Test of Cure in the micro-ITT NTF-S population. Compared to nitrofurantoin, the treatment difference was 4.3% (-3.6,12.1) in the micro-ITT NTF-S population at the interim analysis. • In EAGLE-3, gepotidacin met the prespecified -10% margin for the primary efficacy endpoint at Test of Cure in the micro-ITT NTF-S population. Compared to nitrofurantoin, the treatment difference was 14.6% (6.4, 22.8) in the micro-ITT NTF-S population at the interim analysis.	Gepotidacin was demonstrated to be effective for the treatment of uUTI in two adequate and well-controlled clinical studies. Gepotidacin provides an additional oral option for the treatment of uUTI in female adult and pediatric patients 12 years of age and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The safety database for gepotidacin contained 1570 subjects who received at least one 1500 mg dose of oral gepotidacin. • There was one serious adverse reaction of dysarthia attributed to gepotidacin. There were no deaths in either clinical study. • The most common adverse reactions included diarrhea, nausea, vomiting, and abdominal pain in both arms. • Discontinuations were more frequent in gepotidacin recipients (5% gepotidacin vs 1.9% nitrofurantoin), primarily due to gastrointestinal adverse reactions. • AEs potentially associated with acetylcholinesterase inhibition were observed in 24% of gepotidacin recipients with most adverse reactions consisting of gastrointestinal events (diarrhea, abdominal pain and nausea), but non-gastrointestinal events (e.g., dysarthria) were also reported. • Hypersensitivity reactions, including anaphylaxis, were observed in gepotidacin recipients in the development program. • A dose- and concentration-dependent prolongation of the QTc interval has been observed with gepotidacin. • *Clostridioides difficile (C. difficile)* infection (CDI) was observed in gepotidacin recipients in the development program.	The safety profile of gepotidacin is acceptable for the treatment of uncomplicated urinary tract infections in female adult and pediatric patients 12 years of age and older. Gepotidacin can cause adverse reactions due to acetylcholinesterase inhibition including, but not limited to, neurologic adverse reactions, such as dysarthria. These events were self-limited, but labeling, including a warning in the prescribing information and a Medication Guide, will communicate the risk to healthcare providers and patients, respectively. A warning will be included in labeling to communicate the risk of hypersensitivity reactions. A warning will be included in labeling to communicte the risk of QTc prolongation, including approaches to risk mitigation if the use of gepotidacin cannot be avoided. A warning will be included in labeling to communicte the risk of CDI, including approaches to risk mitigation.

Abbreviations: AE, adverse event; cUTI, complicated urinary tract infection; SAE, serious adverse event; QTc, QT interval corrected for heart rate; uUTI, uncomplicated urinary tract infection

2.2. Conclusions Regarding Benefit-Risk

In NDA 218320, the Applicant submitted safety and effectiveness data to support the use of gepotidacin for the treatment of uncomplicated urinary tract infections due to designated microorganisms in female adult and pediatric patients 12 years of age and older who weigh at least 40 kilograms. Gepotidacin is a novel triazaacenaphthylene type II topoisomerase inhibitor that inhibits bacterial DNA gyrase and topoisomerase IV.

Clinical effectiveness data were provided from two adequate and well-controlled randomized clinical studies of gepotidacin at the proposed dose of 1500 mg twice daily for five days. Both studies utilized a composite primary endpoint assessing clinical and microbiological response of subjects to treatment. In the first study, gepotidacin [162/320 (50.6%)] was noninferior to nitrofurantoin [135/287 (47.0%)] with a treatment difference of 4.3% (-3.6,12.1) in the microbiologic intent-to-treat nitrofurantoin-susceptible (micro-ITT NTF-S) population. In the second study, gepotidacin [162/277 (58.5%)] was noninferior to nitrofurantoin [115/264 (43.6%)] with a treatment difference of 14.6% (6.4, 22.8) in the micro-ITT NTF-S population. Both studies met the prespecified noninferiority margin of -10%.

The safety database included 1570 study subjects who received at least one dose of gepotidacin, plus approximately 500 additional subjects in the phase 1 and 2 studies. The available data indicate that gepotidacin's safety profile is acceptable for its intended use (i.e., the treatment of uUTI). Adverse reactions observed in the clinical studies were generally mild and self-limited, with gastrointestinal events presenting as the most common reported events. However, AEs potentially associated with acetylcholinesterase inhibition, including, but not limited to, dysarthria were reported in subjects in clinical trials. Additionally, hypersensitivity reactions and CDI were observed in gepotidacin recipients in the development program, and a dose and concentration-dependent prolongation of the QTc interval was observed with gepotidacin. These known and potential safety risks can be adequately mitigated through labeling, including a Medication Guide, and via pharmacovigilance.

Based on review of all available efficacy and safety data, NDA 218320 for gepotidacin provides substantial evidence of effectiveness and a favorable benefit-risk profile for the treatment of uUTI in female adult and pediatric patients 12 years of age and older weighing at least 40 kilograms with the designated microorganisms.

II. Interdisciplinary Assessment

3. Introduction

Gepotidacin is a novel triazaacenaphthylene antibacterial type II topoisomerase inhibitor that targets bacterial deoxyribonucleic acid (DNA) gyrase and topoisomerase IV. Oral gepotidacin 1500 mg twice daily (BID) is provided for 5 days to treat uncomplicated urinary tract infections (uUTI) due to designated microorganisms in female adult and pediatric patients 12 years of age and older who weigh at least 40 kilograms. Uncomplicated urinary tract infections are generally treated by short courses of oral antibacterial drugs, such as nitrofurantoin or trimethoprim-sulfamethoxazole, although antimicrobial resistance can reduce the available oral treatment options. Treatment is typically empiric and limits progression to more severe infections, such as complicated urinary tract infections (cUTI).

Two phase 3, randomized, multicenter, double-blind, active-controlled noninferiority clinical studies in which gepotidacin was compared to oral nitrofurantoin for the treatment of uUTI due to eligible nitrofurantoin-susceptible organisms were conducted to assess the safety and effectiveness of gepotidacin. Both studies met the prespecified noninferiority margin of -10% using a composite endpoint assessing clinical and microbiological outcomes. The safety database was composed of 1570 individuals who received at least one dose of gepotidacin. Most adverse events were mild and self-limited, and the overall safety assessment was favorable. Several key safety review issues were identified during the review of the new drug application (NDA), as discussed below.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

None.

3.1.2. Key Safety Review Issues

3.1.2.1. Acetylcholinesterase Inhibition

3.1.2.2. Hypersensitivity Reactions

3.1.2.3. QTc Prolongation

3.2. Approach to the Clinical Review

The primary evidence of effectiveness and safety for gepotidacin was generated by two clinical studies (EAGLE-2 and EAGLE-3) in female adult and pediatric patients 12 years of age and

older with uUTI. Efficacy data were evaluated from each clinical study separately, while the safety data were reviewed for the integrated safety population of subjects from both studies. The submitted clinical studies were adequate to evaluate the safety and efficacy of gepotidacin. The clinical studies submitted to NDA 218320 are summarized in Table 3 below.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

Treatment of female adult and pediatric patients 12 years of age and older weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTI) caused by the following susceptible microorganisms: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii* complex, *Staphylococcus saprophyticus,* and *Enterococcus faecalis*.

SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*

a. Adequate and well-controlled clinical investigation(s):

i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**

ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

OR

c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[2]

Complete response, if applicable

d. ☒ SEE was established

e. ☐ SEE was not established *(if checked, omit item 2)*

1 FDA 1 guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019)*

[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

[3] FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (2023)

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Gepotidacin

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized/ Enrolled	Number of Centers and Countries
206899 Phase 2a, (NCT03568942)	Adult women with uUTI	Control type: None Randomization: None Blinding: None Biomarkers: None Innovative design features: None	Drug: Gepotidacin Dosage: 1500 mg BID Number treated: 22 Duration (quantity and units): 5 d	Primary: To determine the plasma PK parameters following repeat oral doses of gepotidacin in adult female subjects with acute cystitis. Secondary: To determine the urine PK parameters following repeat oral doses of gepotidacin in adult female subjects with acute cystitis. To assess the safety and tolerability of repeat oral doses of gepotidacin	Planned: 20 Enrolled: 22	Centers: 1 Countries: 1
EAGLE-2 (NCT04020341)	Female subjects greater than 12 y of age with uUTI	Control type: Active, concurrent Randomization: Standard, 1:1 ratio Blinding: DB, double dummy Biomarkers: None Innovative design features: None	Drug: Gepotidacin Dosage: 1500 mg BID Number treated: 767 Duration (quantity and units): 5 d Drug: Nitrofurantoin Dosage: 100 mg BID Number treated: 764 Duration (quantity and units): 5 d	Primary: Combined microbiological and clinical response at day 10 Secondary: Clinical and microbiological response at days 10 and 28. To assess the safety and tolerability of gepotidacin compared to nitrofurantoin in female subjects with acute cystitis	Planned: 2500 Randomized: 1531	Centers: 107 Countries: 12

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized/ Enrolled	Number of Centers and Countries
EAGLE-3 (NCT04187144)	Female subjects greater than 12 y of age with uUTI	Control type: Active, concurrent Randomization: Standard, 1:1 ratio Blinding: DB, double dummy Biomarkers: None Innovative design features: None	Drug: Gepotidacin Dosage: 1500 mg BID Number treated: 805 Duration (quantity and units): 5 d Drug: Nitrofurantoin Dosage: 100 mg BID Number treated: 800 Duration (quantity and units): 5 d	Primary: Combined microbiological and clinical response at day 10 Secondary: Clinical and microbiological response at days 10 and 28. To assess the safety and tolerability of gepotidacin compared to nitrofurantoin in female subjects with acute cystitis	Planned: 2500 Randomized: 1605	Centers: 112 Countries: 6

Source: Reviewer.
[1] Includes all submitted clinical studies, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: BID, twice daily; DB, double-blind; d, day(s); PK, pharmacokinetic; uUTI, uncomplicated urinary tract infections; y, year(s)

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 6
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (but not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

To support the activity of gepotidacin against Enterobacterales and *Staphylococcus saprophyticus*, the Applicant conducted in vitro dynamic and neutropenic murine infection models to determine the pharmacokinetic-pharmacodynamic (PK-PD) index and target for efficacy. For a uUTI, there is no established nonclinical model to reliably determine PK-PD targets relevant to the site of the infection. Additionally, there are significant knowledge gaps surrounding urine-specific PK-PD parameters and the selection of PK-PD endpoints that are predictive of clinical efficacy that limit the utility of probability of target attainment (PTA)

analyses to predict the efficacy of gepotidacin for the treatment of a uUTI. Although the nonclinical data support gepotidacin's activity against uropathogens, the limitations mentioned above limit the translational utility of these nonclinical findings.

5.1.1. Summary of Nonclinical Pharmacokinetic-Pharmacodynamic Information

The Applicant conducted several nonclinical PK-PD studies examining the effect of gepotidacin on Enterobacterales and *Staphylococcus aureus* in vivo (neutropenic murine thigh infection models) and *Escherichia coli* in vitro (1-compartment "chemostat" models). Among the three different PK-PD studies, area under the free-drug concentration-time curve to minimum inhibitory concentration ratio (*f*AUC/MIC) was consistently the PK-PD index that best exemplified bacterial burden reduction. Similarly, area under the concentration-time curve (AUC)/minimum inhibitory concentration (MIC) is the index that best correlates with the activity with another antibacterial drug class with a similar mechanism of action (fluoroquinolones). For additional information about PK-PD index determination see Section 14.1.5.

Subsequent PK-PD target determination studies were conducted with the same in vivo and in vitro models mentioned above using a panel of 24 Enterobacterales (17 *E. coli* and 7 *Klebsiella pneumoniae*) and six *S. aureus* strains with gepotidacin MICs ranging from 0.25 to 16 µg/mL and 0.5 to 2 µg/mL, respectively for in vivo, and four *E. coli* strains in vitro with gepotidacin MICs ranging from 1 to 4 µg/mL. As noted in Section 14.1.5.1, six Enterobacterales strains were removed from the PK-PD analyses due to <1 $\log_{10}$ growth over 24 hours in the placebo vehicle control. In the in vivo models, the median *f*AUC/MIC targets for *S. aureus* at stasis, 1-log kill, and 2-log kill were ~13, 59, 257, respectively; meanwhile, the mean *f*AUC/MIC targets for *E. coli* at stasis, 1-log kill, and 2-log kill were ~8, 13, 24, respectively. However, when compared to the in vivo PK-PD targets, the in vitro mean PK-PD targets for *E. coli* strains at the three endpoints were nearly 2.5 to 4-fold higher (stasis, 1-log, and 2-log kill targets of ~32, 46, 63, respectively). For example, one *E. coli* strain that was evaluated in both models exhibited an in vitro target for stasis that was similar to the in vivo 2-log kill target. No reason for the target discrepancies between the two models was provided by the Applicant. In the PTA for plasma and urine, the Applicant used the in vitro pooled 1-log kill PK-PD target of 41 for Enterobacterales and the in vivo median 1-log kill PK-PD target of 59 for *Staphylococcus saprophyticus*.

Additionally, the Applicant evaluated the bactericidal activity of gepotidacin plasma concentrations associated with various gepotidacin dosages using a hollow-fiber infection model. The simulated plasma concentrations suppressed the growth of one *E. coli* strain (with gepotidacin MICs of 2 µg/mL) and prevented the development of resistance at area under the free-drug concentration-time curve from 0 to 24 hours ($f\text{AUC}_{0\text{-}24h}$) of ≥549 mg*h/L for the entire duration of a 10-day study.

The provided information was reviewed and there was general acceptance for *f*AUC/MIC as the index but the PK-PD target for efficacy was not considered acceptable for a uUTI indication (see Sections 6.1.1 and 14.1.5 for additional information).

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Gepotidacin is a triazaacenaphthylene bacterial type II topoisomerase inhibitor. Gepotidacin is the first member of this EPC. The EPC captures both the mode of action, which is clinically meaningful, and a unique chemical structure, allowing it to be differentiated from other antibacterials with the same target, which have distinct chemical structure from gepotidacin. However, while gepotidacin contains a triazaacenaphthylene moiety within the drug chemical structure, it is unclear that this is the defining structural feature critical to its antibacterial activity, but is included to differentiate it from other antibacterials that target bacterial type II topoisomerase inhibitors.
Mechanism of action	Gepotidacin inhibits type II topoisomerase (i.e., bacterial DNA gyrase and topoisomerase IV).
Active moieties	Gepotidacin is the active moiety. It is unknown if the M4 metabolite is active because its instability did not allow assessment for efficacy or toxicity.
QT prolongation	Gepotidacin prolongs the QTc interval in a dose and concentration-dependent manner as demonstrated in a thorough QT study with gepotidacin IV doses (infused over 2 hours) of 1000 mg (mean C_{max} of 7.3 µg/mL) and 1800 mg (mean C_{max} of 13.6 µg/mL) exhibited mean ΔΔQTc of 12 msec and 22 msec, respectively. The concentration-QTc relationship in the TQT study is predicted to increase ΔΔQTcF for the therapeutic dose and high clinical exposure scenario (e.g., severe hepatic impairment) at ~8 and 17 msec, respectively. However, there is uncertainty surrounding the magnitude of the predictions of QTc prolongation: 1) only the unchanged gepotidacin moiety was used in the estimate; 2) M4 (major metabolite) exposures were not assessed on hERG, and it is unknown how the exposures compare between TQT study and the proposed dosage; and 3) the highest exposure clinical scenario (~17 µg/mL) exceeds the highest mean concentration of 13.6 µg/mL from a single 1800 mg IV dose. The available safety data from the two phase 3 studies (EAGLE-2, EAGLE-3) did not identify any significant cardiac safety issues.
General Information	
Bioanalysis	Validated UHPLC-MS/MS and HPLC-MS/MS were used to determine gepotidacin concentrations in human plasma, blood, urine, and dialysate.
Healthy subjects versus patients	No significant differences in C_{max} and AUC between healthy and infected subjects.

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)</td><td>Table 6. Post-Hoc Steady State Plasma Gepotidacin PK Parameters in Females With uUTI (eGFR ≥90 mL/min), (n=448)
<table>
<tr><th>Parameter</th><th>Mean ± SD</th></tr>
<tr><td>$AUC_{0\text{-}12h}$ (µg*hr/mL)</td><td>22.8 (4.8)</td></tr>
<tr><td>C_{max} (µg/mL)</td><td>4.2 (1.0)</td></tr>
</table>
Source: Reviewer's analysis of EAGLE-2 post hoc PK dataset (rtq20-q7-ph3-posthocs-06dec) that was provided by Applicant in information request sequence 32 (12/19/2024)
Abbreviations: $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0 to 12 h; C_{max}, maximum plasma concentration; eGFR, estimated glomerular filtration rate; n, number of subjects with given characteristic; PK, pharmacokinetic; SD, standard deviation; uUTI, uncomplicated urinary tract infection</td></tr>
<tr><td>Range of effective dose(s) or exposure</td><td>No dose-ranging studies were performed.
Effective dosage: Phase 2a and pivotal phase 3 studies (EAGLE-2, 3) evaluated only one gepotidacin dosage (1500 mg oral every 12 hours).
Effective exposure range: exposure-response (steady state fAUC/MIC and fAUC) with composite, clinical, and microbiological response rates in microbiological evaluable population at test-of-cure in the phase 3 study (EAGLE-2) were flat over the range of exposures achieved following gepotidacin 1500 mg every 12 hours.</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>The maximum tolerated doses and highest dosages evaluated in clinical studies were 6000 mg/day (3000 mg × 2 in 6-hour interval for 1 day) and 2000 mg three times daily for 14 days.</td></tr>
<tr><td>Dose proportionality</td><td>Gepotidacin AUC_{inf} and C_{max} was dose proportional within the dose range of 1500 mg to 3000 mg.</td></tr>
<tr><td>Accumulation</td><td>Gepotidacin 1500 mg every 12 hours exhibited minimal accumulation (30% to 40% increase) over 13 days.</td></tr>
<tr><td>Time to achieve steady-state</td><td>At the proposed dosage, steady-state was achieved by Day 3.</td></tr>
<tr><td>Bridge between to-be-marketed and clinical trial/study formulations</td><td>The final to-be-marketed oral formulation (gepotidacin mesylate tablet (b) (4)) is the same formulation used in the pivotal phase 3 clinical studies EAGLE-2 and EAGLE-3.</td></tr>
</table>

Characteristic	Drug Information
Absorption	
Bioavailability	Absolute bioavailability was ~44% following administration of a single dose of 2000 mg oral capsule dose under fasted conditions.
T_{max}	Approximately 2 hours (phase 2a study, 206899)
Food effect (fed/fasted) Geometric least square mean and 90% CI	No clinically meaningful food effect when administered with a moderate fat meal (Table 7). However, gepotidacin was not evaluated with a high fat meal.

Table 7. Effect of Moderate fat Meal on Plasma PK Parameters of Gepotidacin Oral Tablet

Dosage Form	$AUC_{0-\infty}$	C_{max}	T_{max}
	Geometric LS Mean Ratio (90% CI)		Difference from fast
Mesylated tablet	1.07 (0.98, 1.17)	0.87 (0.78, 0.97)	1.25-hour delay

Source: Summarized Table 29 (clinical study report BTZ117349-part 1)
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; PK, pharmacokinetic; T_{max}, time to maximum concentration

Distribution	
Volume of distribution	Mean (±SD) V_{ss} was 173±43L in female patients with uUTI
Plasma protein binding	40% to 41% bound to plasma proteins, concentration independent, while 25% to 33% is bound to alpha-1-glycoprotein.
Drug as substrate of transporters	As shown in vitro, gepotidacin is a potential substrate of P-gp, BCRP, MATE1, and MATE2-K. Clinical DDI studies with itraconazole (P-gp inhibitor) and cimetidine (MATE1 and MATE2-K inhibitor) suggest that there is no clinically significant interaction with P-gp or MATE1 and MATE2-K.
Elimination	
Mass balance results	Following a single 2000 mg oral radiolabeled (45 µCi) gepotidacin dose, ~84% of the dose was recovered by Day 7 (90% of excretion occurred within first 24 hours in urine and 72 hours in feces) with ~50% as unchanged gepotidacin. The primary route of elimination was nonrenal. The mean blood-to-plasma total radioactivity ratio ranged between 0.77-1.32. Unchanged gepotidacin accounted for ~60% of total plasma radioactivity.
Clearance	Mean ± SD total clearance in female patients with uUTI was 33.4±6.7 L/hour.
Half-life	Mean ± SD plasma half-life in female patients with uUTI was 9.3±1.3 hours.
Metabolic pathway(s)	Gepotidacin was oxidized mainly by the cytochrome P450 3A4 (CYP3A4) enzyme producing several circulating metabolites, including major metabolite, M4 (11% of drug related material in plasma).
Primary excretion pathways (% dose)	Gepotidacin was excreted in feces at 52.5% (~60% of which was unchanged drug) and in urine at 31% (~65% of which was unchanged drug).

Characteristic	Drug Information
Intrinsic Factors and Specific Populations	
Body weight	No dosage adjustments are needed based on body weight differences as no clinically significant differences in gepotidacin post-hoc exposures were observed among five body weight categories ranging from 40 kg to 140 kg in uUTI patients.
Age	No clinically significant differences in gepotidacin exposures were observed in uUTI patients based on age ranging from 12 to 89 years; thus, no dosage adjustments are needed based on age.
Renal impairment	No dosage adjustments are needed in patients with eGFR ≥30 mL/min. Use is not recommended in patients with eGFR <30 mL/min or those on dialysis.
Hepatic impairment	No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Use is not recommended in patients with severe hepatic impairment.
Drug Interaction Liability (Drug as Precipitant)	
Inhibition/induction of metabolism	In vitro gepotidacin was shown to be a reversible inhibitor of CYP3A4. No other inhibition or induction was observed at therapeutic plasma concentrations with any other CYP enzyme. A clinical study showed that gepotidacin co-administered with a CYP3A4 substrate (midazolam) exhibited a weak CYP3A4 DDI.
Inhibition/induction of transporter systems	In vitro gepotidacin was shown to inhibit MATE1 and MATE2-K, but no clinical evaluation was performed to confirm the findings. No other inhibition was observed to any other transporter at therapeutic plasma concentrations. A clinical study was performed with P-gp substrate (digoxin), and the observed C_{max} increase of 1.53-fold may be significant for a narrow therapeutic index agent like digoxin.

Source: Summary of Clinical Pharmacology and Study reports
Abbreviations: ΔΔQTc, baseline-adjusted, placebo-corrected QTc; ΔΔQTcF, placebo-corrected change from the predose baseline in QTcF; AUC, area under the concentration-time curve; AUC_{inf}, area under the concentration-time curve estimated to infinity; BMI, body mass index; C_{max}, maximum plasma concentration; CI, confidence interval; DDI, drug-drug interaction; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; *f*AUC, area under the free-drug concentration-time curve; *f*AUC/MIC, area under the free drug concentration–time curve to MIC ratio; h, hours; hERG, human ether-a-go-go-related gene; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; IV, intravenous; PK, pharmacokinetics; QTc, QT interval corrected for heart rate; QTcF, QT interval, corrected for heart rate using Fridericia's formula; T_{max}, time to maximum observed plasma concentration; TQT, thorough QT/QTc; UHPLC-MS/MS, ultra high-performance liquid chromatography-tandem mass spectrometry; uUTI, uncomplicated urinary tract infection

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant's proposed dosage of gepotidacin 1500 mg every 12 hours orally was evaluated in a phase 2a study in adult female subjects with uUTI (206899) and two phase 3 uUTI studies (EAGLE-2 and EAGLE-3) in adolescent and adult female subjects. In the phase 2a study, exploratory efficacy findings from microbiological, clinical, and composite response were promising and supported the progression to phase 3 studies for uUTI. In the EAGLE-2 and EAGLE-3 studies, the proposed dosing regimen of gepotidacin 1500 mg every 12 hours demonstrated noninferiority to nitrofurantoin 100 mg twice daily in composite response at test-of-cure (TOC) for the treatment of uUTI in female subjects. In the EAGLE-3 study, gepotidacin demonstrated noninferiority and superiority of gepotidacin to nitrofurantoin in composite response at test-of-cure (TOC).

6.1.1. Support for Proposed Dosage of Gepotidacin

Probability of Target Attainment Analyses

Urinary drug concentrations are considered important to the successful treatment of uUTI, while the relative importance of plasma drug concentrations to efficacy is unclear. The Applicant conducted PTA analyses for both plasma and urinary drug concentrations using AUC/MIC targets derived from a murine thigh infection model and an in vitro 1-compartment (chemostat) infection model to support the proposed dosage of gepotidacin 1500 mg every 12 hours and susceptibility urine breakpoint value of 16 µg/mL for Enterobacterales and 0.25 µg/mL for *S. saprophyticus* susceptibility (Section 19.7). As mentioned in Sections 5.1 and 14.1.5.1, the findings from both murine thigh infection model and in vitro 1-compartment (chemostat) model were deemed unreliable for assessing uUTI for the following reasons: 1) the in vitro 1-compartment model does not account for bladder tissue architecture, the complexities of urodynamics, or the pH of urine; and 2) murine thigh infection relates to activity that is occurring in blood but not urine and lumen of the bladder wall (Yang et al. 2014; Abbott et al. 2021). Moreover, it is unclear if the derived targets are reasonable surrogates for the relevant infection site. Additionally, it is not clear if *S. aureus* is an appropriate *Staphylococcus* species for evaluating *Staphylococcus saprophyticus*. Nonetheless, PTA based on the pooled in vitro *f*AUC/MIC 1-log kill target of 41 for Enterobacterales and the in vivo *f*AUC/MIC 1-log kill target of 59 for *S. saprophyticus*, were prioritized to support the proposed dosage in the phase 2a and 3 studies. The in vitro endpoint of 1-log kill numerically offered a more conservative appraisal of efficacy than those determined in the murine thigh infection model. PTA results showed that the free plasma concentrations associated with the Applicant's proposed dosage resulted in achievement of the in vitro targets in ≥90% of simulated subjects at an MIC of 0.25 µg/mL in Enterobacterales and 0.125 µg/mL in *S. saprophyticus*. The Applicant primarily used the probability of achieving PK-PD targets in urine to determine susceptibility breakpoints for Enterobacterales and *S. saprophyticus*. Based on the urine concentrations associated with the

Applicant's proposed dosage, urine PTA analyses showed achievement of the in vitro targets in ≥90% of simulated subjects at MIC of 16 µg/mL for Enterobacterales and 16 µg/mL for *S. saprophyticus*.

In Vitro Hollow-Fiber Study

To further support the proposed dosage of gepotidacin 1500 mg BID for the treatment of uUTI, the Applicant evaluated the bactericidal activity of plasma concentrations associated with the proposed dosage and their ability to prevent the emergence of resistant subpopulations of *E. coli*. The simulated plasma concentrations were demonstrated to suppress the growth and prevent the development of resistance of one *E. coli* strain (gepotidacin MIC of 2 µg/mL) for the entire duration of a 10-day study in a hollow-fiber infection model at area under the free-drug concentration-time curve (*f*AUC) of ≥549 mg*h/L (*f*AUC/MIC of ~275) or a gepotidacin dosage of 32 g BID; however, *f*AUC exposures similar to the proposed gepotidacin dosage of 1500 mg every 12 hours exhibited regrowth and the development of resistant subpopulations (see Section 14.1.6). Instead of applying the *f*AUC/MIC target of ~275 to plasma exposures, the Applicant applied the target for urine exposures. They determined that the 1500 mg every 12 hours would be able to suppress the growth and prevent the development of resistance up to an MIC of 4 µg/mL when applying the minimum urine area under the concentration-time curve (AUC) over 12 hours from the phase 1 studies at the proposed dosage. However, the findings from the hollow-fiber infection model (HFIM) were deemed uninterpretable for translating to urine exposures primarily because gepotidacin exposures in the HFIM were simulating drug concentrations in the plasma instead of drug concentrations in the urine (for additional reasons see Section 14.1.6).

Clinical Gepotidacin Exposure-Response for Efficacy Analysis

Gepotidacin exposure-response analyses were conducted by the Applicant using pooled data from the EAGLE-2 study. Flat exposure-response relationships were observed between Bayesian estimated steady-state gepotidacin plasma exposure measures (steady state *f*AUC or *f*AUC/MIC) at the dosage evaluated in the EAGLE-2 study and the composite, clinical, and microbiological response rates in the microbiologically evaluable (ME) population at TOC (with a microbiologically confirmed uUTI for *E. coli* and non-*E. coli* Enterobacterales). The review team agrees with the Applicant's assessment that no consistent trend in responses were observed across the gepotidacin exposures following administration of gepotidacin 1500 mg twice daily dosage in subjects from the EAGLE-2 study, and no clinically derived PK-PD target could be identified. For more details see Section 14.5.2.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Results of Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Two studies were used to evaluate the clinical efficacy of gepotidacin for the treatment of uUTI. See Sections 6.2.1 and 6.2.2 for detailed reviews of each study. Table 8 below summarizes the

pooled analyses of subject disposition of the two studies. A total of 3136 subjects were randomized. The percentage of treatment discontinuations due to adverse events was higher in the gepotidacin group (5.1%) compared to the nitrofurantoin group (1.9%). Approximately 40% of randomized subjects were included in the microbiological intent-to-treat (micro-ITT) nitrofurantoin susceptible (NTF-S) population which was used for most efficacy analyses.

Table 8. Subject Disposition, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Disposition Outcome	Gepotidacin (N=1572) n (%)	Nitrofurantoin (N=1564) n (%)
Subjects randomized		
ITT population	1572 (100)	1564 (100)
Micro-ITT population	732 (46.6)	689 (44.1)
Micro-ITT NTF-S population	628 (39.9)	573 (36.6)
Micro-ITT NTF-NS population	104 (6.6)	116 (7.4)
ME-OT population	639 (40.6)	609 (38.9)
ME-OT NTF-S population	546 (34.7)	504 (32.2)
ME-OT NTF-NS population	93 (5.9)	105 (6.7)
ME-TOC population	620 (39.4)	596 (38.1)
ME-TOC NTF-S population	524 (33.3)	497 (31.8)
ME-TOC NTF-NS population	96 (6.1)	99 (6.3)
ME-FU population	597 (38)	581 (37.1)
ME-FU NTF-S population	502 (31.9)	480 (30.7)
ME-FU NTF-NS population	95 (6)	101 (6.5)
CE-OT population	1401 (89.1)	1429 (91.4)
CE-TOC population	1386 (88.2)	1424 (91)
CE-FU population	1348 (85.8)	1375 (87.9)
Safety population[a]	1570 (99.9)	1558 (99.6)
Discontinued study drug[b]	148 (9.4)	102 (6.5)
Adverse event (AE)	80 (5.1)	30 (1.9)
Withdrawal by subject	25 (1.6)	29 (1.9)
Protocol deviation	20 (1.3)	17 (1.1)
Physician decision	11 (0.7)	7 (0.4)
Lost to follow-up	6 (0.4)	8 (0.5)
Protocol-specified withdrawal criterion met	2 (0.1)	4 (0.3)
Lack of efficacy	0	2 (0.1)
Other	3 (0.2)	5 (0.3)
Reason missing	1 (0.1)	0
Discontinued study[b]	90 (5.7)	69 (4.4)
Withdrawal by subject	36 (2.3)	34 (2.2)
Adverse event	27 (1.7)	10 (0.6)
Lost to follow-up	20 (1.3)	13 (0.8)
Protocol deviation	1 (0.1)	6 (0.4)
Physician decision	5 (0.3)	5 (0.3)
Other	1 (0.1)	1 (0.1)

Source: FDA analysis; adsl.xpt, adds.xpt;
[a] Two subjects who received both gepotidacin and nitrofurantoin were included in the gepotidacin arm.
[b] Percentages are based on number of randomized subjects.
Abbreviations: ITT, Intention-to-treat population; micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; ME, microbiologically evaluable; CE, clinically evaluable; OT, on-therapy; TOC, test-of-cure; FU, follow-up; N, number of subjects in treatment group; n, number of subjects in specified population or group

Pooled demographic characteristics are listed in Table 9. The two groups had similar distributions in these characteristics. Approximately 50% of randomized subjects were >50 years old and approximately 60% had nonrecurrent infections.

Table 9. Baseline Demographics (ITT Population), Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Baseline Demographics	Gepotidacin (N=1572)	Nitrofurantoin (N=1564)
Sex, n (%)		
Female	1572 (100.0)	1564 (100.0)
Age, years		
Mean (SD)	48.9 (17.84)	49.4 (17.96)
Median	49.0	49.5
Min, max	13.0, 89.0	13.0, 91.0
Age categories as randomized, n (%)		
<18	15 (1.0)	11 (<1)
≥18-50	801 (51.0)	800 (51.2)
>50	756 (48.1)	753 (48.1)
Age categories per CRF, n (%)		
<18	14 (<1)	12 (<1)
≥18-50	799 (50.8)	799 (51.1)
>50	759 (48.3)	753 (48.1)
Region, n (%)		
Americas	957 (60.9)	961 (61.4)
Asia-Pacific	67 (4.3)	80 (5.1)
Europe	548 (34.9)	523 (33.4)
Race, n (%)		
American Indian or Alaska Native	64 (4.1)	76 (4.9)
Asian	74 (4.7)	86 (5.5)
Black or African American	114 (7.3)	102 (6.5)
Native Hawaiian or Other Pacific Islander	4 (<1)	1 (<1)
White	1301 (82.8)	1289 (82.4)
Multiple	14 (<1)	10 (<1)
Missing	1 (<1)	0
Ethnicity, n (%)		
Hispanic or Latino	524 (33.3)	502 (32.1)
Not Hispanic or Latino	1048 (66.7)	1062 (67.9)
Baseline height (cm)		
Mean (SD)	162.6 (7.38)	162.0 (7.27)
Median	162.6	162.5
Min, max	125.0, 195.5	125.0, 188.0
Missing	0	1
Baseline weight (kg)		
Mean (SD)	72.5 (14.61)	71.3 (14.47)
Median	71.0	70.1
Min, max	40.1, 139.8	36.7, 132.0
Missing	0	1
BMI (kg/m^2)		
Mean (SD)	27.4 (5.07)	27.1 (5.14)
Median	27.1	26.7
Min, max	15.6, 44.6	15.5, 50.3
Missing	0	1
Acute cystitis recurrence as randomized, n (%)		
Nonrecurrent infection	947 (60.2)	942 (60.2)
Recurrent infection	625 (39.8)	622 (39.8)
Acute cystitis recurrence per CRF, n (%)		
Nonrecurrent infection	926 (58.9)	917 (58.6)
Recurrent infection	646 (41.1)	647 (41.4)

Baseline Demographics	Gepotidacin (N=1572)	Nitrofurantoin (N=1564)
Number of qualified uropathogens at baseline, n (%)		
None	840 (53.4)	875 (55.9)
Only 1 qualifying uropathogens	627 (39.9)	603 (38.6)
One qualifying uropathogen + any # of non-qualified uropathogens	73 (4.6)	53 (3.4)
Two qualifying uropathogens	32 (2.0)	33 (2.1)

Source: FDA analysis; adsl.xpt
Abbreviations: BMI, body mass index; CRF, case report forms; ITT, intent-to-treat population; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Pooled analyses of the primary and secondary endpoints are summarized in Table 10. The results were generally consistent with individual study results, with success rates numerically favoring the gepotidacin group.

Table 10. Summary of Primary and Secondary Efficacy Endpoints, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Efficacy Endpoints	Gepotidacin	Nitrofurantoin
Composite Response at TOC, micro-ITT NTF-S	(N=628)	(N=573)
Success, n (%)	346 (55.1)	261 (45.5)
Adjusted difference in success rate % (95% CI)	9.6 (4.1, 15.2)	
Composite Response at FU, micro-ITT NTF-S	(N=628)	(N=573)
Success, n (%)	243 (38.7)	189 (33.0)
Adjusted difference in success rate % (95% CI)	5.7 (0.4, 11.0)	
Microbiological Response at TOC, micro-ITT NTF-S	(N=628)	(N=573)
Success, n (%)	457 (72.8)	357 (62.3)
Adjusted difference in success rate % (95% CI)	10.4 (5.2, 15.6)	
Microbiological Response at FU, micro-ITT NTF-S	(N=628)	(N=573)
Success, n (%)	328 (52.2)	255 (44.5)
Adjusted difference in success rate % (95% CI)	7.8 (2.2, 13.3)	
Clinical Response at TOC, micro-ITT NTF-S	(N=628)	(N=573)
Success, n (%)	423 (67.4)	371 (64.7)
Adjusted difference in success rate % (95% CI)	2.8 (-2.4, 8.1)	
Clinical Response at FU, micro-ITT NTF-S	(N=628)	(N=573)
Success, n (%)	352 (56.1)	316 (55.1)
Adjusted difference in success rate % (95% CI)	1.1 (-4.4, 6.6)	
Clinical Response at TOC, ITT	(N=1572)	(N=1564)
Success, n (%)	1046 (66.5)	1001 (64.0)
Adjusted difference in success rate % (95% CI)	2.5 (-0.8, 5.8)	
Clinical Response at FU, ITT	(N=1572)	(N=1564)
Success, n (%)	899 (57.2)	847 (54.2)
Adjusted difference in success rate % (95% CI)	3.0 (-0.5, 6.4)	

Source: FDA analysis; adsl.xpt; adeff.xpt; All adjusted difference and corresponding confidence intervals are stratified by age category, acute cystitis recurrence status, and trial.
Abbreviations: CI, confidence interval; FU, follow-up; ITT, Intention-to-treat population; micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; TOC, test-of-cure

6.2.1. Study EAGLE-2

6.2.1.1. Design, Study EAGLE-2

Study EAGLE-2 (clinicaltrials.gov identifier NCT04020341) was a multicenter, parallel-group, double-blind, double-dummy comparator-controlled randomized noninferiority study that enrolled female subjects ≥12 years of age to compare the efficacy and safety of gepotidacin to nitrofurantoin for the treatment of uUTIs. The study enrolled subjects between October 17, 2019, and November 30, 2023, from 107 sites in 12 countries from North America, Europe, and Asia-Pacific regions. Study subjects were randomized 1:1 to receive oral gepotidacin 1500 mg twice daily for 5 days (total of 10 doses) or oral nitrofurantoin 100 mg twice daily for 5 days (total of 10 doses) and stratified by age group and uUTI recurrence.

Subjects were enrolled for 28±3 days, with study visits to assess safety, efficacy and microbiological endpoints occurring at baseline (Day 1), on-therapy (Days 2 through 4), TOC (Days 10 through 13), and follow-up (FU) (Day 28±3). The primary efficacy endpoint was a composite response (referred to as therapeutic response in the protocol) at TOC using the microbiological intent to treat (micro-ITT) NTF-S population. The composite response success was defined as subjects who experienced both a reduction of all qualifying bacterial pathogens on baseline culture (microbiological success) and complete resolution of all signs and symptoms of uUTI present at baseline (clinical success), without receipt of other systemic antimicrobials. Clinical success was assessed for each participant by the study investigators.

The study utilized a non-inferiority design and was designed in accordance with the FDA guidance "Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment (August 2019" (FDA 2019). An algorithm determined which uropathogens qualified for the primary efficacy assessment, with the micro-ITT population limited to gram-negative bacilli, *Staphylococcus saprophyticus*, and *Enterococci sp.*, that were susceptible to nitrofurantoin.

A total of 1531 subjects were enrolled, with 607 subjects (gepotidacin: 320, nitrofurantoin: 287) included within the micro-ITT NTF-S population.

In addition to the primary endpoint of the composite response at TOC, secondary endpoints included the following:

- Clinical outcome and response at TOC and FU in all subjects with acute cystitis
- Clinical outcome and response at TOC and FU in subjects with qualifying bacterial uropathogen(s) at baseline that all are susceptible to nitrofurantoin
- Microbiological outcome and response at TOC and FU
- Composite response at FU
- Pharmacokinetics from plasma and urine
- Safety and tolerability

6.2.1.2. Eligibility Criteria, Study EAGLE-2

Subjects were eligible for enrollment into Study EAGLE-2 if they fulfilled all of the following inclusion criteria:

1. Nonpregnant female subjects≥12 years of age with body weights ≥40 kg.
2. The participant had 2 or more of the following clinical signs and symptoms of acute cystitis with onset <96 hours prior to study entry: dysuria, frequency, urgency, or lower abdominal pain.
3. The participant had nitrite or pyuria (>15 white blood cells (WBC)/high power field or the presence of 3+/large leukocyte esterase) from a pretreatment clean-catch midstream urine sample.
4. The participant was capable of giving signed informed consent/assent.

Subjects were not considered eligible for enrollment if they met any of the following summarized key exclusion criteria:

1. Residence in a nursing home or dependent care-type facility.
2. Body mass index (BMI) ≥40.0 kg/m^2 or a BMI ≥35.0 kg/m^2 with obesity-related health conditions
3. Presence of immunocompromise, altered immune defenses or receipt of immunosuppressive therapy, including corticosteroid therapy
4. Presence of a medical condition that requires medication that could be affected by acetylcholinesterase inhibition, such as: poorly controlled asthma or chronic obstructive pulmonary disease, acute uncontrolled severe pain, active peptic ulcer disease, Parkinson disease, myasthenia gravis or seizure disorders requiring medications
5. Acute porphyria
6. Any surgical or medical condition that may interfere with drug absorption, distribution, metabolism, or excretion of the study drug
7. Glucose-6-phosphate dehydrogenase deficiency
8. Presence of acute cystitis known or suspected to be due to fungal, parasitic, viral pathogens, *Pseudomonas aeruginosa* or non-*E. coli* Enterobacteriaceae
9. Symptoms known or suspected to be caused by another disease process such as asymptomatic bacteriuria, overactive bladder, chronic incontinence or chronic interstitial cystitis.
10. Presence of anatomical, physiological or functional urogenital anomalies or neurogenic bladder
11. Presence of indwelling catheter, nephrostomy, ureter stent, or other foreign material in the urinary tract.
12. Symptoms of a complicated UTI, upper UTI, pyelonephritis, or urosepsis
13. Anuria, oliguria, or significant impairment of renal function defined as creatinine clearance (CrCl) <60 mL/min or clinically significant elevated serum creatinine.
14. Presence of vaginal discharge

15. Congenital long interval from the start of the Q wave to the end of the T wave (QT) syndrome or prolongation of the QT interval corrected for heart rate (QTc).
16. Uncompensated heart failure
17. Severe left ventricular hypertrophy.
18. Family history of QT prolongation or sudden death.
19. Vasovagal syncope or episodes of symptomatic bradycardia or bradyarrhythmia within the last 12 months.
20. Use of QT-prolonging drugs or drugs known to increase the risk of torsades de points
21. Use of a strong cytochrome P450 enzyme 3A4 inhibitor.
22. Abnormal electrocardiogram (ECG) reading in subjects ≥12 to <18 years of age
23. QTc >450 msec or a QTc >480 msec for subjects with bundle-branch block.
24. Uncorrected hypokalemia within the past 3 months
25. Alanine aminotransferase (ALT) value >2 × upper limit of normal (ULN).
26. Bilirubin value >1.5 × ULN
27. Liver disease, or known hepatic or biliary abnormalities, including symptomatic viral hepatitis or moderate-to-severe liver insufficiency (Child Pugh class B or C).
28. History of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin.

Subjects were also excluded if they had previously received systemic antimicrobial/antifungal treatment, had been previously enrolled in the study or received gepotidacin, had a known allergy to study drug or any component, had previously received an investigational drug, had a life-threatening medical condition or otherwise would not complete the study.

6.2.1.3. Statistical Analysis Plan, Study EAGLE-2

The following analysis populations were included in the study:

- Intent-to-treat (ITT) Population: All subjects randomly assigned to study treatment.
- Microbiological ITT (Micro-ITT) Population: All subjects randomly assigned to study treatment who received at least 1 dose of study treatment and had a qualifying baseline uropathogen, from a quantitative bacteriological culture of a pretreatment clean-catch midstream urine specimen.
- Micro-ITT NTF-S Population: All subjects in the micro-ITT Population whose baseline qualifying bacterial uropathogens all were susceptible to nitrofurantoin. Subjects with missing MIC susceptibility results for any qualifying uropathogens were included in the NTF-S subpopulation.

- Micro-ITT not susceptible to nitrofurantoin (NTF-NS) Population: All subjects in the micro-ITT Population who had any qualifying baseline bacterial uropathogens that were NTF-NS, defined as resistant to nitrofurantoin, intermediate to nitrofurantoin, or had no interpretation to nitrofurantoin. Subjects with missing MIC susceptibility results for all qualifying uropathogens were included in the NTF-NS subpopulation.
- ME Population: Subjects who met the definition of the micro-ITT Population, followed important components of the study and had an interpretable quantitative urine culture at the specified visit.
- ME NTF-S Population: All subjects in the ME visit-specific population whose baseline qualifying bacterial uropathogens were susceptible to nitrofurantoin.
- ME NTF-NS Population: All subjects in the ME visit-specific population who have any baseline qualifying bacterial uropathogens that were not susceptible to nitrofurantoin.
- Clinically Evaluable Population: All subjects in the ITT Population who followed important components of the study.
- Pharmacokinetic (PK) Population: All randomized subjects who received at least 1 dose of study treatment and have at least 1 nonmissing plasma or urine PK concentration.
- Safety Population: All randomized subjects who received at least 1 dose of study treatment.

Micro-ITT NTF-S Population was the primary analysis population.

The primary efficacy endpoint was composite response at the TOC Visit in female subjects with acute cystitis with a qualifying bacterial uropathogen(s) at Baseline that all were susceptible to nitrofurantoin. Composite response success refers to subjects who were deemed both a microbiological success and a clinical success. Microbiological success at the TOC Visit was defined as reduction of all qualifying bacterial uropathogens recovered at Baseline to $<10^3$ colony-forming unit (CFU)/mL as observed on quantitative urine culture without the subject receiving other systemic antimicrobials prior to the TOC visit. Clinical success was defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the subject receiving other systemic antimicrobials for the treatment of uUTI prior to or at the TOC visit. The non-inferiority of gepotidacin to nitrofurantoin was evaluated using Farrington and Manning test stratified by age category (≤50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection) combinations (4 strata), with a non-inferiority margin of 10%. If non-inferiority was declared, a superiority test was to be conducted for the primary efficacy endpoint.

One interim analysis (IA) was pre-planned and conducted when approximately 60% of subjects in the Micro-ITT NTF-S Population achieved the TOC Visit. The nominal significance levels for the interim and final analyses were determined by the Lan-DeMets spending function (K 1983) using the Pocock stopping boundary.

The secondary efficacy endpoints included the following:

- Clinical outcome and response at the TOC and Follow-up Visits (ITT Population)
- Clinical outcome and response at the TOC and Follow-up Visits (Micro-ITT NTF-S Population)

- Microbiological outcome and response at the TOC and Follow-up Visits (Micro-ITT NTF-S Population)
- Composite response at the Follow-up Visit (Micro-ITT NTF-S Population)

Secondary efficacy endpoints were summarized descriptively.

6.2.1.4. Results of Analyses, Study EAGLE-2

A total of 1680 subjects were screened, and 1531 subjects were randomized. The conclusion of efficacy was based on interim analysis as pre-specified in the protocol. The interim analysis was conducted when 607 subjects in the Micro-ITT NTF-S set achieved the TOC visit.

Table 11. Subject Disposition, Study EAGLE-2

Disposition Outcome	Gepotidacin (N=767) n (%)	Nitrofurantoin (N=764) n (%)
Subjects randomized	767 (100.0)	764 (100.0)
ITT population	767 (100.0)	764 (100.0)
ITT population (IA Set)	738 (96.2)	736 (96.3)
Micro-ITT population	401 (52.3)	365 (47.8)
Micro-ITT population (IA Set)	381 (49.7)	351 (45.9)
Micro-ITT NTF-S population	336 (43.8)	298 (39.0)
Micro-ITT NTF-S population (IA Set)	320 (41.7)	287 (37.6)
Micro-ITT NTF-NS population	65 (8.5)	67 (8.8)
ME-OT population	358 (46.7)	328 (42.9)
ME-OT NTF-S population	299 (39.0)	267 (34.9)
ME-OT NTF-NS population	59 (7.7)	61 (8.0)
ME-TOC population	350 (45.6)	322 (42.1)
ME-TOC NTF-S population	290 (37.8)	261 (34.2)
ME-TOC NTF-NS population	60 (7.8)	61 (8.0)
ME-FU population	337 (43.9)	303 (39.7)
ME-FU NTF-S population	277 (36.1)	243 (31.8)
ME-FU NTF-NS population	60 (7.8)	60 (7.9)
CE-OT population	704 (91.8)	699 (91.5)
CE-TOC population	695 (90.6)	690 (90.3)
CE-FU population	671 (87.5)	659 (86.3)
PK population	683 (89.0)	0
Safety population[a]	766 (99.9)	760 (99.5)
Discontinued study drug[b]	46 (6.0)	43 (5.6)
Adverse event (AE)	27 (3.5)	18 (2.4)
Withdrawal by subject	10 (1.3)	14 (1.8)
Protocol deviation	2 (0.3)	3 (0.4)
Physician decision	2 (0.3)	2 (0.3)
Lost to follow-up	1 (0.1)	1 (0.1)
Protocol-specified withdrawal criterion met	0	1 (0.1)
Other	3 (0.4)	4 (0.5)
Missing[c]	1 (0.1)	0

Disposition Outcome	Gepotidacin (N=767) n (%)	Nitrofurantoin (N=764) n (%)
Discontinued study[b]	33 (4.3)	28 (3.7)
Withdrawal by subject	16 (2.1)	16 (2.1)
Adverse event	8 (1.0)	6 (0.8)
Lost to follow-up	8 (1.0)	2 (0.3)
Protocol deviation	0	2 (0.3)
Physician decision	0	2 (0.3)
Other	1 (0.1)	0

Source: FDA analysis; adsl.xpt, adds.xpt
[a] One subject who only received placebo treatment was not included in this row.
[b] Percentages are based on number of randomized subjects.
[c] One subject did not have a treatment discontinuation reason in the ADDS dataset.
Abbreviations: ITT, intent-to-treat population; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; ME, microbiologically evaluable; CE, clinically evaluable; IA, interim analysis; OT, on-therapy; TOC, test-of-cure; FU, follow-up; PK, Pharmacokinetic; N, number of subjects in treatment group; n, number of subjects in specified population or group

Demographic characteristics are listed in Table 12. The two groups had similar distributions in these characteristics. Approximately 50% of randomized subjects were >50 years old and approximately 60% of randomized subjects experienced nonrecurrent infections.

Table 12. Baseline Demographics, ITT Population, Study EAGLE-2

Baseline Demographics	Gepotidacin (N=767)	Nitrofurantoin (N=764)
Sex, n (%)		
Female	767 (100.0)	764 (100.0)
Age, years		
Mean (SD)	49.6 (17.82)	50.4 (18.17)
Median	51.0	51.0
Min, max	14.0, 89.0	13.0, 91.0
Age categories as randomized, n (%)		
<18	7 (<1)	6 (<1)
≥18-50	373 (48.6)	372 (48.7)
>50	387 (50.5)	386 (50.5)
Age categories per CRF, n (%)		
<18	6 (<1)	9 (1.2)
≥18-50	372 (48.5)	369 (48.3)
>50	389 (50.7)	386 (50.5)
Region, n (%)		
Americas	411 (53.6)	412 (53.9)
Asia-Pacific	20 (2.6)	15 (2.0)
Europe	336 (43.8)	337 (44.1)
Race, n (%)		
American Indian or Alaska Native	62 (8.1)	75 (9.8)
Asian	23 (3.0)	21 (2.7)
Black or African American	40 (5.2)	40 (5.2)
Native Hawaiian or Other Pacific Islander	3 (<1)	1 (<1)
White	627 (81.7)	621 (81.3)
Multiple	12 (1.6)	6 (<1)
Ethnicity, n (%)		
Hispanic or Latino	278 (36.2)	270 (35.3)
Not Hispanic or Latino	489 (63.8)	494 (64.7)

Baseline Demographics	Gepotidacin (N=767)	Nitrofurantoin (N=764)
Baseline height (cm)		
Mean (SD)	162.4 (7.45)	162.2 (7.18)
Median	162.5	162.5
Min, max	125.2, 195.5	141.0, 182.8
Missing	0	1
Baseline weight (kg)		
Mean (SD)	72.1 (14.84)	70.8 (14.32)
Median	70.0	70.0
Min, max	40.5, 139.8	41.2, 127.1
Missing	0	1
BMI (kg/m^2)		
Mean (SD)	27.3 (5.24)	26.9 (5.09)
Median	27.1	26.6
Min, max	15.6, 44.6	15.5, 40.3
Missing	0	1
Acute cystitis recurrence as randomized, n (%)		
Nonrecurrent infection	465 (60.6)	463 (60.6)
Recurrent infection	302 (39.4)	301 (39.4)
Acute cystitis recurrence per CRF, n (%)		
Nonrecurrent Infection	455 (59.3)	455 (59.6)
Recurrent Infection	312 (40.7)	309 (40.4)
Number of qualified uropathogens at baseline, n (%)		
None	366 (47.7)	399 (52.2)
Only 1 qualifying uropathogen	334 (43.5)	312 (40.8)
One qualifying uropathogen + any # of non-qualified uropathogens	45 (5.9)	34 (4.5)
Two qualifying uropathogens	22 (2.9)	19 (2.5)

Source: FDA analysis; adsl.xpt
Abbreviations: BID, twice daily; BMI, body mass index; CRF, case report forms; ITT, intent-to-treat population; N, number of subjects in treatment group; max, maximum; min, minimum; n, number of subjects in specified population or group; SD, standard deviation

Composite Response (Including the Primary Efficacy Analysis)

Table 13 displays analysis results for the primary efficacy endpoint of composite response at TOC evaluated in the Micro-ITT NTF-S IA population. Treatment with gepotidacin demonstrated non-inferiority to the active control of nitrofurantoin with a non-inferiority margin of 10% at the interim analysis. Superiority was not demonstrated.

Most composite response failures were due to only microbiological failure or only clinical failure. See secondary endpoint analyses for evaluation of each individual response.

Table 13. Proportion of Subjects With Composite Response at TOC, Micro-ITT NTF-S (IA Set), Study EAGLE-2

Composite Response at TOC	Gepotidacin (N=320)	Nitrofurantoin (N=287)
Success, n (%)	162 (50.6)	135 (47.0)
Adjusted difference in success rate %	4.3	
Z statistics for non-inferiority (IA boundary)	3.5554 (2.0646)	
Two-sided p-value for non-inferiority (IA boundary)	0.0004 (0.0390)	
CI corresponding to 1-adjusted α	-4.0, 12.5	
95% CI	-3.6, 12.1	
Failure, n (%)	158 (49.4)	152 (53.0)
Microbiological success & clinical failure	70 (21.9)	59 (20.6)
Microbiological failure & clinical success	48 (15.0)	52 (18.1)
Microbiological failure & clinical failure	40 (12.5)	41 (14.3)
Failure due to UTD[a], n (%)	35 (10.9)	17 (5.9)

Source: FDA analysis; adsl.xpt;
[a] Failure due to UTD cases include: microbiological success and clinical UTD, microbiological UTD and clinical success, microbiological UTD and clinical UTD.
Abbreviations: CI, confidence interval; IA, interim analysis; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; TOC, test-of-cure; UTD, unable to determine

The reviewer conducted additional sensitivity analyses on the primary efficacy endpoint in the Micro-ITT NTF-S IA set, with details summarized in Table 14.

Firstly, the primary analysis was conducted excluding subjects from one site which received a Corrective and Preventive Action. The stopping boundary was adjusted given the smaller total number of subjects. The non-inferiority of gepotidacin to nitrofurantoin was still demonstrated in this analysis.

Secondly, to evaluate the effect of unable to determine (UTD) outcomes, a worst-case scenario analysis was conducted. All failures due to UTD cases (microbiological success and clinical UTD, microbiological UTD and clinical success, microbiological UTD and clinical UTD) in the nitrofurantoin arm were imputed as composite response success, while all failures due to UTD cases in the gepotidacin arm stayed as composite response failures. In this analysis, the non-inferiority of gepotidacin to nitrofurantoin was still demonstrated.

Thirdly, to evaluate the uropathogens that were non-qualifying or not observed at baseline, a sensitivity analysis was conducted. A total of 32 subjects in the Micro-ITT NTF-S IA set who had composite response success at TOC had detectable uropathogens ($\geq 10^3$ CFU/mL) at TOC. Among those 32 subjects, 3 subjects had detectable uropathogens at TOC that were the non-qualifying uropathogens detected at baseline (2 from the gepotidacin arm and 1 from the nitrofurantoin arm). Among the 32 subjects, 4 subjects had qualifying uropathogens at TOC (2 from the gepotidacin arm and 2 from the nitrofurantoin arm) based on the protocol defined algorithm. The non-inferiority of gepotidacin to nitrofurantoin was still demonstrated if considering any detectable uropathogen at TOC as composite response failure.

Lastly, a sensitivity analysis was conducted to include considerations of gepotidacin resistance. In study EAGLE-2, a total of 49 gepotidacin subjects (in the ITT population) developed gepotidacin resistant uropathogen(s) during post-baseline visits. Resistance was defined as ≥ 4-fold increase in MIC compared to baseline. In this sensitivity analysis, subjects from the gepotidacin arm who developed gepotidacin resistant uropathogen(s) on therapy (OT), TOC, or FU visits were imputed as composite response failures. The non-inferiority of gepotidacin to nitrofurantoin was still demonstrated in this analysis. For further discussion on resistance issues

(including the genetic determination), please refer to the clinical microbiology review, Section 19.

Table 14. Proportion of Subjects With Composite Response at TOC Sensitivity Analyses, Micro-ITT NTF-S (IA Set), Study EAGLE-2

Composite Response at TOC, Sensitivity Analyses	Gepotidacin	Nitrofurantoin
Composite response at TOC, CAPA site excluded	(N=308)	(N=279)
Success, n (%)	155 (50.3)	130 (46.6)
Adjusted difference in success rate %	4.4	
Z statistics for non-inferiority (IA boundary)	3.5392 (2.0742)	
Two-sided p-value for non-inferiority (IA boundary)	0.0004 (0.0381)	
CI corresponding to 1-adjusted α	(-4.0, 12.8)	
95% CI	(-3.6, 12.4)	
Composite Response at TOC, worst case scenario	(N=320)	(N=287)
Success, n (%)	162 (50.6)	152 (53.0)
Adjusted difference in success rate %	-1.6	
Z statistics for non-inferiority (IA boundary)	2.0877 (2.0646)	
Two-sided p-value for non-inferiority (IA boundary)	0.0368 (0.0390)	
CI corresponding to 1-adjusted α	(-9.9, 6.6)	
95% CI	(-9.5, 6.2)	
Composite Response at TOC, all uropathogen at TOC included for response evaluation	(N=320)	(N=287)
Success, n (%)	143 (44.7)	122 (42.5)
Adjusted difference in success rate %	3.0	
Z statistics for non-inferiority (IA boundary)	3.2720 (2.0646)	
Two-sided p-value for non-inferiority (IA boundary)	0.0011 (0.0390)	
CI corresponding to 1-adjusted α	(-5.2, 11.2)	
95% CI	(-4.8,10.7)	
Composite response at TOC, gepotidacin resistance as failure	(N=320)	(N=287)
Success, n (%)	153 (47.8)	135 (47.0)
Adjusted difference in success rate %	1.6	
Z statistics for non-inferiority (IA boundary)	2.8865 (2.0646)	
Two-sided p-value for non-inferiority (IA boundary)	0.0039 (0.0390)	
CI corresponding to 1-adjusted α	(-6.7, 9.8)	
95% CI	(-6.3, 9.4)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; IA, interim analysis; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; TOC, test-of-cure

Analyses of composite response at TOC using complete study data in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations, including data collected after the interim analysis, were summarized in Table 15. Results were generally consistent with the primary analysis.

Table 15. Proportion of Subjects With Composite Response at TOC, Complete Data, Study EAGLE-2

Composite Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at TOC, Micro-ITT NTF-S	(N=336)	(N=298)
Success, n (%)	174 (51.8)	140 (47.0)
Adjusted difference in success rate % (95% CI)	5.3 (-2.4%, 13.0)	
Composite response at TOC, Micro-ITT NTF-NS	(N=65)	(N=67)
Success, n (%)	24 (36.9)	17 (25.4)
Adjusted difference in success rate % (95% CI)	10.7% (-4.7, 26.1)	

Composite Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at TOC, Micro-ITT	(N=401)	(N=365)
Success, n (%)	198 (49.4)	157 (43.0)
Adjusted difference in success rate % (95% CI)	6.8 (-0.2, 13.7)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; TOC, test-of-cure

Analyses of sustained composite response at FU in complete study data in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations were summarized in Table 16. Results were generally consistent with results at TOC, with response rates numerically favoring the gepotidacin arm.

Table 16. Proportion of Subjects With Sustained Composite Response at FU, Complete Data, Study EAGLE-2

Sustained Composite Response at FU, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at FU, Micro-ITT NTF-S	(N=336)	(N=298)
Success, n (%)	117 (34.8)	94 (31.5)
Adjusted difference in success rate % (95% CI)	4.1 (-3.1, 11.3)	
Composite response at FU, Micro-ITT NTF-NS	(N=65)	(N=67)
Success, n (%)	20 (30.8)	13 (19.4)
Adjusted difference in success rate % (95% CI)	11.0 (-3.9, 25.9)	
Composite response at FU, Micro-ITT	(N=401)	(N=365)
Success, n (%)	137 (34.2)	107 (29.3)
Adjusted difference in success rate % (95% CI)	5.6 (-0.9, 12.1)	

Source: FDA analysis;; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible

Complete study data analyses of composite response at FU independent of TOC response in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations were summarized in Table 17. Results were generally consistent with results of sustained composite response at FU.

Table 17. Proportion of Subjects With Composite Response at FU Independent of TOC Response, Complete Data, Study EAGLE-2

Composite Response at FU Independent of TOC Response, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at FU, Micro-ITT NTF-S	(N=336)	(N=298)
Success, n (%)	181 (53.9)	146 (49.0)
Adjusted difference in success rate % (95% CI)	6.0 (-1.6, 13.5)	
Composite response at FU, Micro-ITT NTF-NS	(N=65)	(N=67)
Success, n (%)	38 (58.5)	30 (44.8)
Adjusted difference in success rate % (95% CI)	12.7 (-3.2, 28.6)	
Composite response at FU, Micro-ITT	(N=401)	(N=365)
Success, n (%)	219 (54.6)	176 (48.2)
Adjusted difference in success rate % (95% CI)	7.2 (0.3, 14.0)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; TOC, test-of-cure

Microbiological Response

The uropathogen level microbiological response was defined as follows:

- Microbiological eradication: A quantitative urine culture taken at the TOC Visit showed reduction of the qualifying uropathogen recovered at Baseline to $<10^3$ CFU/mL without the subject receiving other systemic antimicrobials before the TOC Visit.
- Microbiological persistence: A quantitative urine culture taken at the TOC Visit showed that the qualifying uropathogen recovered at Baseline, and which was also shown to persist or is unable to determine at the OT Visit, grows $\geq 10^3$ CFU/mL without the subject receiving other systemic antimicrobials before the TOC Visit.
- Microbiological recurrence: A quantitative urine culture taken at the TOC Visit showed that the qualifying uropathogen recovered at Baseline, and which was also shown to be eradicated at the OT Visit, grows $\geq 10^3$ CFU/mL without the subject receiving other systemic antimicrobials before the TOC Visit.
- Unable to determine: (1) The TOC urine culture result was missing or (2) The subject received other systemic antimicrobials before the TOC Visit.
- The patient-level microbiological response was defined as follows:
- Microbiological eradication (success): All qualifying baseline uropathogens had a microbiological outcome of eradication at TOC
- Microbiological persistence (failure): At least one qualifying baseline uropathogen had an outcome of persistence at TOC
- Microbiological recurrence (failure): At least one qualifying baseline uropathogen had an outcome of recurrence and none had an outcome of persistence at TOC
- Unable to determine (failure): All qualifying baseline uropathogen outcomes were unable to determine at TOC

Table 18 summarizes analyses of microbiological response at TOC in complete study data. Results numerically favored the gepotidacin arm in the Micro-ITT NTF-S, Micro-ITT NTF-NS, and Micro-ITT populations.

Table 18. Proportion of Subjects With Microbiological Response at TOC, Complete Data, Study EAGLE-2

Microbiological Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Microbiological Response at TOC Micro-ITT NTF-S	(N=336)	(N=298)
Success, n (%)	244 (72.6)	199 (66.8)
Adjusted difference in success rate % (95% CI)	6.0 (-1.2, 13.1)	
Failure, n (%)	92 (27.4)	99 (33.2)
Microbiological persistence	15 (4.5)	21 (7.0)
Microbiological recurrence	36 (10.7)	52 (17.4)
UTD	41 (12.2)	26 (8.7)
Total number of subjects with missing microbiological data	36 (10.7)	21 (7.0)
Microbiological Response at TOC Micro-ITT NTF-NS	(N=65)	(N=67)
Success, n (%)	50 (76.9)	38 (56.7)
Adjusted difference in success rate % (95% CI)	17.9 (2.8, 33.0)	

Microbiological Response at TOC Micro-ITT	(N=401)	(N=365)
Success, n (%)	294 (73.3)	237 (64.9)
Adjusted difference in success rate % (95% CI)	8.5 (2.0, 15.0)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; TOC, test-of-cure; UTD, unable to determine

Analyses of sustained microbiological response at FU in complete study data in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations were summarized in Table 19. Results were generally consistent with results at TOC, with response rates numerically favoring the gepotidacin arm.

Table 19. Proportion of Subjects With Sustained Microbiological Response at FU, Complete Data, Study EAGLE-2

Sustained Microbiological Response at FU, Complete Data	Gepotidacin	Nitrofurantoin
Microbiological Response at FU Micro-ITT NTF-S	(N=336)	(N=298)
Success, n (%)	174 (51.8)	136 (45.6)
Adjusted difference in success rate % (95% CI)	6.7 (-0.9, 14.3%)	
Microbiological Response at FU Micro-ITT NTF-NS	(N=65)	(N=67)
Success, n (%)	46 (70.8)	31 (46.3)
Adjusted difference in success rate % (95% CI)	21.8 (6.5, 37.0)	
Microbiological Response at FU Micro-ITT	(N=401)	(N=365)
Success, n (%)	220 (54.9)	167 (45.8)
Adjusted difference in success rate % (95% CI)	9.5 (2.6, 16.4)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; Micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; TOC, test-of-cure

Clinical Response

The clinical signs and symptoms included dysuria, frequency, urgency, and lower abdominal or suprapubic pain. Each of the signs and symptoms were scored from 0 to 3. The patient level clinical response was defined as follows:

- Clinical resolution (success): Resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms), without the participant receiving any other systemic antimicrobials before or on the date of TOC Visit for the current infection
- Clinical improvement (failure): Improvement in total symptom scores from Baseline, but not complete resolution, without the participant receiving other systemic antimicrobials before the TOC Visit or on the date of TOC Visit for the current infection
- Clinical worsening (failure): Worsening or no change in total symptom scores from Baseline or the participant received other systemic antimicrobials for the current infection before or on the date of the TOC Visit
- Unable to determine (failure): (1) The baseline score was missing (but not meeting clinical resolution) or (2) The TOC assessment was missing or (3) The participant received other systemic antimicrobials not for the current infection before the TOC Visit (unless clinical worsening outcome criteria were met)

Table 20 summarizes analyses of clinical response at TOC in complete study data. Response rates of the gepotidacin arm and the nitrofurantoin arm were similar in micro-ITT NTF-S, micro-

ITT, and ITT populations. Consistent results were also observed if looking at each individual symptom (dysuria, frequency, urgency, and lower abdominal or suprapubic pain).

Table 20. Proportion of Subjects With Clinical Response at TOC, Complete Data, Study EAGLE-2

Clinical Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Clinical Response at TOC Micro-ITT NTF-S	(N=336)	(N=298)
Success, n (%)	224 (66.7)	196 (65.8)
Adjusted difference in success rate % (95% CI)	1.5 (-5.8, 8.8)	
Failure, n (%)	112 (33.3)	102 (34.2)
Clinical improvement	82 (24.4)	75 (25.2)
Clinical worsening	9 (2.7)	16 (5.4)
UTD	21 (6.3)	11 (3.7)
Total number of subjects with missing TOC clinical data[a]	18 (5.4)	10 (3.4)
Clinical Response at TOC Micro-ITT	(N=401)	(N=365)
Success, n (%)	254 (63.3)	230 (63.0)
Adjusted difference in success rate % (95% CI)	0.9% (-5.9%, 7.6)	
Clinical Response at TOC ITT	(N=767)	(N=764)
Success, n (%)	497 (64.8)	484 (63.4)
Adjusted difference in success rate % (95% CI)	1.5 (-3.3, 6.2)	

Source: FDA analysis; adsl.xpt; adeff.xpt
[a] One Gepotidacin subject considered as UTD due to missing baseline clinical data was not included in this row.
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; ITT, intent-to-treat; NTF-S nitrofurantoin susceptible; TOC, test-of-cure; UTD, unable to determine

Table 21 summarizes analyses of sustained clinical response at FU in complete study data. Response rates of the gepotidacin arm and the nitrofurantoin arm were similar in micro-ITT NTF-S, micro-ITT, and ITT populations.

Table 21. Proportion of Subjects With Sustained Clinical Response at FU, Complete Data, Study EAGLE-2

Clinical Response at FU, Complete Data	Gepotidacin	Nitrofurantoin
Clinical Response at FU Micro-ITT NTF-S	(N=336)	(N=298
Success, n (%)	184 (54.8%)	162 (54.4%)
Adjusted difference in success rate % (95% CI)	1.1% (-6.6%, 8.7%)	
Failure, n (%)	152 (45.2%)	136 (45.6%)
UTD	40 (11.9%)	31 (10.4%)
Clinical Response at FU Micro-ITT	(N=401)	(N=365)
Success, n (%)	210 (52.4%)	186 (51.0%)
Adjusted difference in success rate % (95% CI)	2.0% (-5.1%, 9.0%)	
Clinical Response at FU ITT	(N=767)	(N=764)
Success, n (%)	421 (54.9%)	404 (52.9%)
Adjusted difference in success rate % (95% CI)	2.0% (-2.9%, 7.0%)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; Micro-ITT, microbiological intent-to-treat; ITT, intent-to-treat; NTF-S nitrofurantoin susceptible; TOC, test-of-cure

6.2.2. Study EAGLE-3

6.2.2.1. Design, Study EAGLE-3

Study EAGLE-3 (clinicaltrials.gov identifier NCT04187144) was a multicenter, parallel-group, double-blind, double-dummy, comparator-controlled randomized noninferiority study that

enrolled female subjects ≥12 years of age to compare the efficacy and safety of gepotidacin to nitrofurantoin for the treatment of uUTI. The study enrolled subjects between April 23, 2020, and December 01, 2022, from 112 sites in 6 countries from North America, Europe, and Asia-Pacific regions. Study subjects were randomized 1:1 to receive oral gepotidacin 1500 mg twice daily for 5 days (total of 10 doses) or oral nitrofurantoin 100 mg twice daily for 5 days (total of 10 doses) and stratified by age group and uUTI recurrence. Studies EAGLE-2 and EAGLE-3 were nearly identically designed, with the only differences pertaining to the collection and analysis of PK data (EAGLE-2 only) and post-treatment electrocardiograms (EAGLE-3 only).

Subjects were enrolled for 28 ± 3 days, with study visits to assess safety, efficacy and microbiological endpoints occurring at baseline (Day 1), on-therapy (Days 2 through 4), test-of-cure (TOC) (Days 10 through 13), and follow-up (Day 28 ± 3). The primary efficacy endpoint was composite response (referred to as "therapeutic response" in the protocol) at TOC using the micro-ITT NTF-S population. Composite response success was defined as subjects who experienced both a reduction of all qualifying bacterial pathogens on baseline culture (microbiological success) and complete resolution of all signs and symptoms of uUTI present at baseline (clinical success), without receipt of other systemic antimicrobials. Clinical success was assessed for each subject by the study investigators.

The study utilized a non-inferiority design and was designed in accordance with the FDA guidance "Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment (August 2019)" (FDA 2019). An algorithm determined which uropathogens qualified for the primary efficacy assessment. The Micro-ITT population was limited to gram-negative bacilli, *Staphylococcus saprophyticus,* and *Enterococci sp.*, that were susceptible to nitrofurantoin. A total of 1605 subjects were enrolled, with 541 subjects (Gepotidacin: 277, Nitrofurantoin: 264) included within the Micro-ITT NTF-S population.

In addition to the primary endpoint of composite response at TOC, secondary endpoints included the following:

- Clinical outcome and response at TOC and FU in all subjects with acute cystitis
- Clinical outcome and response at TOC and FU in subjects with qualifying bacterial uropathogen(s) at baseline that all are susceptible to nitrofurantoin
- Microbiological outcome and response at TOC and FU
- Composite response at FU
- Safety and tolerability

6.2.2.2. Eligibility Criteria, Study EAGLE-3

The inclusion and exclusion criteria from Study EAGLE-3 were the same as for Study EAGLE-2. Please see Section 6.2.1.2 for details.

6.2.2.3. Statistical Analysis Plan, Study EAGLE-3

The analysis populations of EAGLE-3 were the same as those of EAGLE-2, with the exception that EAGLE-3 did not have a PK population. The primary efficacy endpoint, secondary efficacy

endpoints, and the corresponding analyses were the same as EAGLE-2. Please see Section 6.2.1.3 for details.

6.2.2.4. Results of Analyses, Study EAGLE-3

A total of 1731 subjects were screened, and 1605 subjects were randomized. Conclusion of efficacy was based on interim analysis as pre-specified in the protocol. The interim analysis was conducted when 541 subjects in the Micro-ITT NTF-S set achieved the TOC visit. Percentage of treatment discontinuation due to adverse event was higher from the gepotidacin arm (6.6%) compared to the nitrofurantoin arm (1.5%).

Table 22. Subject Disposition, Study EAGLE-3

Disposition Outcome	Gepotidacin (N=805) n (%)	Nitrofurantoin (N=800) n (%)
Subjects randomized	805 (100.0)	800 (100.0)
ITT population	805 (100.0)	800 (100.0)
ITT population (IA Set)	757 (94.0)	755 (94.4)
Micro-ITT population	331 (41.1)	324 (40.5)
Micro-ITT population (IA Set)	312 (38.8)	310 (38.8)
Micro-ITT NTF-S population	292 (36.3)	275 (34.4)
Micro-ITT NTF-S population (IA Set)	277 (34.4)	264 (33.0)
Micro-ITT NTF-NS population	39 (4.8)	49 (6.1)
ME-OT population	281 (34.9)	281 (35.1)
ME-OT NTF-S population	247 (30.7)	237 (29.6)
ME-OT NTF-NS population	34 (4.2)	44 (5.5)
ME-TOC population	270 (33.5)	274 (34.2)
ME-TOC NTF-S population	234 (29.1)	236 (29.5)
ME-TOC NTF-NS population	36 (4.5)	38 (4.8)
ME-FU population	260 (32.3)	278 (34.8)
ME-FU NTF-S population	225 (28.0)	237 (29.6)
ME-FU NTF-NS population	35 (4.3)	41 (5.1)
CE-OT population	697 (86.6)	730 (91.2)
CE-TOC population	691 (85.8)	734 (91.8)
CE-FU population	677 (84.1)	716 (89.5)
Safety population[a]	804 (99.9)	798 (99.8)
Discontinued study drug[b]	102 (12.7)	59 (7.4)
Adverse event (AE)	53 (6.6)	12 (1.5)
Withdrawal by subject	15 (1.9)	15 (1.9)
Protocol deviation	18 (2.2)	14 (1.8)
Physician decision	9 (1.1)	5 (0.6)
Lost to follow-up	5 (0.6)	7 (0.9)
Protocol-specified withdrawal criterion met	2 (0.2)	3 (0.4)
Lack of efficacy	0	2 (0.3)
Other	0	1 (0.1)

Disposition Outcome	Gepotidacin (N=805) n (%)	Nitrofurantoin (N=800) n (%)
Discontinued study[b]	57 (7.1)	41 (5.1)
Withdrawal by subject	20 (2.5)	18 (2.2)
Adverse event	19 (2.4)	4 (0.5)
Lost to follow-up	12 (1.5)	11 (1.4)
Protocol deviation	1 (0.1)	4 (0.5)
Physician decision	5 (0.6)	3 (0.4)
Other	0	1 (0.1)

Source: FDA analysis; adsl.xpt, adds.xpt
[a] Two subjects who received both gepotidacin and nitrofurantoin were included in the gepotidacin arm.
[b] Percentages are based on number of randomized subjects.
Abbreviations: CE, clinically evaluable; FU, follow-up; IA, interim analysis; ITT, Intention-to-treat population; ME, microbiologically evaluable; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; OT, on-therapy; TOC, test-of-cure

Demographic characteristics are listed in Table 23. The two groups had similar distributions in these characteristics. Approximately 50% of randomized subjects were >50 years old and approximately 60% of randomized subjects experienced nonrecurrent infections.

Table 23. Baseline Demographics, ITT Population, Study EAGLE-3

Demographic Information	Gepotidacin (N=805)	Nitrofurantoin (N=800)
Sex, n (%)		
Female	805 (100.0)	800 (100.0)
Age, years		
Mean (SD)	48.2 (17.84)	48.4 (17.72)
Median	48.0	49.0
Min, max	13.0, 89.0	13.0, 91.0
Age categories as randomized, n (%)		
<18	8 (1.0)	5 (<1)
≥18-50	428 (53.2)	428 (53.5)
>50	369 (45.8)	367 (45.9)
Age categories per CRF, n (%)		
<18	8 (1.0)	3 (<1)
≥18-50	427 (53.0)	430 (53.8)
>50	370 (46.0)	367 (45.9)
Region, n (%)		
Americas	546 (67.8)	549 (68.6)
Asia-Pacific	47 (5.8)	65 (8.1)
Europe	212 (26.3)	186 (23.2)
Race, n (%)		
American Indian or Alaska Native	2 (<1)	1 (<1)
Asian	51 (6.3)	65 (8.1)
Black or African American	74 (9.2)	62 (7.8)
Native Hawaiian or Other Pacific Islander	1 (<1)	0
White	674 (83.7)	668 (83.5)
Multiple	2 (<1)	4 (<1)
Missing	1 (<1)	0
Ethnicity, n (%)		
Hispanic or Latino	246 (30.6)	232 (29.0)
Not Hispanic or Latino	559 (69.4)	568 (71.0)

Demographic Information	Gepotidacin (N=805)	Nitrofurantoin (N=800)
Baseline height (cm)		
Mean (SD)	162.8 (7.32)	161.9 (7.37)
Median	162.6	162.5
Min, max	125.0, 188.0	125.0, 188.0
Baseline weight (kg)		
Mean (SD)	72.9 (14.40)	71.7 (14.60)
Median	71.9	70.7
Min, max	40.1, 131.0	36.7, 132.0
BMI (kg/m^2)		
Mean (SD)	27.5 (4.90)	27.3 (5.18)
Median	27.2	26.7
Min, max	17.1, 43.2	16.8, 50.3
Acute cystitis recurrence as randomized, n (%)		
Nonrecurrent infection	482 (59.9)	479 (59.9)
Recurrent infection	323 (40.1)	321 (40.1)
Acute cystitis recurrence per CRF, n (%)		
Nonrecurrent infection	471 (58.5)	462 (57.8)
Recurrent infection	334 (41.5)	338 (42.2)
Number of qualified uropathogens at baseline, n (%)		
None	474 (58.9)	476 (59.5)
Only 1 qualifying uropathogens	293 (36.4)	291 (36.4)
One qualifying uropathogen + any # of non-qualified uropathogens	28 (3.5)	19 (2.4)
Two qualifying uropathogens	10 (1.2)	14 (1.8)

Source: FDA analysis; adsl.xpt
Abbreviations: BID, twice daily; BMI, body mass index; CRF, case report forms; ITT, intent-to-treat, N, number of subjects in treatment group; n, number of subjects in specified population or group; SD, standard deviation

Composite Response (Including the Primary Efficacy Analysis)

Table 24 displays analysis results for the primary efficacy endpoint of composite response at TOC evaluated in the Micro-ITT NTF-S IA population. Treatment with gepotidacin demonstrated non-inferiority to the active control of nitrofurantoin with a non-inferiority margin of 10% at the interim analysis. Superiority of gepotidacin to nitrofurantoin in this study was also demonstrated.

Table 24. Proportion of Subjects With Composite Response at TOC, micro-ITT NTF-S (IA Set), Study EAGLE-3

Composite Response at TOC	Gepotidacin (N=277)	Nitrofurantoin (N=264)
Success, n (%)	162 (58.5)	115 (43.6)
Adjusted difference in success rate %	14.6	
Z statistics for non-inferiority (IA boundary)	5.8838 (2.0977)	
Two-sided p-value for non-inferiority (IA boundary)	<0.0001 (0.0359)	
Z statistics for superiority (IA boundary)	3.4960 (2.0977)	
Two-sided p-value for superiority (IA boundary)	0.0005 (0.0359)	
CI corresponding to 1-adjusted α	5.9, 23.4	
95% CI	6.4, 22.8	

Composite Response at TOC	Gepotidacin (N=277)	Nitrofurantoin (N=264)
Failure, n (%)	115 (41.5)	149 (56.4)
Microbiological success & clinical failure	38 (13.7)	36 (13.6)
Microbiological failure & clinical success	26 (9.4)	52 (19.7)
Microbiological failure & clinical failure	51 (18.4)	61 (23.1)
Failure due to UTD[a]	26 (9.4)	22 (8.3)

Source: FDA analysis; adsl.xpt
[a] Failure due to UTD cases include: microbiological success and clinical UTD, microbiological UTD and clinical success, microbiological UTD and clinical UTD.
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; IA, interim analysis; TOC, test-of-cure; UTD, unable to determine

The reviewer conducted additional sensitivity analyses on the primary efficacy endpoint in the Micro-ITT NTF-S IA set, with details summarized in Table 25.

Firstly, to evaluate the effect of UTD outcomes, a worst-case scenario analysis was conducted. All failures due to UTD cases (microbiological success and clinical UTD, microbiological UTD and clinical success, microbiological UTD and clinical UTD) in the nitrofurantoin arm were imputed as composite response success, while all failures due to UTD cases in the gepotidacin arm stayed as composite response failures. In this analysis, the non-inferiority of gepotidacin to nitrofurantoin was still demonstrated.

Secondly, to evaluate the uropathogens that were non-qualifying or not observed at baseline, a sensitivity analysis was conducted. A total of 22 subjects in Micro-ITT NTF-S IA set who had composite response success at TOC had detectable uropathogens ($\geq 10^3$ CFU/mL) at TOC. Among those 22 subjects, 2 subjects had detectable uropathogens at TOC that were the non-qualifying uropathogens detected at baseline (1 from gepotidacin arm and 1 from nitrofurantoin arm). Among the 22 subjects, 2 subjects had qualifying uropathogens at TOC (both from the nitrofurantoin arm) based on the protocol defined algorithm. The non-inferiority of gepotidacin to nitrofurantoin was still demonstrated if any detectable uropathogen at TOC was considered to be a composite response failure.

Lastly, a sensitivity analysis was conducted to include considerations of gepotidacin resistance. In Study EAGLE-3, a total of 10 gepotidacin subjects (in the ITT population) developed gepotidacin resistant uropathogen(s) during post-baseline visits. Resistance was defined as ≥4-fold increase in MIC compared to baseline. In this sensitivity analysis, subjects from the gepotidacin arm who developed gepotidacin resistant uropathogen(s) at OT, TOC, or FU visits were imputed as composite failures. The non-inferiority of gepotidacin to nitrofurantoin was still demonstrated in this analysis. For further discussion on resistance issues (including the genetic determination), please refer to the clinical microbiology review Section 19.

Table 25. Proportion of Subjects With Composite Response at TOC Sensitivity Analyses, micro-ITT NTF-S (IA Set), Study EAGLE-3

Composite Response at TOC Sensitivity Analyses	Gepotidacin	Nitrofurantoin
Composite response at TOC, worst case scenario	(N=277)	(N=264)
Success, n (%)	162 (58.5)	137 (51.9)
Adjusted difference in success rate %	6.6	
Z statistics for non-inferiority (IA boundary)	3.9530 (2.0977)	
Two-sided p-value for non-inferiority (IA boundary)	<0.0001 (0.0359)	
CI corresponding to 1-adjusted α	(-2.2, 15.4)	
95% CI	(-1.6, 14.8)	

Composite Response at TOC Sensitivity Analyses	Gepotidacin	Nitrofurantoin
Composite response at TOC, worst case scenario	(N=277)	(N=264)
Composite response at TOC, all uropathogen at TOC included for response evaluation	(N=277)	(N=264)
Success, n (%)	150 (54.2)	105 (39.8)
Adjusted difference in success rate %	14.2	
Z statistics for non-inferiority (IA boundary)	5.7732 (2.0977)	
Two-sided p-value for non-inferiority (IA boundary)	<0.0001 (0.0359)	
CI corresponding to 1-adjusted α	(5.4, 23.0)	
95% CI	(6.0, 22.4)	
Composite response at TOC, gepotidacin resistance as failure	(N=277)	(N=264)
Success, n (%)	160 (57.8)	115 (43.6)
Adjusted difference in success rate %	13.9	
Z statistics for non-inferiority (IA boundary)	5.7157 (2.0977)	
Two-sided p-value for non-inferiority (IA boundary)	<0.0001 (0.0359)	
CI corresponding to 1-adjusted α	(5.2, 22.7)	
95% CI	(5.7, 22.2)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; IA, interim analysis; TOC, test-of-cure

Analyses of composite response at TOC using complete study data in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations, including data collected after the interim analysis, were summarized in Table 26. Results were generally consistent with the primary analysis.

Table 26. Proportion of Subjects With Composite Response at TOC, Complete Data, Study EAGLE-3

Composite Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at TOC, micro-ITT NTF-S	(N=292)	(N=275)
Success, n (%)	172 (58.9)	121 (44.0)
Adjusted difference in success rate % (95% CI)	14.4 (6.4, 22.4)	
Composite response at TOC, micro-ITT NTF-NS	(N=39)	(N=49)
Success, n (%)	27 (69.2)	15 (30.6)
Adjusted difference in success rate % (95% CI)	33.9 (16.4, 51.5)	
Composite response at TOC, micro-ITT	(N=331)	(N=324)
Success, n (%)	199 (60.1)	136 (42.0)
Adjusted difference in success rate % (95% CI)	17.7 (10.3, 25.1)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; IA, interim analysis; TOC, test-of-cure

Analyses of sustained composite response at FU in complete study data in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations were summarized in Table 27. Results were generally consistent with results at TOC, with response rates numerically favoring the gepotidacin arm.

Table 27. Proportion of Subjects With Sustained Composite Response at FU, Complete Data, Study EAGLE-3

Composite Response at FU, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at FU, micro-ITT NTF-S	(N=292)	(N=275)
Success, n (%)	126 (43.2)	95 (34.5)
Adjusted difference in success rate % (95% CI)	7.6 (-0.2, 15.4)	

Composite Response at FU, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at FU, micro-ITT NTF-NS	(N=39)	(N=49)
Success, n (%)	24 (61.5)	11 (22.4)
Adjusted difference in success rate % (95% CI)	35.5 (17.9, 53.0)	
Composite response at FU, micro-ITT	(N=331)	(N=324)
Success, n (%)	150 (45.3)	106 (32.7)
Adjusted difference in success rate % (95% CI)	11.6 (4.4%, 18.9)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; IA, interim analysis; TOC, test-of-cure

Complete study data analyses of composite response at FU independent of TOC response in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations were summarized in Table 28. Results were generally consistent with results of sustained composite response at FU.

Table 28. Proportion of Subjects With Composite Response at FU Independent of TOC Response, Complete Data, Study EAGLE-3

Composite Response at FU Independent of TOC Response, Complete Data	Gepotidacin	Nitrofurantoin
Composite response at FU, micro-ITT NTF-S	(N=292)	(N=275)
Success, n (%)	161 (55.1)	137 (49.8)
Adjusted difference in success rate % (95% CI)	4.7 (-3.3, 12.7)	
Composite response at FU, micro-ITT NTF-NS	(N=39)	(N=49)
Success, n (%)	27 (69.2)	21 (42.9)
Adjusted difference in success rate % (95% CI)	21.6 (3.0, 40.1%)	
Composite response at FU, micro-ITT	(N=331)	(N=324)
Success, n (%)	188 (56.8)	158 (48.8)
Adjusted difference in success rate % (95% CI)	7.5 (0.0, 14.9)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; IA, interim analysis; TOC, test-of-cure

Microbiological Response

Please see detailed definitions of uropathogen level microbiological response and patient level microbiological response in Section 6.2.2.4 (as defined for EAGLE-2).

Table 29 summarizes analyses of microbiological response at TOC in complete study data. Results favored the gepotidacin arm in the Micro-ITT NTF-S, Micro-ITT NTF-NS, and Micro-ITT populations.

Table 29. Proportion of Subjects With Microbiological Response at TOC, Complete Data, Study EAGLE-3

Microbiological Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Microbiological response at TOC micro-ITT NTF-S	(N=292)	(N=275)
Success, n (%)	213 (72.9)	158 (57.5)
Adjusted difference in success rate % (95% CI)	15.5% (7.9%, 23.1)	
Failure, n (%)	79 (27.1)	117 (42.5)
Microbiological persistence	13 (4.5)	31 (11.3)
Microbiological recurrence	19 (6.5)	52 (18.9)
UTD	47 (16.1)	34 (12.4)
Total number of subjects with missing microbiological data	37 (12.7)	28 (10.2)

Microbiological Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Microbiological response at TOC micro-ITT NTF-NS	(N=39)	(N=49)
Success, n (%)	31 (79.5)	24 (49.0)
Adjusted difference in success rate % (95% CI)	24.7 (6.8, 42.6)	
Microbiological response at TOC micro-ITT	(N=331)	(N=324)
Success, n (%)	244 (73.7)	182 (56.2)
Adjusted difference in success rate % (95% CI)	17.2 (10.1%, 24.3)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; TOC, test-of-cure; UTD, unable to determine

Analyses of sustained microbiological response at FU in complete study data in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations were summarized in Table 30. Results were generally consistent with results at TOC, with response rates favoring the gepotidacin arm.

Table 30. Proportion of Subjects With Sustained Microbiological Response at FU, Complete Data, Study EAGLE-3

Microbiological Response at FU, Complete Data	Gepotidacin	Nitrofurantoin
Microbiological response at FU micro-ITT NTF-S	(N=292)	(N=275)
Success, n (%)	154 (52.7)	119 (43.3)
Adjusted difference in success rate % (95% CI)	9.0 (0.9, 17.0)	
Microbiological response at FU micro-ITT NTF-NS	(N=39)	(N=49)
Success, n (%)	29 (74.4)	17 (34.7)
Adjusted difference in success rate % (95% CI)	32.9 (15.2, 50.6)	
Microbiological response at FU micro-ITT	(N=331)	(N=324)
Success, n (%)	183 (55.3)	136 (42.0)
Adjusted difference in success rate % (95% CI)	12.8 (5.3, 20.3)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; TOC, test-of-cure

Clinical Response

Please see detailed definition of patient level clinical response in Section 6.2.2.4 (as defined for EAGLE-2).

Table 31 summarizes analyses of clinical response at TOC in complete study data. Response rates of the gepotidacin arm and the nitrofurantoin arm were similar in the Micro-ITT NTF-S, Micro-ITT, and ITT populations, numerically favoring the gepotidacin arm. Generally consistent results were also observed if looking at each individual symptom (dysuria, frequency, urgency, and lower abdominal or suprapubic pain).

Table 31. Proportion of Subjects With Clinical Response at TOC, Complete Data, Study EAGLE-3

Clinical Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Clinical response at TOC Micro-ITT NTF-S	(N=292)	(N=275)
Success, n (%)	199 (68.2)	175 (63.6)
Adjusted difference in success rate % (95% CI)	4.3 (-3.4, 12.0)	
Failure, n (%)	93 (31.8)	100 (36.4)
Clinical improvement	51 (17.5)	68 (24.7)
Clinical worsening	20 (6.8)	17 (6.2)
UTD	22 (7.5)	15 (5.5)
Total number of subjects with missing clinical data	21 (7.2)	14 (5.1)

Clinical Response at TOC, Complete Data	Gepotidacin	Nitrofurantoin
Clinical response at TOC micro-ITT	(N=331)	(N=324)
Success, n (%)	231 (69.8)	201 (62.0)
Adjusted difference in success rate % (95% CI)	7.8 (0.7, 15.0)	
Clinical response at TOC ITT	(N=805)	(N=800)
Success, n (%)	549 (68.2)	517 (64.6)
Adjusted difference in success rate % (95% CI)	3.4% (-1.2%, 8.0)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; Micro-ITT, microbiological intent-to-treat; N, number of subjects in treatment group; n, number of subjects in specified population or group; NTF-S nitrofurantoin susceptible; NTF-NS nitrofurantoin non-susceptible; TOC, test-of-cure; UTD, unable to determine

Analyses of sustained clinical response at FU in complete study data in the Micro-ITT NTF-S, Micro-ITT NTF-NS and Micro-ITT populations were summarized in Table 32. Results were generally consistent with results at TOC.

Table 32. Proportion of Subjects With Sustained Clinical Response at FU, Complete Data, Study EAGLE-3

Clinical Response at FU, Complete Data	Gepotidacin	Nitrofurantoin
Clinical response at FU Micro-ITT NTF-S	(N=292)	(N=275)
Success, n (%)	168 (57.5%)	154 (56.0%)
Adjusted difference in success rate % (95% CI)	1.1% (-6.8%, 9.1%)	
Clinical response at FU micro-ITT	(N=331)	(N=324)
Success, n (%)	196 (59.2%)	175 (54.0%)
Adjusted difference in success rate % (95% CI)	5.0% (-2.4%, 12.4%)	
Clinical response at FU ITT	(N=805)	(N=800)
Success, n (%)	478 (59.4%)	443 (55.4%)
Adjusted difference in success rate % (95% CI)	3.9% (-0.9%, 8.7%)	

Source: FDA analysis; adsl.xpt; adeff.xpt
Abbreviations: CI, confidence interval; FU, follow-up; ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; N, number of subjects in treatment group; n, number of subjects in specified population or group

6.3. Key Efficacy Review Issues

None.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical safety studies submitted to support the safety evaluation of gepotidacin included pharmacology studies (primary, secondary, and safety pharmacology), pharmacokinetics studies (absorption, distribution, metabolism, and excretion), toxicology studies (repeat-dose studies in rats (up to 13 weeks) and dogs (up to 13 weeks)), genetic toxicology assays (in vitro and in vivo), and reproductive and developmental toxicity in rats and mice.

Secondary Pharmacology and Safety Pharmacology

As measured through in vitro studies using isolated enzyme, gepotidacin inhibited acetylcholinesterase with a half maximal inhibitory concentration (IC_{50}) of 10.7 μM (4.8 μg/mL). In an in vitro human ether-a-go-go related gene (hERG) study, gepotidacin inhibited hERG currents in a concentration-dependent manner with an IC_{50} of 0.588 mg/mL, which is more than 100-fold higher than the maximum plasma concentration (C_{max}) calculated from clinical studies. No arrhythmias or heart-rate corrected QT interval (QTc) prolongation were detected in an oral safety pharmacology study in dogs; however, gepotidacin was associated with increases in heart rate, mean arterial pressure, cardiac contractility, and cardiac load. In monkeys administered gepotidacin by the intravenous (IV) route at doses about 3-to-16-fold the clinical exposure based on C_{max}, there were dose-dependent increases in average heart rate (16%-37%), mean arterial pressure (6%-13%), cardiac contractility (11%-17%), and QTc interval (4%-9%), and at the high dose, increase in QRS interval (6-8%). Neurobehavioral effects following a single oral dose in dogs included increased spontaneous locomotor activity that seemed related to agitation at the mid and high doses (125 and 250 mg/kg, which are about 3-fold and 4-fold the clinical exposure, respectively, based on AUC), frequent licking, slight ptosis, head shaking/bobbing, loose feces at the high dose in individual animals and unsteady gait seen at the mid-dose in one animal. More frequent and severe vomiting was reported at the mid and high doses, and dose dependent increased salivation was reported in low, mid, and high doses (50, 125, and 250 mg/kg, which are about equal to, 3-fold, and 4-fold the clinical exposure, respectively, based on AUC). These effects were transient and resolved by 3 hours following the end of dosing.

Target Organs

Kidney

In a 4-week repeat dose study of gepotidacin in rats, tubular basophilia and dilation of proximal and distal tubules in the kidney were observed at doses at and above 450 mg/kg/day (about equal to the clinical exposure based on AUC), with more severe renal changes at the high dose including single cell necrosis, and tubular dilation or sloughed necrotic cells within the lumen of a few animals. Mottled discoloration of the kidneys was observed in a high dose male rat sacrificed on Day 11. The presence of mild chronic progressive nephropathy (a common background change) in one rat in the high dose recovery group made it difficult to ascertain the extent of recovery from tubular degeneration (partial recovery vs. complete recovery) in the high dose group. In a second 28-day repeat-dose rat toxicology study and a 13-week repeat-dose rat study up to about 4-fold the clinical exposure (based on AUC comparison), no adverse effects on the kidneys were reported. In a 28-day dog study, limited histopathology findings of minimal dilation, slight basophilia and pigment deposits were observed in scattered proximal renal tubules of one high dose male (about 8-fold the clinical exposure). Mid and high dose males had 2- to 3-fold increases in protein excretion during week 4. In a 13-week repeat dose dog study, increased protein excretion was observed in 2 high dose females (about 5-fold the clinical exposure based on AUC); however, no renal histopathology changes were reported in the 13-week rat (up to about 4-fold the clinical exposure based on AUC) or dog study (up to about 5-fold the clinical exposure based on AUC). Based on the inconsistency in the findings between studies, the significance of the kidney findings is uncertain.

Stomach

In a 4-week study in rats, mild ulceration of the non-glandular mucosa and minimal erosion and/or inflammation in the glandular mucosa was observed in the stomach of a few high dose rats (about 6-fold the clinical exposure based on AUC).

Bone Marrow/Blood

In a 13-week dog study, at the high dose of 125 mg/kg/day (about 5-fold the clinical exposure based on AUC) a severe reduction (up to about 90%) in neutrophil count was seen in about half of the high dose females. A bone marrow smear showed an increase in granulocytic lineage cells, which suggests compensation. Recovery was reported after dosing stopped.

Neurobehavioral

In a 28-day dog study, behavioral clinical signs of tremor, abnormal gait, and increased vocalization were sporadically observed at the high dose (about 8-fold the clinical exposure). Tremor was observed once in the mid-dose group (about 3-fold the clinical exposure). Adverse neurobehavioral effects were also noted in the safety pharmacology study at doses about 3-fold the clinical exposure and above. In both studies, behavioral clinical observations resolved following cessation of dosing. The pathophysiological cause of the neurobehavioral findings was uncertain.

Exposure Multiples

Table 33. Safety Margins

Study	NOAEL (mg/kg/day)	Nonclinical Exposure (µg*h/mL)	Safety Margin Multiples Based on Exposure[1]
4-week rat	150	12.7	0.3
28-day dog	125	143.5	3
13-week rat	750	197	4
13-week dog	60	82.3	2
28-day rat impurities qualification	750	167	4

Source: FDA analysis
[1] Exposure multiples were based on population pharmacokinetics analysis from phase 3 studies, where the maximum clinical dosage resulted in systemic geometric mean exposures of $AUC_{0\text{-}12h}$ of 22.7 µg•hr/mL which was doubled to make an $AUC_{0\text{-}24h}$ comparison. Exposures in nonclinical studies were based on mean combined sex calculations.
Abbreviations: $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0 to 12 h; $AUC_{0\text{-}24h}$, area under the concentration-time curve from time 0 to 24 h; NOAEL, no-observed-adverse-effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibacterial drug that inhibits bacterial DNA replication through inhibition of two different type II topoisomerase enzymes. Its mechanism of action is similar to the fluoroquinolones, but it is not structurally similar to that class.

Adverse events of special interest (AESI) monitored by the Applicant during the clinical development program included cardiovascular events, gastrointestinal events, *Clostridioides difficile* infection (CDI) or colitis events, and AEs related to acetylcholinesterase inhibition

(AChE-I). Acetylcholinesterase inhibition adverse events were first observed in the phase 1 study of gepotidacin. These are further described in Sections 7.6.1.5, 7.7.1, and 7.7.3.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Gepotidacin is not approved or marketed in any country at this time.

7.4. FDA Approach to the Safety Review

The clinical development program for gepotidacin included 20 clinical studies, including 3 phase 3, randomized, active-controlled efficacy studies and 3 open-label phase 2 studies assessing safety, tolerability, and PK. The safety review was primarily focused upon the data from the two phase 3 efficacy studies (EAGLE-2 and EAGLE-3) submitted at the time of NDA filing; summarized results from a third phase 3 efficacy study (EAGLE-J) were submitted during the NDA review and were reviewed. The study investigated the efficacy and safety of gepotidacin in Japanese females with uUTI. However, complete datasets were not submitted and were not incorporated into the primary safety analysis. Of note, complete datasets for EAGLE-J will be submitted in an upcoming supplemental NDA.

The safety data from the phase 2 studies were not combined into the primary safety analysis due to differences in study design. Thirteen phase 1 studies were also conducted; however, these generally were small studies that administered a variety of gepotidacin oral doses ranging from 100 mg (single dose) to a daily dose of 6000 mg (2000 mg three times daily (TID)) or IV doses ranging from a single 1-hour 200-mg dose to a 4500 mg daily dose (3-hour 1500 mg TID infusions) to healthy volunteers (n = 561).

See Section 17.1 for additional information from the completed phase 1 and 2 studies.

No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in the two phase 3 studies, EAGLE-2 and EAGLE-3, were reviewed and found to be acceptable. Treatment-emergent adverse events (TEAEs) were protocol defined as an adverse event with start date/time after the first dose date/time of the study treatment. All TEAEs in the reviewed studies were graded using US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases criteria for adult toxicity assessment, which was reviewed and found to be acceptable.

7.5. Adequacy of the Clinical Safety Database

The primary safety database consists of 1570 subjects who received at least one dose of gepotidacin. Table 34 presents demographic characteristics of the safety population in the combined phase 3 studies (EAGLE-2 and EAGLE-3). The studies included female subjects with a mean age of 48.9 years. Most subjects were white (82.8%), not Hispanic (66.6%), and from the

United States (54.8%). Fourteen (0.9%) adolescent subjects were exposed to gepotidacin while twelve (0.8%) were exposed to nitrofurantoin.

Table 34. Baseline Demographic and Clinical Characteristics, Safety Population

Characteristic	Gepotidacin 1500 mg BID (N=1570)	Nitrofurantoin 100 mg BID (N=1558)
Sex, n (%)		
Female	1570 (100)	1558 (100)
Age, years		
Mean (SD)	48.9 (17.8)	49.4 (18)
Median (min, max)	49 (13, 89)	50 (13, 91)
Age group, years, n (%)		
Adolescents (12 to 17)	14 (0.9)	12 (0.8)
Adult (18 to 64)	1203 (76.6)	1169 (75.0)
≥65 to 74	226 (14.4)	229 (14.7)
≥65 to 84	340 (21.7)	361 (23.2)
≥85	13 (0.8)	16 (1.0)
Age group ≥65, years, n (%)		
≥65	353 (22.5)	377 (24.2)
Age group ≥75, years, n (%)		
≥75	127 (8.1)	148 (9.5)
Race, n (%)		
American Indian or Alaska Native	64 (4.1)	76 (4.9)
Asian	74 (4.7)	86 (5.5)
Black or African American	113 (7.2)	102 (6.5)
Multiple	14 (0.9)	10 (0.6)
Native Hawaiian or other Pacific Islander	4 (0.3)	1 (0.1)
White	1300 (82.8)	1283 (82.3)
Missing	1 (0.1)	0
Ethnicity, n (%)		
Hispanic or Latino	524 (33.4)	500 (32.1)
Not Hispanic or Latino	1046 (66.6)	1058 (67.9)
Country of participation, n (%)		
Bulgaria	351 (22.4)	339 (21.8)
United States	861 (54.8)	863 (55.4)
Others	358 (22.8)	356 (22.8)
Geographic Location, n (%)		
United States	861 (54.8)	863 (55.4)
Non-United States	709 (45.2)	695 (44.6)

Source: FDA analysis; adsl.xpt; Software: R
Abbreviations: BID, twice daily; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Table 35 provides the duration of exposure in the phase 3 safety population. A total of 1570 subjects received at least one dose of gepotidacin in these studies. The dosing, duration, and number of subjects in the safety database of the submitted phase 3 studies were considered sufficient to conduct a safety review.

Table 35. Duration of Exposure, Safety Population

Parameter	Gepotidacin 1500 mg BID (N=1570)	Nitrofurantoin 100 mg BID (N=1558)
Duration of treatment, days		
Mean (SD)	5 (1)	5.1 (0.9)
Median (Q1, Q3)	5 (5, 5)	5 (5, 6)
Min, max	1, 10	1, 13
Total exposure (person years)	22	22
Subjects treated, by duration, n (%)		
<1 days	0	0
≥1 to <4 days	105 (6.7)	69 (4.4)
≥4 to <7 days	1460 (93.0)	1484 (95.3)
≥7 days	5 (0.3)	5 (0.3)

Source: FDA analysis; adex.xpt and adsl.xpt; Software: R
Duration is 5 days
Abbreviations: BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

7.6.1.1. Overview of Treatment-Emergent Adverse Events, Pooled Analyses

As shown in Table 36, the overall incidence of TEAEs was 35.1% in the gepotidacin arm and 23.4% in the nitrofurantoin arm. Most TEAEs were mild or moderate in severity. The rate of serious adverse events (SAEs) was balanced between gepotidacin (0.4%) and nitrofurantoin arms (0.5%). No grade 4 or 5 TEAEs were observed, and no deaths were observed. TEAEs leading to permanent discontinuation of study drug occurred more frequently in the gepotidacin arm (79, 5%) compared to the nitrofurantoin arm (30, 1.9%).

Table 36. Overview of Treatment Emergent Adverse Events, Safety Population

Event Category	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
SAE	7 (0.4)	8 (0.5)
SAEs with fatal outcome	0	0
Life-threatening SAEs	0	0
SAEs requiring hospitalization	6 (0.4)	7 (0.4)
Other	1 (0.1)	1 (0.1)

Event Category	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
AE leading to permanent discontinuation of study drug	79 (5.0)	30 (1.9)
AE leading to dose modification of study drug	2 (0.1)	1 (0.1)
AE leading to interruption of study drug	2 (0.1)	1 (0.1)
AE leading to reduction of study drug	0	0
AE leading to dose delay of study drug	0	0
Any AE	551 (35.1)	365 (23.4)
Severe and worse	24 (1.5)	14 (0.9)
Moderate	201 (12.8)	136 (8.7)
Mild	326 (20.8)	215 (13.8)

Source: FDA analysis; adae.xpt; Software: R
Note: Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Note: Duration is 5 days
Severity as assessed by the investigator
Abbreviations: AE, adverse event; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

No deaths were reported in studies EAGLE-2 or EAGLE-3.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Table 37 summarizes the SAEs in studies EAGLE-2 and EAGLE-3. Serious adverse events were defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or was a congenital anomaly or birth defect. The incidence of all SAEs was similar between the gepotidacin (0.4%) and nitrofurantoin (0.5%) arms. The clinical reviewer assessed all narratives for subjects who experienced SAEs and found one SAE that was related to gepotidacin; this narrative is detailed below.

Table 37. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population

System Organ Class Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Any SAE	7 (0.4)	8 (0.5)
Blood and lymphatic system disorders (SOC)	0	1 (0.1)
Lymphadenopathy	0	1 (0.1)
Cardiac disorders (SOC)	1 (0.1)	0
Atrial fibrillation	1 (0.1)	0

System Organ Class Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Gastrointestinal disorders (SOC)	3 (0.2)	1 (0.1)
Abdominal pain	1 (0.1)	0
Enterovesical fistula	1 (0.1)	0
Gastroesophageal reflux disease	1 (0.1)	0
Pancreatitis	0	1 (0.1)
Infections and infestations (SOC)	2 (0.1)	4 (0.3)
COVID-19	2 (0.1)	0
Dengue fever	0	1 (0.1)
Urosepsis	0	1 (0.1)
Pyelonephritis acute	0	2 (0.1)
Metabolism and nutrition disorders (SOC)	0	1 (0.1)
Food intolerance	0	1 (0.1)
Nervous system disorders (SOC)	1 (0.1)	1 (0.1)
Dysarthria	1 (0.1)	0
Lumbar radiculopathy	0	1 (0.1)
Sciatica	0	1 (0.1)
Pregnancy, puerperium, and perinatal conditions (SOC)	0	1 (0.1)
Abortion spontaneous	0	1 (0.1)

Source: FDA analysis; adae.xpt; Software: R
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 5 days.
Abbreviations: BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

- A 58-year-old female who reported no significant past medical history developed a Grade 3 SAE of dysarthria 46 minutes after dose 5 of gepotidacin. The episode lasted for approximately one hour and was characterized as ‘slurred speech’ by study staff. The subject informed study staff that she had experienced similar symptoms after taking gepotidacin that self-resolved on study days 1 and 2. A neurologist evaluated the subject on Days 3 and 4 and did not identify any focal abnormalities on imaging or exam. IV magnesium, IV sodium chloride, and theophylline + etofylline were provided with significant improvement in dysarthria. The SAE was considered resolved by Day 3; no further doses of gepotidacin were administered. The study investigator and Applicant considered this event related to gepotidacin. The clinical reviewer concurs that the episode of dysarthria was related to gepotidacin. Additional discussion of dysarthria is provided in Section 7.7.1.

Other SAEs that occurred in subjects who received gepotidacin included enterovesical fistula (Day 22), COVID-19 infection (Days 2, 11), atrial fibrillation (Day 4), abdominal pain following a motor vehicle accident (day 30), and gastroesophageal reflux (Day 11). The clinical reviewer concurs that these SAEs are unlikely to be related to gepotidacin. Subgroup analyses of SAEs examining age, ethnicity, and race were not conducted, as the number of SAEs were too small to draw any meaningful conclusions.

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Seventy-nine (5%) subjects who received gepotidacin reported at least one TEAE that led to treatment discontinuation compared to 30 (1.9%) subjects who received nitrofurantoin (Table 38). Gastrointestinal TEAEs were the most common events that resulted in discontinuation, with a greater proportion of subjects who received gepotidacin reporting occurrences of nausea, vomiting, and diarrhea that led to treatment discontinuation. Nervous system disorders were also observed, and more episodes of dizziness, dysarthria, and presyncope occurred in the gepotidacin arm. Many of the observed gastrointestinal and nervous system events in the gepotidacin arm were potentially related to AChE-I and are discussed in Section 7.7.1.

Cardiac adverse events leading to treatment discontinuation were observed only in the gepotidacin arm. Some cardiac TEAEs, such as tachycardia (n=2) and palpitations (n=1), were related to study drug by the investigator. The SAE of atrial fibrillation was unlikely to be related to study drug given the subject's underlying medical conditions.

Three subjects discontinued gepotidacin due to hypersensitivity reactions; no hypersensitivity reactions resulting in treatment discontinuation were reported in the nitrofurantoin arm. All cases of hypersensitivity are described in Section 7.7.2.

One subject discontinued gepotidacin due to vulvovaginal candidiasis which can occur with antibacterial drugs due to alterations in host flora. Equal rates of discontinuations due to aspartate aminotransferase (AST) or ALT increases were noted in both study arms. Most of these subjects had baseline enzyme elevations, but results were not available to investigators prior to starting study drug. No definitive conclusions by the clinical reviewer were made on relatedness to study drug.

Table 38. Subjects With Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population

System Organ Class Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Any AE leading to discontinuation	79 (5.0)	30 (1.9)
Cardiac disorders (SOC)	5 (0.3)	0
Palpitations	2 (0.1)	0
Atrial fibrillation	1 (0.1)	0
Sinus tachycardia	1 (0.1)	0
Tachycardia	1 (0.1)	0
Ear and labyrinth disorders (SOC)	0	1 (0.1)
Vertigo	0	1 (0.1)

System Organ Class Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Gastrointestinal disorders (SOC)	58 (3.7)	15 (1.0)
Diarrhea	40 (2.5)	6 (0.4)
Nausea	21 (1.3)	6 (0.4)
Vomiting	13 (0.8)	3 (0.2)
Abdominal discomfort	2 (0.1)	0
Feces soft	1 (0.1)	0
Gastrointestinal disorder	1 (0.1)	0
Gastrointestinal pain	1 (0.1)	0
Mouth swelling	1 (0.1)	0
Abdominal pain	2 (0.1)	1 (0.1)
Abdominal pain upper	3 (0.2)	2 (0.1)
Retching	0	1 (0.1)
General disorders and administration site conditions (SOC)	4 (0.3)	4 (0.3)
Chest discomfort	1 (0.1)	0
Chest pain	1 (0.1)	0
Drug intolerance	1 (0.1)	0
Fatigue	1 (0.1)	0
Asthenia	0	1 (0.1)
Non-cardiac chest pain	0	1 (0.1)
Pyrexia	0	2 (0.1)
Immune system disorders (SOC)	3 (0.2)	0
Hypersensitivity	2 (0.1)	0
Drug hypersensitivity	1 (0.1)	0
Infections and infestations (SOC)	4 (0.3)	4 (0.3)
COVID-19	1 (0.1)	0
Pelvic inflammatory disease	1 (0.1)	0
Pharyngitis streptococcal	1 (0.1)	0
Vulvovaginal candidiasis	1 (0.1)	0
Suspected COVID-19	0	1 (0.1)
Urosepsis	0	1 (0.1)
Pyelonephritis acute	0	2 (0.1)
Investigations (SOC)	3 (0.2)	2 (0.1)
Blood creatinine increased	2 (0.1)	0
Blood urea increased	1 (0.1)	0
Creatinine renal clearance decreased	1 (0.1)	0
Aspartate aminotransferase increased	1 (0.1)	1 (0.1)
Alanine aminotransferase increased	1 (0.1)	2 (0.1)
Metabolism and nutrition disorders (SOC)	0	3 (0.2)
Decreased appetite	0	1 (0.1)
Diabetes mellitus	0	1 (0.1)
Food intolerance	0	1 (0.1)
Hyperlipidemia	0	1 (0.1)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.1)	0
Muscle spasms	1 (0.1)	0

System Organ Class Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Nervous system disorders (SOC)	13 (0.8)	6 (0.4)
Dizziness	6 (0.4)	1 (0.1)
Dysarthria	2 (0.1)	0
Presyncope	1 (0.1)	0
Tremor	2 (0.1)	1 (0.1)
Headache	3 (0.2)	3 (0.2)
Lumbar radiculopathy	0	1 (0.1)
Sciatica	0	1 (0.1)
Tension headache	0	1 (0.1)
Renal and urinary disorders (SOC)	0	1 (0.1)
Hydronephrosis	0	1 (0.1)
Reproductive system and breast disorders (SOC)	1 (0.1)	1 (0.1)
Vulvovaginal burning sensation	1 (0.1)	0
Vulvovaginal pruritus	1 (0.1)	0
Vulvovaginal pain	0	1 (0.1)
Respiratory, thoracic, and mediastinal disorders (SOC)	2 (0.1)	3 (0.2)
Pharyngeal disorder	1 (0.1)	0
Atelectasis	0	1 (0.1)
Dyspnea	1 (0.1)	2 (0.1)
Skin and subcutaneous tissue disorders (SOC)	3 (0.2)	2 (0.1)
Rash	2 (0.1)	0
Rash erythematous	0	1 (0.1)
Hyperhidrosis	1 (0.1)	2 (0.1)
Vascular disorders (SOC)	1 (0.1)	1 (0.1)
Hot flush	1 (0.1)	0
Hypertension	1 (0.1)	1 (0.1)

Source: FDA analysis; adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Duration is 5 days.
Abbreviations: AE, adverse event; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

TEAEs occurred in 35.1% of subjects who received gepotidacin and 23.4% of subjects who received nitrofurantoin (Table 39). Risk differences were defined as differences in incidence rates of TEAEs between the gepotidacin arm compared to the nitrofurantoin arm. The TEAEs with risk differences of ≥1% included diarrhea, nausea, vomiting, flatulence, and abdominal pain. The role of acetylcholinesterase inhibition in gastrointestinal (GI) TEAEs is discussed in Section 7.7.1. Diarrhea was the most common TEAE reported in both clinical studies and was observed to occur more commonly after gepotidacin administration compared to nitrofurantoin. GI TEAEs were designated as AESI; please refer to Section 7.6.1.5.1 for additional information.

Headache, dizziness, and vulvovaginal candidiasis occurred in gepotidacin subjects at 1% or more and may be related to gepotidacin exposure. UTI also occurred in gepotidacin subjects at >1% but is unlikely to be related to gepotidacin exposure.

Table 39. Subjects With Treatment Emergent Adverse Events Occurring at ≥0.1% Frequency, Safety Population

Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Any TEAE	551 (35.1)	365 (23.4)
Diarrhea	258 (16.4)	51 (3.3)
Nausea	146 (9.3)	64 (4.1)
Abdominal pain [1]	60 (3.8)	34 (2.2)
Flatulence	43 (2.7)	8 (0.5)
Soft feces	37 (2.4)	8 (0.5)
Vomiting	28 (1.8)	10 (0.6)
Dizziness	29 (1.8)	19 (1.2)
Abdominal distension	11 (0.7)	4 (0.3)
Vulvovaginal pruritus	7 (0.4)	1 (0.1)
Hot flush	5 (0.3)	0
Alanine aminotransferase increased	11 (0.7)	6 (0.4)
Clostridium difficile colitis	4 (0.3)	0
Clostridium difficile infection	4 (0.3)	0
Rash	5 (0.3)	1 (0.1)
Dysarthria	3 (0.2)	0
Gastroesophageal reflux disease	3 (0.2)	0
Insomnia	3 (0.2)	0
Pain	3 (0.2)	0
Frequent bowel movements	4 (0.3)	1 (0.1)
Aspartate aminotransferase increased	9 (0.6)	6 (0.4)
COVID-19	13 (0.8)	10 (0.6)
Blood potassium decreased	2 (0.1)	0
Blood urea increased	2 (0.1)	0
Feces hard	2 (0.1)	0
Hemorrhoids	2 (0.1)	0
Hypersensitivity	2 (0.1)	0
Hypoglycemia	2 (0.1)	0
Ligament sprain	2 (0.1)	0
Presyncope	2 (0.1)	0
Rhinorrhea	2 (0.1)	0
Hematuria	3 (0.2)	1 (0.1)
Vision blurred	3 (0.2)	1 (0.1)
Vulvovaginal discomfort	3 (0.2)	1 (0.1)
Back pain	6 (0.4)	4 (0.3)
Dyspepsia	8 (0.5)	6 (0.4)
Vulvovaginal candidiasis	20 (1.3)	18 (1.2)
Blood magnesium decreased	2 (0.1)	1 (0.1)
Nipple pain	2 (0.1)	1 (0.1)
Pharyngitis streptococcal	2 (0.1)	1 (0.1)
Somnolence	2 (0.1)	1 (0.1)
Tremor	2 (0.1)	1 (0.1)
Type 2 diabetes mellitus	2 (0.1)	1 (0.1)
Vertigo	2 (0.1)	1 (0.1)
Blood creatinine increased	3 (0.2)	2 (0.1)
Dyspnea	3 (0.2)	2 (0.1)
Muscle spasms	3 (0.2)	2 (0.1)
Creatinine renal clearance decreased	4 (0.3)	3 (0.2)
Vaginal infection	5 (0.3)	4 (0.3)
Asthenia	2 (0.1)	2 (0.1)

Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Blood alkaline phosphatase increased	2 (0.1)	2 (0.1)
Gastritis	2 (0.1)	2 (0.1)
Hepatic enzyme increased	2 (0.1)	2 (0.1)
Hyperhidrosis	2 (0.1)	2 (0.1)
Constipation	3 (0.2)	3 (0.2)
Palpitations	3 (0.2)	3 (0.2)
Hyperglycemia	4 (0.3)	4 (0.3)
Blood glucose increased	1 (0.1)	2 (0.1)
Chills	1 (0.1)	2 (0.1)
Flank pain	1 (0.1)	2 (0.1)
Heart rate increased	1 (0.1)	2 (0.1)
Hyperkalemia	1 (0.1)	2 (0.1)
Hypokalemia	1 (0.1)	2 (0.1)
Rash erythematous	1 (0.1)	2 (0.1)
Rosacea	1 (0.1)	2 (0.1)
Suspected COVID-19	1 (0.1)	2 (0.1)
Decreased appetite	2 (0.1)	3 (0.2)
Pollakiuria	2 (0.1)	3 (0.2)
White blood cell count increased	2 (0.1)	3 (0.2)
Blood potassium increased	3 (0.2)	4 (0.3)
Hypertension	3 (0.2)	4 (0.3)
Fatigue	10 (0.6)	11 (0.7)
Urinary tract infection	19 (1.2)	20 (1.3)
Body temperature increased	0	2 (0.1)
Bronchitis	0	2 (0.1)
Diabetes mellitus	0	2 (0.1)
Ear discomfort	0	2 (0.1)
Hyponatremia	0	2 (0.1)
Otitis media	0	2 (0.1)
Pyelonephritis acute	0	2 (0.1)
Rash pruritic	0	2 (0.1)
Sciatica	0	2 (0.1)
Tension headache	0	2 (0.1)
Thermal burn	0	2 (0.1)
Urticaria	0	2 (0.1)
Vaginal discharge	0	2 (0.1)
Bacterial vaginosis	1 (0.1)	3 (0.2)
Glycosuria	1 (0.1)	3 (0.2)
Micturition urgency	1 (0.1)	3 (0.2)
Cough	2 (0.1)	4 (0.3)
Headache	38 (2.4)	40 (2.6)
Blood bilirubin increased	1 (0.1)	4 (0.3)
Oropharyngeal pain	1 (0.1)	4 (0.3)
Pyrexia	1 (0.1)	4 (0.3)
Dry mouth	2 (0.1)	5 (0.3)
Creatinine renal clearance increased	3 (0.2)	6 (0.4)
Anemia	0	4 (0.3)
Nasopharyngitis	1 (0.1)	5 (0.3)
Dysuria	0	5 (0.3)

Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Cystitis	0	9 (0.6)

Source: FDA analysis; adae.xpt; Software: R
[1] Abdominal Pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness, and gastrointestinal pain
Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Duration is 5 days.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.5.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) monitored by the Applicant during the clinical development program included cardiovascular events, gastrointestinal events, CDI or colitis, and TEAEs related to AChE-I. 7.7.3

Cardiovascular Events

Cardiac AESIs reported during the clinical studies included right bundle branch block, nodal rhythm, atrial fibrillation, and tachycardia, and were observed in study subjects who received gepotidacin or nitrofurantoin. While most events were mild or moderate in severity, one episode of atrial fibrillation was an SAE (see Section 7.6.1.3). No significant difference in the frequency of cardiac AESI were observed between the gepotidacin and nitrofurantoin arms. See Section 7.7.3 for additional information on QTc prolongation.

Gastrointestinal Events

Gastrointestinal events were the most common TEAEs reported with gepotidacin (27.1%) and occurred at a higher rate than with nitrofurantoin (10.9%). Diarrhea/soft feces (17.8% gepotidacin; 3.8% nitrofurantoin), nausea/vomiting (10.1% gepotidacin; 4.5% nitrofurantoin), and abdominal pain (3.8% gepotidacin; 2.2% nitrofurantoin) were the most frequently reported GI TEAEs. Most diarrhea TEAEs were designated as mild to moderate severity and related to study drug (Table 40). Potential causes of gastrointestinal TEAEs in gepotidacin subjects include but are not limited to CDI, gastrointestinal dysbiosis, and AChE-I.

Table 40. Adverse Events Assessment of Diarrhea FDA Medical Query (Narrow), Safety Population

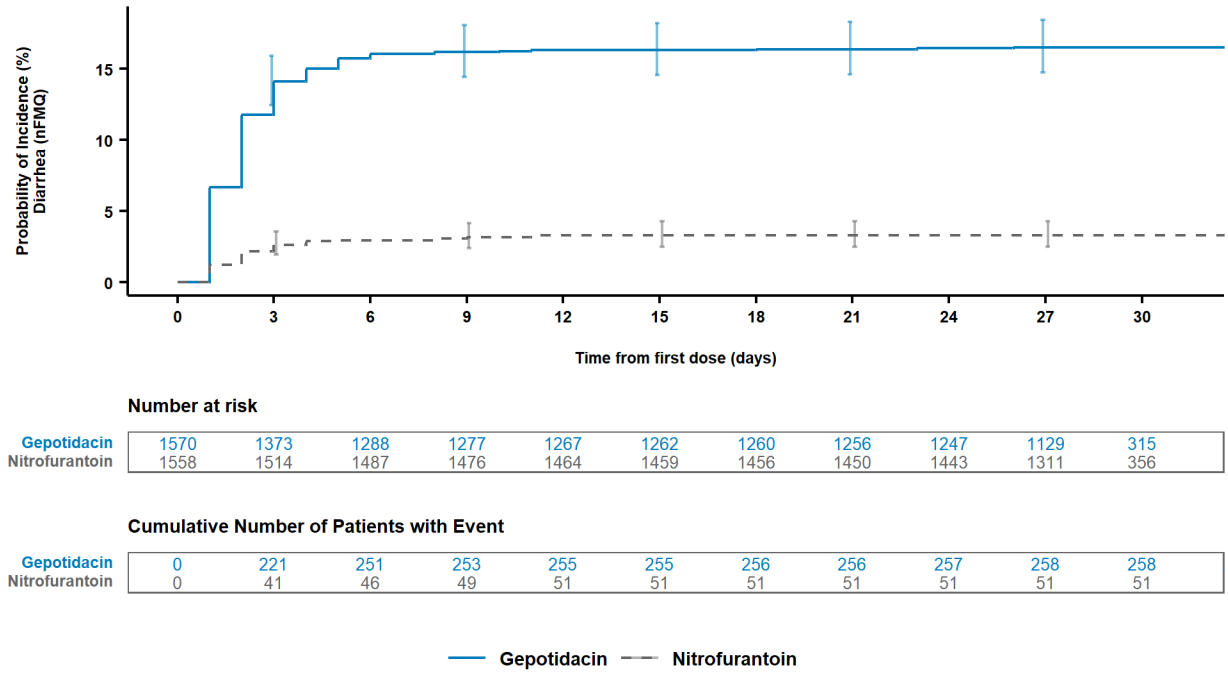
FMQ (Narrow) Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Diarrhea (FMQ)[1]	258 (16.4)	51 (3.3)
Maximum severity		
Severe	8 (0.5)	2 (0.1)
Moderate	77 (4.9)	6 (0.4)
Mild	173 (11.0)	43 (2.8)
Resulting in discontinuation	40 (2.5)	6 (0.4)

FMQ (Narrow) Preferred Term	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Relatedness	231 (14.7)	43 (2.8)

Source: FDA analysis; adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Duration is 5 days.
Relatedness is determined by the investigator.
[1] PT Soft feces was not included in the diarrhea FMQ (narrow).
Abbreviations: AE, adverse event; BID, twice daily; FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; PT, preferred term

Of study subjects who developed diarrhea or soft feces, 45% (n = 125) of the gepotidacin subjects and 46% (n = 27) of nitrofurantoin subjects developed diarrhea/soft feces within 12 hours of initiating study drug, while 64% of gepotidacin subjects and 71% of nitrofurantoin subjects developed diarrhea within the first day of initiating study drug. The probability of developing diarrhea was highest in the first three days after study drug initiation for both treatment arms, but the overall incidence was higher in the gepotidacin arm. (Figure 1).

Figure 1. Time to Onset of Diarrhea FDA Medical Query (Narrow), Safety Population**



Source: FDA figure; adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Duration is 5 days.
** PT Soft feces was not included in the diarrhea nFMQ.
Abbreviations: nFMQ, narrow FDA medical query; PT, preferred term

C. difficile Infection

To meet the prespecified study definition of CDI, study subjects were required to have clinical signs and symptoms, in association with positive glutamate dehydrogenase and toxin A/B

antigen testing. Seven study subjects (<1%) met the study definition of CDI, all of whom received gepotidacin. One study subject did not meet the study definition of CDI, but the study investigator diagnosed and treated the episode as CDI. Mean onset of diarrhea after first gepotidacin exposure was 16 days (range 12 to 25 days) and all episodes were moderate in severity. Most subjects were successfully treated, and the CDI was considered resolved or resolving at the end of the study.

No subjects who received nitrofurantoin developed CDI during the study.

AEs Related to Acetylcholinesterase Inhibition

Please see Section 7.7.1 for further details on acetylcholinesterase inhibition adverse events.

7.6.1.5.2. Analysis of TEAEs Known to be Associated with Fluoroquinolones

As discussed in Section 7.2, gepotidacin is a novel, first-in-class antibacterial drug that inhibits bacterial DNA replication through inhibition of two type II topoisomerase enzymes. Gepotidacin has structural differences compared to the fluoroquinolone class of drugs, however, due to the similar mechanism of actions, a post-hoc exploratory analysis of specific TEAEs associated with fluoroquinolone drugs was conducted. The preferred terms (PTs) analyzed included tendonitis and tendon rupture, peripheral neuropathy, central nervous system (CNS) effects, aortic aneurysm/dissection, hepatotoxicity, photosensitivity, crystalluria, and symptomatic glucose alterations.

Four-point-five percent of gepotidacin subjects and 3.9% of nitrofurantoin subjects had TEAEs known to occur with fluoroquinolone use. The most common TEAEs in the gepotidacin arm compared to the nitrofurantoin arm were dizziness (1.8% versus 1.2%), insomnia (0.2% versus 0%), anxiety (0.1% versus 0%), depression (0.1% versus 0%), myalgia (0.1% versus 0%), and tremor (0.2% versus 0.1%). These nonspecific TEAEs occurred at low rates, precluding an assessment of the potential relationship to study drug. No cases were reported of tendonitis, tendon rupture, aortic aneurysm/dissection, hepatotoxicity, photosensitivity, crystalluria, or symptomatic glucose perturbations in study subjects. Based on the available data, gepotidacin does not appear to share common TEAEs associated with fluoroquinolone drugs.

7.6.1.6. Laboratory Findings, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Chemistry and Hematology

Chemistry and hematology laboratory values between the two arms were similar. There were no significant differences between treatment arms in baseline average chemistry and hematology values or significant interval changes in mean values between baseline and TOC. In addition, no differences in outlier laboratory values were noted between the treatment arms.

Renal Function

One-hundred and thirty-seven (9.3%) subjects who received gepotidacin and 145 (9.8%) subjects who received nitrofurantoin had a ≥25% decrease in creatinine clearance from baseline (Table

41). Of these study subjects, 63 (46%) subjects who received gepotidacin and 47 (32%) subjects who received nitrofurantoin returned to baseline renal function during the study period.

The etiology of the decrease in creatinine clearance over the study period is unclear. Review of subject narratives identified confounding subject characteristics or clinical factors that may have contributed to the observed reduction in creatinine clearance. These factors included comorbid medical conditions (e.g., hypertension, diabetes mellitus), concomitant medications (e.g., diuretics and angiotensin II receptor blockers), age, and potential dehydration due to restriction of fluid intake or diarrhea. The rates of reduced creatinine clearance and elevated blood urea nitrogen were similar between the treatment arms, suggesting that gepotidacin does not present an increased risk of renal injury compared to other antimicrobials used to treat uUTI.

Table 41. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population

Laboratory Parameter	Gepotidacin 1500 mg BID (N=1570) n/N_w (%)	Nitrofurantoin 100 mg BID (N=1558) n/N_w (%)
CrCl, low (mL/min)		
Level 1 (≥25% decrease)	137/1478 (9.3)	145/1476 (9.8)
Level 2 (≥50% decrease)	12/1478 (0.8)	17/1476 (1.2)
Level 3 (≥75% decrease)	2/1478 (0.1)	7/1476 (0.5)
Blood urea nitrogen, high (mg/dL)		
Level 1 (>23)	98/1517 (6.5)	98/1518 (6.5)
Level 2 (>27)	53/1517 (3.5)	54/1518 (3.6)
Level 3 (>31)	21/1517 (1.4)	29/1518 (1.9)

Source: FDA analysis; adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 5 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable
Abbreviations: BID, twice daily; CrCl, creatinine clearance; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

7.6.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

There were no significant differences between the two treatment arms in the proportions of subjects with abnormal liver chemistry values (ALT, AST, alkaline phosphatase [AP], total bilirubin). Peak post-baseline elevations of ALT, AST, AP, and bilirubin among all subjects are shown in Table 42. One (0.1%) subject in the gepotidacin arm had elevations in AP >3 × ULN compared to three (0.2%) subjects in the nitrofurantoin arm. Two (0.2%) subjects in the gepotidacin arm had an elevated bilirubin level >2 × ULN compared to 1 (0.1%) subject in the nitrofurantoin arm. No subjects in the gepotidacin arm had ALT >10 × ULN, but one (0.1%) subject in the gepotidacin arm had AST >10 × ULN. In general, the incidence of elevation in liver enzymes and bilirubin values was low and balanced between the treatment arms Table 42.

Table 42. Subjects With One or More Post-Baseline Liver Biochemistry Analyte Value Exceeding Specified Levels, Safety Population

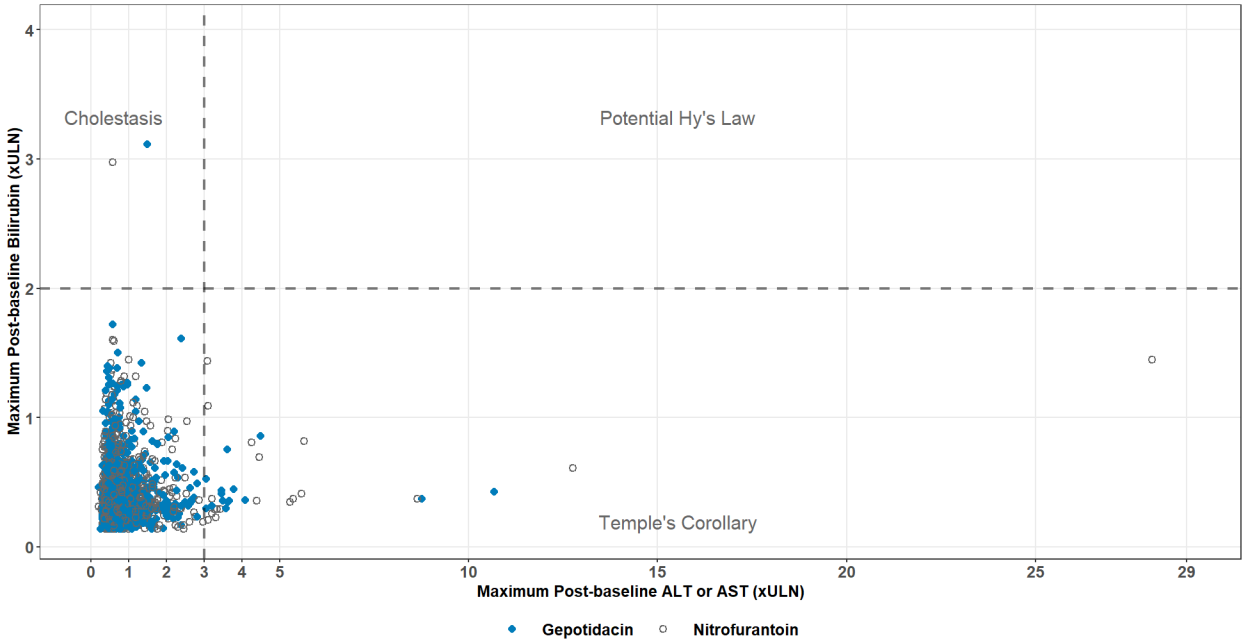
Laboratory Parameter	Gepotidacin 1500 mg BID (N=1570) n/N_w (%)	Nitrofurantoin 100 mg BID (N=1558) n/N_w (%)
Alkaline phosphatase, high (U/L)		
Level 1 (>1.5X ULN)	14/1516 (0.9)	18/1517 (1.2)
Level 2 (>2X ULN)	4/1516 (0.3)	5/1517 (0.3)
Level 3 (>3X ULN)	1/1516 (0.1)	3/1517 (0.2)
Alanine aminotransferase, high (U/L)		
Level 1 (>3X ULN)	14/1515 (0.9)	12/1516 (0.8)
Level 2 (>5X ULN)	1/1515 (0.1)	4/1516 (0.3)
Level 3 (>10X ULN)	0/1515 (0)	2/1516 (0.1)
Aspartate aminotransferase, high (U/L)		
Level 1 (>3X ULN)	6/1517 (0.4)	12/1517 (0.8)
Level 2 (>5X ULN)	1/1517 (0.1)	5/1517 (0.3)
Level 3 (>10X ULN)	1/1517 (0.1)	2/1517 (0.1)
Bilirubin, total, high (mg/dL)		
Level 1 (>1.5X ULN)	4/1510 (0.3)	3/1506 (0.2)
Level 2 (>2X ULN)	1/1510 (0.1)	1/1506 (0.1)
Level 3 (>3X ULN)	1/1510 (0.1)	0/1506 (0)

Source: FDA analysis; adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 5 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: BID, twice daily; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Figure 2 and Table 43 show a screening assessment for potential cases of serious drug-induced liver injury. Overall, the number of subjects in the four screening quadrants for drug-induced

liver injury were balanced between the two treatment arms (Table 43). There were no identified cases of Hy's law in study subjects.

Figure 2. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population



Source: FDA figure; adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of subjects in each quadrant, see the Table 12
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 43. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population

Quadrant	Gepotidacin 1500 mg BID (N=1570) n/N_w (%)	Nitrofurantoin 100 mg BID (N=1558) n/N_w (%)
Potential Hy's Law (right upper)	0/1510 (0)	0/1505 (0)
Cholestasis (left upper)	1/1510 (0.1)	1/1505 (0.1)
Temple's corollary (right lower)	15/1510 (1)	19/1505 (1.3)
Total	16/1510 (1.1)	20/1505 (1.3)

Source: FDA analysis; adlb.xpt; Software: R
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

7.6.1.8. Vital Signs, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Review of mean values and mean changes in vital signs from baseline to Day 10 did not reveal significant differences between the two study arms.

7.6.1.9. Subgroups, Pooled Analyses, Studies EAGLE-2 and EAGLE-3

The proportion of subjects with at least one TEAE in demographic subgroups is shown in Table 44. As observed in the overall safety analysis, rates of TEAEs were higher in study subjects who received gepotidacin across all demographic subgroups for which there were data. However, the small number of subjects in some subgroups (e.g., adolescents, age >85 years, non-White/non-Black race) precluded interpretation of the observed imbalances in TEAEs. Of note, TEAEs were reported more commonly from US sites than non-US sites.

Table 44. Overview of Adverse Events by Demographic Subgroup, Safety Population

Characteristic	Gepotidacin 1500 mg BID (N=1570) n/N_s (%)	Nitrofurantoin 100 mg BID (N=1558) n/N_s (%)
Sex		
Female	551/1570 (35.1)	365/1558 (23.4)
Age group, years		
Adolescents (12 to 17)	4/14 (28.6)	1/12 (8.3)
Adult (18 to 64)	418/1203 (34.7)	262/1169 (22.4)
≥65 to 84	124/340 (36.5)	96/361 (26.6)
≥85	5/13 (38.5)	6/16 (37.5)
Age group ≥65, years		
≥65	129/353 (36.5)	102/377 (27.1)
Age group ≥75, years		
≥75	48/127 (37.8)	52/148 (35.1)
Race		
American Indian or Alaska Native	17/64 (26.6)	9/76 (11.8)
Asian	14/74 (18.9)	10/86 (11.6)
Black or African American	41/113 (36.3)	29/102 (28.4)
Multiple	4/14 (28.6)	2/10 (20.0)
Native Hawaiian or other Pacific Islander	2/4 (50.0)	0/1 (0)
White	473/1300 (36.4)	315/1283 (24.6)
Missing	0/1 (0)	0/0 (NA)
Ethnicity		
Hispanic or Latino	194/524 (37.0)	104/500 (20.8)
Not Hispanic or Latino	357/1046 (34.1)	261/1058 (24.7)
Geographic Location		
United States	359/861 (41.7)	235/863 (27.2)
Non-United States	192/709 (27.1)	130/695 (18.7)

Source: FDA analysis; adae.xpt; Software: R
Abbreviations: BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

A comparison of rates of TEAEs by subject weight and BMI found no relationships between the rate of all TEAEs and subject weight or BMI (Table 45).

Table 45. Subjects With TEAEs Compared by Subject Weight and BMI, Safety Population

Characteristic	Gepotidacin 1500 mg BID (N=1570) n/N_w, (%)	Nitrofurantoin 100 mg BID (N=1558) n/N_w, (%)
Baseline Weight (kg)		
<39	0/0	0/1
40≤60	121/300 (40.3)	73/367 (19.9)
60≤80	277/819 (33.8)	183/764 (24)
80≤100	128/385 (33.2)	98/372 (26.3)
≥100	24/66 (36.4)	10/54 (18.5)
Baseline BMI		
Underweight (<18.5)	13/42 (31)	9/40 (22.5)
Healthy weight (18.5≤25)	191/489 (39.1)	111/529 (21)
Overweight (25≤30)	192/574 (33.4)	136/548 (24.8)
Obesity (≥30)	154/465 (33.1)	108/441 (24.5)

Source: FDA analysis
TEAEs are defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Abbreviations: BID, twice daily; BMI, body mass index; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_w, number of subjects with data; TEAE, treatment-emergent adverse event

7.6.1.10. Exposure-Adjusted Pooled Analyses, Studies EAGLE-2 and EAGLE-3

Not applicable.

7.6.2. Safety Results, Study 206899

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study 206899

Study 206899 (Section 15.1) was an open label study in which all study subjects received 1500 mg of gepotidacin twice daily for the treatment of uUTI. 22 total subjects received at least a single dose of gepotidacin and were included in the safety analysis dataset. 21 (95%) study subjects reported 70 TEAEs during Study 206899. Fifty-two TEAE were assessed as related to gepotidacin, and no TEAEs resulted in discontinuation of gepotidacin, or study withdrawal. No deaths, SAEs related to gepotidacin, or Grade 4/5 TEAEs were reported during the study.

Table 46. Overview of TEAEs,[1] Safety Population, Study 206899[2]

Event	Gepotidacin 1500 mg BID (N=22), n (%)
SAE	1 (4.5)
SAEs with fatal outcome	0 (0)
Life-threatening SAEs	0 (0)
SAEs requiring hospitalization	1 (4.5)
SAEs resulting in substantial disruption of normal life functions	0 (0)
Congenital anomaly or birth defect	0 (0)
Other	0 (0)
AE leading to permanent discontinuation of study drug	0 (0)
AE leading to dose modification of study drug	0 (0)
AE leading to interruption of study drug	0 (0)
AE leading to reduction of study drug	0 (0)
AE leading to dose delay of study drug	0 (0)
Other	0 (0)
Any AE[3]	21 (95.4)
Severe	1 (4.5)
Moderate	17 (77.3%)
Mild	17 (77.3

Source: FDA Analysis, JMP Clinical v17.0
[1] TEAE defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period. Medical Dictionary for Regulatory Activities, version 21.0.
[2] Duration = 5 days
[3] Severity as assessed by the investigator.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Abbreviations: AE, adverse event; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.2.2. Deaths, Study 206899

No deaths were reported in Study 206899.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Study 206899

One SAE was reported in one study subject in 206899. The nonfatal SAE of major depression occurred in a study subject with a history of depression, nine days after the final dose of gepotidacin and required psychiatric hospitalization. The episode of depression was associated with significant psychosocial stressors, including death of a family member and illicit drug use. The investigator and Applicant determined this episode to be unrelated to gepotidacin and this reviewer concurs with the causality assessment.

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study 206899

No TEAEs resulted in treatment discontinuation in Study 206899.

7.6.2.5. Treatment-Emergent Adverse Events, Study 206899

95% of study subjects in the safety analysis set experienced at least one TEAE during Study 206899. The most frequent category of TEAEs was gastrointestinal disorders, with 21 (95%) study subjects reporting at least one gastrointestinal TEAE. Nausea, diarrhea, and vomiting were the most common gastrointestinal TEAEs reported and 44 (93.6%) gastrointestinal TEAE were assessed as related to gepotidacin. Other TEAEs assessed as related to gepotidacin included chest discomfort (n=1), headache (n=1) and vulvovaginal mycotic infection (n=2).

Table 47. Subjects With Common TEAEs[1] Occurring at ≥10% Frequency, Safety Population, Study 206899[2]

Preferred Term[3]	Gepotidacin 1500 mg BID (N=22), n (%)
Diarrhea	18 (81.8)
Nausea	18 (81.8)
Vomiting	5 (22.7)
Headache	5 (22.7)

Source: FDA Analysis, JMP Clinical v17.0
[1] TEAEs defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period. MedDRA version 21.0.
[2] Duration = 5 days
[3] Coded as MedDRA preferred terms.
Abbreviations: BID, twice daily, MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

Most TEAEs were Grade 1 or Grade 2 in severity; only a single Grade 3 TEAE was reported as discussed in Section 7.6.2.3. No Grade 4 or Grade 5 TEAEs were reported. Most TEAEs had resolved by the end of the study, with an average duration of 1 to 5 days. Adverse events of special interest included gastrointestinal events as described above and cardiovascular events. No subject reported a cardiovascular TEAE during Study 206899.

7.6.2.6. Laboratory Findings, Study 206899

Clinically significant laboratory findings were not identified in study subjects and no TEAEs related to laboratory test results were reported. No notable changes in renal function were observed. All study subjects were assessed via ECG prior to the first dose of gepotidacin, and after the first and fourth doses of gepotidacin. No clinically significant changes in QTc interval were observed in Study 206899.

7.6.2.7. Assessment of Drug-Induced Liver Injury, Study 206899

No study subjects met criteria for Hy's law. Five study subjects had increased ALT, AST or bilirubin values, but no laboratory values were 2x higher than the upper limit of normal. Three of the five subjects had mildly elevated ALT values on baseline laboratory testing; two subjects' ALT values declined or normalized during the study.

7.6.2.8. Vital-Sign Analyses, Study 206899

No clinically significant changes in vital signs were observed in subjects who received gepotidacin during Study 206899.

7.6.2.9. Subgroup Analyses, Study 206899

Subjects in Study 206899 were women (100%) between 19 and 64 years of age (100%) and predominantly Caucasian (82%) and not Hispanic or Latino (73%). The small number of subjects available for subgroup analysis precluded additional assessments of SAEs and TEAEs.

7.6.2.10. Exposure-Adjusted Analyses, Study 206899

Not applicable.

7.7. Key Safety Review Issues

7.7.1. Acetylcholinesterase Inhibition

Issue

Gepotidacin is a known inhibitor of acetylcholinesterase and was found to cause cholinergic adverse events in clinical studies.

Background

In vitro testing showed gepotidacin to be a reversible inhibitor of acetylcholinesterase and TEAEs associated with AChE-I were identified in phase 1 studies.

Acute cholinergic symptoms secondary to acetylcholinesterase inhibition can present with several clinical features. These signs and symptoms can be caused by stimulation of either muscarinic or nicotinic receptors. Stimulation of muscarinic receptors can lead to diaphoresis, skin erythema, miosis, visual disturbances, lacrimation, salivation, bronchorrhea, bronchospasm, abdominal pain, vomiting, diarrhea, urinary incontinence, hypotension, bradycardia, heart block or prolonged QTc. Stimulation of nicotinic receptors can cause tremor, fasciculations, proximal muscle weakness, paralysis, decreased tendon reflexes, tachycardia, and hypertension (Attalla M). Other symptoms including muscle spasms, headaches, and seizures have also been described.

AChE-I associated TEAEs observed in the phase 1 studies included dizziness, abdominal pain, oropharyngeal discomfort, salivary hypersecretion, hot flush, diarrhea, fatigue, and nausea/vomiting. A higher rate of AChE-I events was reported with higher doses of gepotidacin in phase 2 studies. Due to the AChE-I associated TEAEs reported in phase 1 clinical studies, AChE-I associated TEAEs were identified as an AESI for the phase 3 clinical studies. During review of the NDA, FDA conducted additional exploratory analyses of AChE-I associated TEAEs to better understand this safety issue and identify potential approaches to risk mitigation.

Assessment

In the phase 3 clinical studies, the Applicant defined TEAEs to be related to AChE-I if they occurred within 12 hours of study drug and were present on a prespecified list of preferred terms. Potential AChE-I TEAEs were further differentiated as GI or non-GI events. TEAEs with missing time of onset after study drug were excluded from analysis of AChE-I TEAEs.

The initial assessment by the Applicant identified 22.1% (n = 347) and 8.0% (n = 124) of subjects who experienced at least one potential AChE-I event in the gepotidacin and nitrofurantoin treatment arms, respectively. Potential AChE-I TEAEs were further differentiated as GI or non-GI events. 22.1% (n = 347) of subjects who received gepotidacin reported a GI AChE-I TEAE, while 7.8% (n = 121) of subjects who received nitrofurantoin reported a GI AChE-I TEAE. Non-GI AChE-I events were reported in <1% of study subjects in each treatment arm.

FDA Cholinergic TEAE Exploratory Analyses

As gepotidacin can remain in circulation for more than 12 hours, exploratory analyses of potential AChE-I events that occurred within 60 hours (estimated 5 half-lives) of drug exposure were performed. The Applicant prespecified PTs for their analysis of potential AChE-I associated TEAEs. These PTs were adjudicated by the FDA clinical team to determine if the PTs met FDA's potential AChE-I definitions. Additional PTs were identified from the TEAEs observed in the studies and classified as potential AChE-I PTs based on scientific literature review and concurrence with FDA neurologists.

Urinary frequency can occur during uUTI and is a potential cholinergic effect; therefore, FDA analyses were performed with and without urinary AChE-I PTs. FDA analyses were separated into three categories: Flag 1 included potential AChE-I PTs identified by the Applicant that occurred within 60 hours after study drug exposure, Flag 2 included potential AChE-I PTs identified by FDA that occurred within 60 hours of drug exposure including urinary PTs, and Flag 3 included potential AChE-I PTs identified by FDA that occurred within 60 hours of drug exposure but excluded urinary PTs.

The FDA review identified 3 additional subjects who met the Applicant's potential AChE-I TEAE definition, two of which were subjects excluded from Applicant's analyses due to missing time of TEAE onset. Twenty-five additional gepotidacin-exposed subjects with potential AChE-I TEAEs were identified through FDA's expanded analyses (Table 48). Five subjects reported potential AChE-I that occurred within 60 hours of drug exposure (Flag 1) and twenty subjects reported potential AChE-I TEAEs included in the expanded list of AChE-I PTs (Flag 2). No urinary AChE-I TEAEs were identified in gepotidacin subjects (Flag 3).

Table 48. Analyses of Potential AChE-I TEAEs, Safety Population

Analysis	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Applicant	347 (22.1)	124 (8.0)
Flag 1	355 (22.6)	126 (8.1)
Flag 2	375 (23.9)	160 (10.3)
Flag 3	375 (23.9)	157 (10.1)

Source: FDA analysis
TEAEs defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Flag 1: AChE-I PTs identified by the Applicant that occurred within 60 hours after study drug exposure.
Flag 2: AChE-I PTs identified by FDA that occurred within 60 hours of drug exposure including urinary PTs.
Flag 3: AChE-I PTs identified by FDA that occurred within 60 hours of drug exposure but excluded urinary PTs.
Abbreviations: AChE-I, acetylcholinesterase inhibition; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

More study drug discontinuations related to AChE-I TEAEs were observed in the gepotidacin arm compared to the nitrofurantoin arm (Table 49). Most AChE-I TEAEs that resulted in discontinuation were grade 1 or 2 events. One possible explanation for why the study drug was stopped in subjects with mild symptoms is that investigators were looking for potential AChE-I events and may have discontinued study drug if such events occurred. This would be a reasonable approach in subjects with AChE-I TEAEs as uUTI is a non-life-threatening infection with alternative treatments available. For subjects who discontinued study drug due to potential AChE-I TEAEs, the mean time to discontinuation was 1.6 days after first study drug exposure. Subjects who did not discontinue study drug reported a mean time to the first AChE-I TEAE of 2.4 days.

Table 49. Discontinuations due to FDA Potential AChE-I TEAEs, Safety Population

TEAE Grade	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Discontinuations	62/1570 (3.9)	20/1558 (1.3)
Grade 1 AChE-I TEAE	25/1570 (1.6)	7/1558 (0.4)
Grade 2 AChE-I TEAE	32/1570 (2.0)	10/1558 (0.6)
Grade 3 AChE-I TEAE	5/1570 (0.3)	3/1558 (0.2)

Source: FDA analysis
If Applicant coded more than one AChE-I TEAE as cause of discontinuation, highest grade of such events is included in the table.
TEAE(s): treatment-emergent adverse event defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Abbreviations: AChE-I: acetylcholinesterase inhibition, BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event

Most potential AChE-I TEAEs were gastrointestinal disorders with diarrhea presenting as the most common TEAE (Table 50). Nausea, vomiting, abdominal pain, and flatulence were more frequently observed in the gepotidacin arm. Neurologic and neuromuscular symptoms including fatigue, muscle spasms, dizziness, presyncope, tremor, and dysarthria were observed less frequently. Headache was not reported more frequently in subjects who received gepotidacin compared to those who received nitrofurantoin. Insomnia, dyspnea, rhinorrhea, and sweating were also reported in the gepotidacin arm. Although these TEAEs are potential cholinergic effects, the nonspecific nature of the events precluded causality assessments.

Table 50. Subjects With Potential AChE-I TEAEs by PT, Safety Population,

TEAE	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Diarrhea*	232 (14.8)	48 (3.1)
Nausea/vomiting**	136 (8.7)	56 (3.6)
Abdominal pain***	42 (2.7)	24 (1.5)
Flatulence	28 (1.8)	7 (0.3)
Headache	27 (1.7)	34 (2.1)
Dizziness	23 (1.5)	16 (1)
Fatigue	9 (0.6)	6 (0.4)
Cold sweats/Hyperhidrosis	3 (0.2)	2 (0.1)
Dyspnea	3 (0.2)	2 (0.1)
Muscle spasms	3 (0.2)	2 (0.1)
Dry mouth	2 (0.1)	4 (0.3)
Dysarthria	2 (0.1)	0
Gastritis	2 (0.1)	7 (0.4)
Rhinorrhea	2 (0.1)	0
Gastrointestinal disorder	1 (0.1)	0
Gastrointestinal hypermotility	1 (0.1)	0
Insomnia	1 (0.1)	0
Presyncope	1 (0.1)	0
Tremor	1 (0.1)	1 (0.1)
Seizure	0	1 (0.1)

Source: FDA analysis
* Diarrhea includes diarrhea, feces soft, frequent bowel movements
** Nausea/Vomiting includes nausea, vomiting, retching
*** Abdominal Pain includes abdominal discomfort, pain, pain lower, pain upper, gastrointestinal pain
TEAEs are defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Abbreviations: AChE-I, acetylcholinesterase inhibition; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred terms; TEAE, treatment-emergent adverse event

Time to onset of diarrhea in subjects who met FDA potential AChE-I TEAE was similar to that of all subjects with diarrhea (see Section 7.6.1.5.1) and did not appear to occur more quickly in the gepotidacin arm. For most of the subjects in both arms who experienced diarrhea, the diarrhea started in the first 24 hours after starting study drug.

Sixteen-point-three percent of subjects who received gepotidacin reported a single potential AChE-I TEAE, and 7.6% of gepotidacin subjects reported 2 or more potential AChE-I events (Table 51). Of 119 subjects who received gepotidacin and experienced multiple potential AChE-I TEAEs, 77 (64.7%) had GI TEAEs only, 41 (34.5%) had GI and non-GI TEAEs, and 1 (0.8%) experienced only non-GI AChE-I TEAEs.

Table 51. Subjects With Potential AChE-I TEAEs by Number of AChE-I AEs, Safety Population

Subjects with Potential AChE-I TEAEs	Gepotidacin 1500 mg BID (N=1570) n (%)	Nitrofurantoin 100 mg BID (N=1558) n (%)
Total number of subjects with Potential AChE-I TEAE	375 (23.9)	160 (10.3)
Subjects with 1 potential AChE-I TEAE	256 (16.3)	124 (8.0)
Subjects with 2 potential AChE-I TEAEs	80 (5.1)	23 (1.5)
Subjects with 3 potential AChE-I TEAEs	25 (1.6)	10 (0.6)
Subjects with 4 potential AChE-I TEAEs	11 (0.7)	3 (0.2)
Subjects with 5 potential AChE-I TEAEs	2 (0.1)	0
Subjects with 7 potential AChE-I TEAEs	1 (0.1)	0

Source: FDA analysis
Multiple instances of the same PT were counted as one event.
TEAEs are defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Abbreviations: AChE-I, acetylcholinesterase inhibition; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

Dysarthria

Dysarthria was observed in 8 subjects who received gepotidacin (Table 52) including 2 subjects in Study BTZ115198 who received a single dose of gepotidacin 1800 mg IV, 5 subjects in the phase 3 studies (EAGLE-2, EAGLE-3 and EAGLE-J) who received gepotidacin 1500 mg oral twice daily for the treatment of uUTI, and 1 subject in Study BTZ116577 who received gepotidacin 3000 mg oral twice daily.

Dysarthria was often reported within 1 hour of study drug exposure (range 0 minutes to 3 hours, one subject did not report timing from dose to TEAE). Concomitant TEAEs in subjects with dysarthria included abdominal pain, abnormal coordination, diarrhea, disorientation, disturbance in attention, dizziness, dysphoria, fatigue, feeling abnormal (brain fog), headache, myoclonus, pharyngeal disorder, salivary hypersecretion, and unilateral eyelid twitching/blepharospasm. Two cases of dysarthria appeared to recur after re-exposure to gepotidacin. The mean duration of dysarthric symptoms was 4 hours (range: 6 minutes to 1 day).

There was one grade 3 SAE of dysarthria reported (Section 7.6.1.3).The subject in question underwent urgent neurologic consultation and diagnostic evaluations with ECG, computed tomography cerebral angiogram, magnetic resonance imaging brain, and carotid ultrasound, all of which were reported as normal. Therapeutic interventions included intravenous magnesium sulfate, sodium chloride, theophylline, etofylline, and enteral aspirin.

Table 52. Subjects Exposed to Gepotidacin With Dysarthria TEAE, Safety Population, All Studies

Study	Age (Years) Sex (F/M)	AE Grade	Dose	Time	Duration	Other AEs	Drug Discontinued
BTZ115198	29M	1	1800 mg IV single dose	30 min into infusion of gepotidacin	61 min	Abdominal pain, dizziness, disorientation, salivary hypersecretion, headache, dysphoria, fatigue, disturbance in attention	N/A
BTZ115198	20M	1	1800 mg IV single dose	1 hr after start of infusion	6 min	Dizziness	N/A
EAGLE-2	27F	1	1500 mg PO BID ×10 doses	Study day 1, time/last dose not recorded	6 days, intermittently	Diarrhea, feeling abnormal (brain fog), coordination abnormal	No
EAGLE-2	58F	3 (SAE)	1500 mg PO ×5 doses	46 min after dose 5, unknown time after doses 1 and 3	30-45 min for doses 1 and 3; 1 hr for dose 5	Facial muscle clonus/unilateral eyelid twitching (blepharospasm)	Yes
EAGLE-3	38F	2	1500 mg PO BID ×2 doses	3 hr after dose 1	18 hr	Pharyngeal disorder (relaxed throat)	Yes
BTZ116577	23M	2	3000 mg PO BID ×2 doses	1.5 hr after dose 1	3 hr for first dysarthric event, 1.5 hr for second dysarthric event	dizziness, myoclonus	N/A
EAGLE-J	64F	1	1500 mg PO BID ×4 doses	8.75 hr after dose 2	1 day	Diarrhea	Yes
EAGLE-J	24F	2	1500 mg PO BID ×1 dose	1 hr after dose 1	3 hr	Eyelid muscle twitching (blepharospasm), diarrhea palpitations, dizziness	Yes

Source: FDA analysis
TEAE(s) are defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
Abbreviations: AE(s), adverse event(s); BID, twice daily; F, female; hr, hours; IV, intravenous; M, male; min, minutes; PO, orally; TEAE, treatment-emergent adverse event

Salivary Hypersecretion

While most potential cholinergic TEAEs were gastrointestinal, 31 episodes of salivary hypersecretion occurred in 28 subjects in phase 1 and phase 2 clinical studies. These cholinergic TEAEs occurred with both oral (PO) and IV administration of gepotidacin, with subjects receiving a single or multiple doses of gepotidacin that ranged from 1000 to 1800 mg IV or 1500 to 3000 mg PO. Most cases were reported after IV gepotidacin administration. No cases of hypersalivation occurred in the two phase 3 studies. All episodes of hypersalivation were categorized as mild and resolved without intervention.

Additional Phase 3 Clinical Study

EAGLE-J was a phase 3, multicenter, randomized, double blind uUTI study of Japanese females 12 years and older. The following review of potential AChE-I events was based on summarized safety data submitted by the Applicant after this NDA was filed. 374 total subjects were enrolled, of whom 281 subjects received oral gepotidacin 1500 mg BID and 93 subjects received nitrofurantoin 100 mg BID. The intended duration of treatment was 5 days for all subjects. Of all study subjects, 72% of subjects who received gepotidacin reported at least 1 TEAE (n = 201) compared to 19% of subjects who received nitrofurantoin (n = 18). Most TEAEs were Grade 1 or Grade 2 in severity, with the majority of TEAEs reported to be gastrointestinal events. Potential AChE-I events (using the Applicant's definition) were reported in 63% of subjects (n = 178) who received gepotidacin and 9% of subjects (n = 11) who received nitrofurantoin. While most potentially AChE-I associated TEAEs in subjects who received gepotidacin were Grade 1 (n = 116) or Grade 2 (n = 54) gastrointestinal events, one subject experienced two grade 4 potentially AChE-I associated TEAEs (vomiting and diarrhea) that were considered serious and led to study discontinuation. Two (0.7%) gepotidacin exposed subjects developed Grade 1 or Grade 2 dysarthria. The pooled rate of potentially AChE-I associated TEAEs in gepotidacin subjects in Studies EAGLE-2 and EAGLE-3 was 22.1% (using the Applicant's definition). The cause of the higher rate of AChE-I TEAEs in study EAGLE-J is unclear, but cultural, dietary, or genetic factors may have contributed to the higher rates of these adverse events. An analysis of AChE-I events and plasma exposure was conducted using data from studies EAGLE-2 and EAGLE-J (see Section 14.5.4). The difference in the incidence of potentially AChE-I associated TEAEs between the two studies was not found to be due to a difference in gepotidacin exposure.

Conclusion

Potential cholinergic TEAEs were not uncommon in subjects who received gepotidacin in the two phase 3 studies (375, 24%) and most events were gastrointestinal in nature (diarrhea [14.8%], nausea/vomiting [8.7%], and abdominal pain [2.7%]). Most study subjects experienced a single potentially AChE-I -related TEAE that was mild or moderate in severity. Additionally, the majority of cholinergic TEAEs occurred within the first 24 hours after study drug initiation. No cholinergic TEAEs were considered ongoing at the time of study completion.

Some neurologic TEAEs potentially related to AChE-I were identified including, but not limited to, dysarthria. While the dysarthria associated with gepotidacin administration was uncommon, strokes and transient ischemic attacks can also present similarly, leading to potentially extensive neurologic evaluations (see Section 7.6.1.3). To mitigate the potential risks of AChE-I associated

adverse reactions, the product labeling will contain a warning describing AChE-I and a Medication Guide will be provided to patients.

7.7.2. Hypersensitivity Reactions

Issue

Hypersensitivity reactions were reported in the clinical studies.

Background

Many drugs, including antibacterial drugs, can cause significant hypersensitivity reactions. Affected individuals should be cautioned against additional drug exposure. Hypersensitivity adverse events were reported by the Applicant in subjects who received gepotidacin. However, the Applicant did not propose a warning statement or contraindication regarding hypersensitivity reactions in the labeling.

Assessment

In all clinical studies, 21 subjects exposed to gepotidacin reported TEAEs of hypersensitivity, drug hypersensitivity, pruritis, rash, or mouth swelling. Of note, per the Applicant, three additional subjects who received gepotidacin experienced hypersensitivity reactions in Study 208541, an open label study in adults undergoing tonsillectomy or prostatectomy conducted by Institut National de la Santé et de la Recherche Médicale (INSERM) in France. However, as this clinical study was not conducted by the Applicant, limited information describing these 3 cases was available for review.

Of the 21 subjects with TEAEs related to hypersensitivity, 8 were unrelated to study drug per the investigator. Generally, the FDA review team agreed with the causality assessments, however, FDA considered an additional 2 cases to be likely unrelated to study drug as the subjects continued therapy without exacerbation of symptoms or had isolated pruritis secondary to their primary disease (urethral gonococcal infection). Additional information regarding the remaining 11 subjects with drug-related hypersensitivity is provided in Table 53. Therapeutic interventions included administration of an antihistamine, oral steroids, parenteral steroids, or intramuscular epinephrine. The drug-related events generally exhibited a temporal relationship with gepotidacin administration, with most events occurring within 6 hours of administration.

Three subjects in the phase 3 studies had hypersensitivity/drug hypersensitivity TEAEs with gepotidacin that constituted possible study drug related anaphylactic reactions:

- A 43-year-old female in Study EAGLE-2 received 3 oral doses of 1500 mg gepotidacin and developed a Grade 2 hypersensitivity reaction (verbatim term: allergy reaction) 35 minutes after dose 3. Symptoms included tongue, underlip, and eyelid edema and tingling of limbs and body. Study treatment was discontinued, and the subject received oral methylprednisolone 4 mg BID and oral desloratadine 5 mg BID starting on the day of the event. This TEAE was reported resolved 23 hours later and no rechallenge was undertaken.

- A 48-year-old female in Study EAGLE-2 received a single oral dose of 1500 mg gepotidacin and developed a Grade 1 hypersensitivity (verbatim term: allergy reaction) 2.5 hours later. Symptoms included tongue swelling, difficulty with word pronunciation, dizziness, rash, and redness of the skin of the decollete and chest. Study treatment was discontinued, and the subject received intramuscular methylprednisolone 40 mg once on day 1 for this allergic reaction. This TEAE was reported resolved approximately 2 hours after onset and no rechallenge was undertaken.
- A 69-year-old female in Study EAGLE-3 received a single oral dose of 1500 mg gepotidacin and developed a related Grade 2 drug hypersensitivity (verbatim term: allergic reaction to investigational product) 1 hour later. Symptoms included swollen face. Study treatment was discontinued, and the subject received oral methylprednisolone once, intramuscular epinephrine 0.3 mg as needed, and oral diphenhydramine 25 mg once. This TEAE was reported resolved on day 1 and no rechallenge was undertaken.

Table 53. Subjects With Hypersensitivity Reactions Related to Gepotidacin, All Clinical Studies

Study	Gepotidacin Dose	Time to Event	Event (Preferred Term)
EAGLE-2	1500 mg PO BID	3 hr after dose 4	Rash
EAGLE-2	1500 mg PO BID	2.5 hr after dose 1	Hypersensitivity
EAGLE-2	1500 mg PO BID	35 min after dose 3	Hypersensitivity
EAGLE-2	1500 mg PO BID	3.5 hr after dose 1	Mouth swelling
EAGLE-2	1500 mg PO BID	5 hr after dose 10	Rash
EAGLE-2	1500 mg PO BID	3 hr after dose 3	Rash
EAGLE-3	1500 mg PO BID	2 hr after dose 4	Rash
EAGLE-3	1500 mg PO BID	1 hr after dose 1	Drug hypersensitivity
BTZ115198	Single dose 1500 mg IV infusion over 3 hr followed by 1500 mg IV TID for 10 days on days 3-12	5 hr after dose 10	Rash
BTZ115775	1800 mg IV over 2 hr in two separate periods of time 14 days apart	2 min after start of first IV dose	Pruritis; pruritis generalized
BTZ116704	1000 mg IV for 5 doses followed by 2000 mg PO for 15 doses	6 hr after dose 1	Pruritis

Source: FDA analysis
Abbreviations: BID, twice daily; hr, hours; IV, intravenous; min, minutes PO, orally; TID, three times daily

Conclusion

Hypersensitivity reactions were attributed to eleven subjects who received gepotidacin. Although these events were classified as mild events, prompt medical intervention may have confounded the potential severity. To mitigate the risk of hypersensitivity reactions in affected individuals, the product labeling will include a warning describing the risk of hypersensitivity reactions and a contradiction for patients with a history of severe hypersensitivity reactions to gepotidacin.

7.7.3. QTc Prolongation

Issue

Gepotidacin caused QTc prolongation in preclinical and clinical studies.

Background

Non-clinical studies indicated gepotidacin causes dose dependent QTc prolongation likely due to hERG current inhibition.

Assessment

Clinical phase 1 and 2 studies identified 8 subjects with cardiac AESIs, of which the majority were not assessed as related to study treatment. No episodes of QTc prolongation were observed in phase 1 or phase 2 clinical studies.

In Study EAGLE-3, triplicate 12-lead ECGs were collected at baseline and on Study Day 2 to 4 in a subset of study subjects. ECGs were conducted at 2 hours (range 1.5 to 4 hours) post-dose to assess the highest serum concentration of gepotidacin. No subjects had a QTc >500 msec or a QTc increase from baseline of >60 msec which were the predefined thresholds for QTc prolongation for this study (Table 54). Two subjects, one in the gepotidacin arm and one in the nitrofurantoin arm, experienced TEAEs possibly related to prolonged QTc/Torsade de pointes based on review by the FDA cardiac safety team. Additionally, there was one subject in the gepotidacin arm who was found to have QTc measurements >480 msec. Narratives for these three subjects are provided below.

- A 21-year-old female received gepotidacin and was reported to have TEAE of QTc prolongation (QTcB 460 msec). However, QTc prolongation was not confirmed via manual over-read.
- An 18-year-old female received nitrofurantoin and experienced an unrelated grade 1 TEAE of seizure approximately 10 hours after study drug dose 3. No treatment was received for the seizure and the event was considered recovered/resolved on the same day. The subject completed the course of study drug. No additional cardiac evaluation was performed for this TEAE.
- A 59-year-old female received gepotidacin and had mild QTc prolongation based on triplicate 12-lead ECGs OT. QTcF values were 499 msec, 499 msec, and 500 msec with a right bundle branch block present at baseline and OT visit. No clinical symptoms associated with QTc prolongation were reported. As the baseline QTcF was 470 msec and the associated increase was 30 msec, the prespecified definition of QTc prolongation was not met.

In Study EAGLE-2, post-dose ECGs were not performed and TEAEs related to prolonged QTc or torsade de pointes were not identified. In Study EAGLE-J, a phase 3 uUTI study of Japanese adolescent and adult females, two subjects discontinued gepotidacin due to QTc prolongation, defined as an increase from baseline >60 msec. However, the QTc prolongations were not confirmed via manual over-read in either case.

Table 54. Maximum Post-Dose QTcF and QRS in Study EAGLE-3, Safety Population

Parameter Level	Gepotidacin 1500 mg BID[1] n/N_w (%)	Nitrofurantoin 100 mg BID n/N_w (%)
QTcF, high, (msec)		
Level 1 (>480)	1/718 (0.1)	1/729 (0.1)
Level 2 (>500)	0/718 (0.0)	0/729 (0.0)
Level 3 (>500 & CFB > 60)	0/718 (0.0)	0/729 (0.0)

Parameter Level	Gepotidacin 1500 mg BID[1] n/N_w (%)	Nitrofurantoin 100 mg BID n/N_w (%)
QTcF, high (delta), (msec)		
Level 1 (>30)	12/718 (1.7)	4/729 (0.5)
Level 2 (>60)	0/718 (0.0)	0/729 (0.0)
QRS, high, (msec)		
Level 1 (>120)	11/725 (1.5)	8/739 (1.1)
Level 2 (>120 & >25%)	0/725 (0.0)	0/739 (0.0)

Source: FDA analysis
[1] Includes two subjects treated with gepotidacin 1500 mg BID and nitrofurantoin 100 mg BID.
Abbreviations: BID, twice daily, msec, millisecond; N, number of subjects in treatment arm; N_w, number of subjects in treatment arm with data; n, number of subjects with adverse event; QRS, QRS complex; QTcF, QT interval corrected for heart rate using Fridericia's formula

Conclusion

As gepotidacin can cause QTc prolongation at the proposed uUTI dose, a warning will be included in the labeling. To ensure patient safety, the product labeling will recommend avoiding use in patients with a history of QTc interval prolongation, those with relevant pre-existing cardiac disease, patients taking antiarrhythmic agents or other medications that may potentially prolong the QTc interval, patients taking strong CYP3A inhibitors, and patients with severe renal impairment. Labeling will specify that if administration of gepotidacin cannot be avoided in these patients, serum electrolyte abnormalities should be corrected and ECGs should be collected prior to administration and during treatment, as clinically indicated.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Hepatic Impairment

Gepotidacin undergoes ~30% metabolism in blood; the drug is mainly oxidized via cytochrome P450 (CYP)3A4. As described in the clinical mass balance study, biliary excretion appears to be a major route of elimination as ~30% of unchanged gepotidacin was eliminated in feces (see Section 14.2.1.4).

In the hepatic impairment (HI) clinical study (BTZ117352), a single oral gepotidacin dose of 1500 mg was administered to subjects with three degrees of hepatic function (Child Pugh score 7 to 9- moderate hepatic impairment, Child Pugh score 10 to 15- severe hepatic impairment, and normal hepatic function). The differences in gepotidacin $AUC_{0\text{-}inf}$ and C_{max} estimates in severe hepatic impairment when compared to normal hepatic function are considered clinically meaningful as the C_{max} was nearly 2-fold higher. However, moderate hepatic impairment exposures were not considered clinically meaningful as C_{max} and AUC only increased by ~1.2-fold as compared to normal hepatic function (Section 14.2.1.5). In the phase 3 studies, subjects with hepatic impairment were excluded from the study, and no post hoc estimates within this population were reported from these studies.

Given these observations and the fact that gepotidacin exposures are increased by <2-fold for both C_{max} and AUC in subjects with moderate HI when compared to subjects with normal

hepatic function, gepotidacin may be administered to patients with mild or moderate hepatic impairment without a dosage adjustment. For severe HI, gepotidacin should be avoided for the following reasons: 1) exposures are predicted to be nearly 2-fold higher; and 2) subjects with HI were excluded from the phase 3 studies, so no data are available to properly evaluate the safety in these subjects.

8.1.2. Renal Impairment

As described in the clinical mass balance study, oral gepotidacin undergoes ~30% urinary excretion with 67% being excreted as unchanged drug (see Section 14.2.1.4- Mass Balance). In addition, the final population PK model estimates a renal clearance of 12.5 L/hour or over 200 mL/min (see Section 14.5); this suggests that gepotidacin undergoes renal tubular secretion.

In the dedicated renal impairment (RI) study, following administration of a single 750 mg IV dose of gepotidacin (over 2-hour infusion), AUC was 1.6- and 2.1-fold higher in subjects with moderate and severe RI/end stage renal disease (ESRD) not on intermittent hemodialysis (IHD), respectively, as compared to subjects with normal renal function. In subjects with ESRD on IHD, administration of a single 750-mg dose of gepotidacin administered within 2 hours prior to IHD or 2 hours post IHD, gepotidacin AUC increased by 2.5- and 4.2-fold, respectively, as compared to subjects with normal renal function (Section 14.2.1.5).

From an efficacy perspective, there is theoretical concern for a reduction in efficacy with declining renal function given that renal impairment is associated with decreases in renal clearance and ultimately, lower urinary concentrations of gepotidacin. Composite response at the TOC visit for micro-ITT NTF-S population was evaluated for different renal classifications by pooling subjects from both EAGLE-2 and EAGLE-3. Renal function for these studies was determined using creatinine clearance (CrCl), which was estimated by Cockcroft Gault equation. For mild RI (CrCl 60 to 89 mL/min), 116 pooled subjects were in each of the two cohorts (gepotidacin and nitrofurantoin) with gepotidacin appearing to show a significantly higher rate of success as compared to nitrofurantoin (risk difference 23.8% [95% confidence interval (CI) 11.5, 36]). Composite response at the TOC visit appeared similar between subjects with CrCl <60 mL/min on gepotidacin and nitrofurantoin based on a risk difference of 3.3% [95% CI -19.2, 25.7].

From a safety perspective, the safety population consisted of 265, 70, and six pooled subjects with mild, moderate, and severe renal impairment, respectively, from the EAGLE-2 and EAGLE-3 studies. When compared to subjects with normal renal function, there appeared to be minimal difference in adverse event percentage and severity for subjects with mild and moderate renal impairment. In subjects with severe renal impairment, despite a small sample size, 3 of 6 subjects experienced an adverse event with one subject having an event of grade 3 severity.

Given these observations, gepotidacin's plasma half-life of approximately 9 hours, and the proposed 5-day duration of therapy, gepotidacin 1500 mg BID may be administered to all patients with estimated glomerular filtration rate (eGFR) ≥30 mL/min without a dosage adjustment. Conversely, gepotidacin should be avoided in patients with eGFR <30 mL/min for the following reasons: 1) exposures are predicted to be ≥2-fold higher than in patients with normal renal function; 2) ≥50% of subjects exhibited a serious adverse event in phase 3 pooled safety data (although the sample size was only 6 subjects); 3) ≥50% of subjects exhibited QTcB/QTcFs >450 msec, some of which were at ≥480 msec; and 4) eGFR <30 mL/min would

not be considered a uncomplicated urinary tract infection but a complicated urinary tract infection.

8.1.3. Age

Population PK post hoc estimates based on age were not considered statistically significant as gepotidacin exposure increases for both adolescent (12 to <18 years of age) and elderly (65 to 89 years of age) subjects were <2-fold as compared to adults (18 to 64 years of age). In addition, age was not considered a significant covariate in the population PK model (Section 14.5).

Two phase 1 studies (BTZ117349-Part 3 and Study 209611) were conducted to investigate the PK of gepotidacin in elderly (≥65 years old) and adolescent (12 to <18 years old) subjects (Section 14.2.1.5). In the study with elderly subjects, gepotidacin 1500 mg oral tablet was administered twice daily for 5 days under a fed (moderate fat meal) and fasted state, and the gepotidacin exposures were similar to adult subjects who were administered the same dosage over 15 days (Study 116778). In Study 209611, adolescent subjects were administered two different oral gepotidacin dosages (1500 mg × 1 and 3000 mg × 2 over a 6-hour interval). The gepotidacin exposures were numerically higher (1.10 to 1.35-fold) for adolescent subjects when compared to the adult subjects administered the same dosages in the study. Although the higher exposures of gepotidacin were thought to be attributed to the lower body weight in adolescents (mean 64.1 kg) as compared to adults (79.4 kg), they were not considered clinically relevant.

With regards to treatment related adverse events in elderly subjects, 22 of 25 subjects experienced an adverse event regardless of fed or fasted state; however, none were above Grade 2 severity. Gastrointestinal treatment related adverse events were the most common events under both fed and fasted conditions. Three subjects experienced treatment related liver events (i.e., elevated ALT and/or AST) with only 1 subject experiencing a value ≥3x ULN. No abnormal clinically significant ECG findings were observed in the population.

In the adolescent study, 15 of 17 subjects experienced a treatment related adverse event, none of which were considered more than Grade 2 severity. Gastrointestinal treatment related adverse events were the most common with the majority occurring when the subject received two 3000-mg gepotidacin doses 6 hours apart.

From a safety perspective in the pooled phase 3 studies, 14 female adolescents with uUTI received gepotidacin with four subjects (29%) exhibiting a Grade 2 or lower severity adverse event, mostly gastrointestinal related, compared to 8% with nitrofurantoin. Among the 353 elderly female subjects with uUTI that received gepotidacin that were evaluated for safety, ~37% exhibited an adverse event on gepotidacin versus 27% on nitrofurantoin; seven subjects (~2%) on gepotidacin had an adverse event beyond a Grade 2 severity (three subjects with gastrointestinal and one subject with cardiovascular) compared to <1% with nitrofurantoin.

From an efficacy perspective in the pooled phase 3 studies among the micro-ITT NTF-S population, only one subject <18 years old was evaluated in the gepotidacin cohort. Among the 166 elderly subjects on gepotidacin, ~63% exhibited composite response compared to ~41% on nitrofurantoin (risk difference 21.5% [95% CI 11.3, 31.8]). Given this information, gepotidacin 1500 mg every 12 hours may be administered to all patients regardless of age without a dosage adjustment.

8.1.4. Race

Population PK post hoc estimates comparing white/other versus black subjects were not considered statistically significant as gepotidacin exposure increases were <2-fold. In addition, race was not considered a significant covariate in the population PK model. See Section 14.5 and Table 149 for additional information about the distribution of races. Additional comparisons between other races could not be made as the Applicant grouped together other races (American Indian, non-Japanese Asian, Native Hawaiian, multiple races) with the white race.

In two phase 1 studies (Study 213678- part 4, Study BTZ117351- part 2 and 3), gepotidacin PK was evaluated in Japanese healthy adult subjects (Section 14.2.1.5). The gepotidacin exposures for Japanese healthy subjects compared to other races (i.e., Western white/Caucasian and black/African American subjects) with the same formulation, dosage, and fed/fasted state were not clinically significant, as the mean C_{max} and $AUC_{0\text{-}inf}$ in Japanese subjects was no higher than 1.6-fold and 1.3-fold, respectively. The adverse events were mild (mostly gastrointestinal related). A comparison between other Western races (excluding white/Caucasian and black/African Americans) with Japanese subjects could not be made due to limited sample size.

Given this information, gepotidacin 1500 mg every 12 hours may be administered to all patients regardless of race without a dosage adjustment.

8.1.5. Other Intrinsic Factors

Population PK analysis involving gepotidacin PK data from phase 1 studies, a phase 2 study, and the phase 3 study, EAGLE-2 indicated that sex, body weight (40 to 140 kg), and baseline BMI categories, did not have a clinically significant effect on gepotidacin exposures (i.e., <2-fold increase in exposures). Therefore, no dosage adjustment of gepotidacin 1500 mg every 12 hours is necessary. See Section 14.5 (Pharmacometrics) for additional information.

8.2. Extrinsic Factors

8.2.1. Food Effect

Four phase 1 studies evaluated the effect of food on PK with a moderate fat meal (caloric content and fat content are unknown) or Japanese standard meal (875 kcal, 40% fat) with various formulations (capsule, mesylated salt tablet [to-be-marketed formulation], and roller compacted free base tablet) at dosages of 1500 mg × 1, 2300 mg × 1, or 1500 mg every 12 hours over 5 days (Section 14.2.1.3 and Section 14.2.1.5- Study BTZ117351). Although no clinically meaningful food effect was observed in any of the studies, gepotidacin was not evaluated with a high fat meal as recommended in the *2022 FDA Food Effect Guidance* (FDA 2022a) (total calories- 800-1000, fat calories-500 to 600, 50% of calories are fat). It is not clear if a high fat meal will alter the PK of gepotidacin, as gepotidacin is noted by the Applicant to be a Biopharmaceutical Classification System Class 3 (BCS 3) drug (i.e., drug with high solubility and low permeability). Published literature suggests that high fat meal ingestion may decrease systemic absorption of BCS 3 drugs and delay time to maximum concentration (T_{max}); however, it may

also inhibit gastrointestinal transporters (e.g., efflux or influx transporters) which could lead to unexpected increases in the extent of bioavailability (Custodio et al. 2008).

Given these uncertainties, the effect of coadministration of high fat meal with gepotidacin is unknown.

8.2.2. Summary of Drug-Drug Interaction Studies

Gepotidacin as an Object

In vitro studies indicated that gepotidacin is a substrate of CYP3A4, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug and toxin extrusion proteins (MATEs) 1 and 2-K (Section 14.1.4). No clinical study of gepotidacin as a BCRP substrate was conducted by the Applicant. Although a clinical evaluation of BCRP would be important, considering gepotidacin is an orally administered drug and the efflux transporter is found in the gastrointestinal tract, it is likely to not be a safety concern for the proposed dosage of 1500 mg every 12 hours administered for a short 5-day duration.

In clinical Study BTZ117349-part 2, gepotidacin 1500 mg × 1 when co-administered with oral itraconazole (a strong CYP3A and P-gp inhibitor) 200 mg daily for 3 days under fed state exhibited an ~1.4 and 1.5-fold increase in C_{max} and AUC, respectfully (Section 14.2.1.6). Despite this less than 2-fold increase in C_{max} and AUC, the Applicant has proposed to avoid concomitant administration of gepotidacin with strong CYP3A4 inhibitors to prevent potential increases in QTc prolongation beyond 20 msec as shown in the Applicant's simulations. The Applicant's proposal was deemed acceptable by the review team.

In clinical Study 213678-cohort 2, gepotidacin 1500 mg × 1 was co-administered under fed conditions with oral rifampicin, a strong CYP3A4 inducer (Section 14.2.1.6). Rifampicin was dosed at 600 mg daily, 7 days prior to co-administration with gepotidacin. The results showed that when gepotidacin was co-administered with rifampicin, the gepotidacin exposures decreased by >50% for both plasma and urine AUC. Although gepotidacin is currently indicated for uncomplicated urinary tract infections and the site of action is the bladder lumen, urine exposures may be considered more important to efficacy. However, the review team still considers this interaction clinically significant for the following efficacy and safety reasons: 1) as mentioned in Sections 5.1, 6.1, and 14.1.5, appropriate urine concentration threshold for clinical efficacy has not been determined for gepotidacin; and 2) drug metabolism induction is likely to increase M4 metabolite (>10% of drug related material in plasma as determined from clinical mass balance study).

Since gepotidacin renal clearance (CLr) is >125 mL/min (indicator for renal tubular section) and in vitro assays show it is a potential MATE1 and MATE2-K substrate, a clinical Study (213678-cohort 1) was performed with an organic cation transporter (OCT) and MATE inhibitor, oral cimetidine at 400 mg four times daily. The results indicate no gepotidacin interaction with MATE1 and MATE2-K given a <1.25-fold change in AUC (Section 14.2.1.6).

Given the clinical drug interaction information, gepotidacin should be avoided with strong CYP3A4 inducers and inhibitors.

Gepotidacin as a Precipitant

In vitro studies evaluated gepotidacin for reversible, time-dependent, and metabolism-dependent inhibition (Section 14.2.1.3). The results indicate gepotidacin was not an inhibitor of any CYP isoforms as the IC_{50} values were beyond therapeutic exposure values for the proposed dosage, and there was no shift in IC_{50} by gepotidacin on CYP substrate probes. In addition, gepotidacin was also evaluated for the potential to induce expression of CYPs 1A2, 2B6, and 3A4, and showed little to no change in messenger ribonucleic acid (mRNA) expression. Despite the in vitro results, a clinical study was performed to evaluate gepotidacin as a CYP3A4 inhibitor of oral midazolam (14.2.1.6). In Study 213678-cohort 3, gepotidacin 3000 mg × 2 (12 hours apart) was co-administered with midazolam (CYP3A4 substrate) under a fed state, and the results showed gepotidacin weakly interacted with CYP3A4 (1.9-fold increase in AUC).

In vitro studies evaluated gepotidacin as an inhibitor of drug transporters (Section 14.1.4). The results only indicate that gepotidacin is a possible inhibitor of MATE1 and MATE2-K given the IC_{50} values of ~17 and 7 µM are clinically relevant, while others like P-gp and BCRP were beyond clinically relevant exposures. Despite these results, a clinical study evaluating gepotidacin as an inhibitor was performed for P-gp (Section 14.2.1.6), but not MATE1 and MATE2-K. It is unlikely that inhibition of MATEs will be a clinical concern given the proposed indication of uUTI, for a short duration of 5 days. It should be noted that MATE inhibition can lead to elevated creatinine levels in the blood which could lead to false decreases in the creatinine-based estimations of renal function (e.g., CrCl, eGFR). In the phase 3 studies (EAGLE-2 and 3), creatinine clearance decreases of >25% were only observed in about 9% of the subjects administered gepotidacin (n = 137) and nitrofurantoin (n = 145). However, numerically more subjects' renal function returned to baseline post-treatment of gepotidacin than nitrofurantoin (46% versus 32%); it is not clear if some contribution to the return of renal function is due to return of MATE function in the secretion of creatinine to urine.

For the clinical evaluation of gepotidacin as an inhibitor of P-gp, subjects were co-administered oral gepotidacin (3000 mg × 2 to 12 hours apart) with oral digoxin (0.5 mg) in Study 213678-cohort 3 (Section 14.2.1.6). The results showed no interaction based on AUC, but as indicated by the Applicant, a potentially clinically significant interaction based on the 1.5-fold C_{max} increase of digoxin when co-administered with gepotidacin. We concur with the Applicant that the interaction may be clinically significant given that digoxin is a narrow therapeutic index drug.

Given the above results, gepotidacin should not be administered with drugs that have a narrow therapeutic index and are extensively metabolized by CYP3A4. In addition, therapeutic drug monitoring of digoxin, a narrow therapeutic index drug, should be considered, as appropriate, when co-administered with gepotidacin.

8.3. Plans for Pediatric Drug Development

The Applicant plans to conduct a single dose PK study in pediatric subjects 2 years to less than 12 years of age to confirm the appropriate pediatric dose. A second study is planned that enrolls pediatric subjects 2 years to less than 12 years of age with uUTI to evaluate safety, PK, and efficacy. (b) (4) See Section 24 for details on the pediatric postmarketing requirements.

UTIs in pediatric patients less than 2 years of age are generally considered complicated and outside of the proposed indication of uUTI.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section 14.

Table 55. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In an embryo fetal development (EFD) rat study, 0 (vehicle), 150, 450, or 750 mg/kg/day gepotidacin was administered by oral gavage during organogenesis. Reduced feed consumption was observed during gestational day (GD) 6-9 in the 450 and 750 mg/kg/day dose groups, but no group differences in maternal body weights. Mean fetal body weights were statistically significantly reduced in the high dose group (3%-7%) and in the mid-dose group compared to one of the two control groups (3%-5%). No gepotidacin malformations or variations were found. The NOAEL was 150 mg/kg/day based on the reduced body weights in the fetuses. In an EFD mouse study, 0 (vehicle), 200, 500, or 1000 mg/kg/day gepotidacin was administered by oral gavage during organogenesis. Mean fetal body weights were reduced by 4% and 5% in male and female fetuses in the 500 mg/kg (mid dose) group and by 7% at 1000 mg/kg compared to controls. Mean late resorptions were increased in 1000 mg/kg dose group litters (10.79%) compared to controls (7.24%) leading to an increase in percent post-implantation loss. As fetal body weights in the mid and high dose groups were statistically significantly lower than controls, the investigators considered the increases in late resorptions at the mid dose and the increases in late resorptions and post-implantation loss at the high dose possibly indicative of fetal toxicity. No gepotidacin malformations or variations were found. The NOAEL was 200 mg/kg/day based on the reduced body weights in the fetuses. In a critical window EFD mouse study, 0 (vehicle) or 1000 mg/kg/day gepotidacin was administered by oral gavage during GD 6-9. No maternal toxicity was noted. Mean fetal body weights were reduced by 7%-8% compared to controls. No differences in late resorptions were found. No gepotidacin malformations or variations were found. In a pre- and postnatal development mouse study, 0 (vehicle), 200, 500, or 1000 mg/kg/day gepotidacin was administered by oral gavage to female mice from GD6 to lactation day 20 (LD20). The NOAEL was 1000 mg/kg/day, the highest dose tested.

Labeling Section	Nonclinical Data
8.2 Lactation	Exposure data from pups on post-natal day 10 in a pre- and postnatal development mouse study, indirectly showed exposure of the mouse pups from the milk based on plasma drug levels in the pups.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	In a fertility and early embryonic development rat study 0 (vehicle), 150, 350, or 750 mg/kg/day gepotidacin was administered via oral gavage to male and female animals starting 15 days prior to cohabitation through conception and until GD6 (mated females) or day 46 of dosing (males). Litters from pregnant females were delivered on GD20. There were no effects on the reproductive performance in the male or female animals, pregnancy parameters, placental morphology, or external fetal malformations. The NOAEL was the highest dose tested, 750 mg/kg/day.

Source: FDA table
Abbreviations: EFD, embryo fetal development; GD, gestational day; NOAEL, no-observed-adverse-effect level

Table 56. Safety Margins From Reproductive and Developmental Toxicity Studies

Study	NOAEL (mg/kg/day)	Nonclinical Exposure (µg*h/mL)	Safety Margin Multiples Based on Exposure[a] or [Multiples Based on HED]
Rat FEED	750	[b]	4 [2]
Rat EFD	150	[b]	0.3 [0.5]
Mouse EFD	200	[b]	0.3 [0.3]
Mouse PPND	1000	[b]	3 [2]
Juvenile Rat	300/1250	252, 128, and 107 for postnatal days 13, 22, and 32.[c]	6, 3, 2

Source: FDA table
[a] Exposure multiples were based on population pharmacokinetics analysis from phase 3 studies, where the maximum clinical dosage resulted in systemic geometric mean exposures of $AUC_{0\text{-}12h}$ of 22.5 µg•hr/mL which was doubled to make an $AUC_{0\text{-}24h}$ comparison. Exposures in nonclinical studies were based on mean combined sex calculations.
[b] Safety margin was calculated using TK data from other studies in that species using the noted dose when available. Safety margin was also calculated on a body surface area (BSA) basis and provided in square brackets when no toxicokinetic measurements were available in the study.
[c] Dose range finding study. Animals were administered 300 mg/kg from postnatal day 4 to 21 and 1250 from postnatal day 22 to 32 or 35. Value for day 13 was from different group administered 300/1000 mg/kg/day.
Abbreviation: $AUC_{0\text{-}12h}$, area under the concentration curve from time 0 to 12 hours; $AUC_{0\text{-}24h}$, area under the concentration curve from time 0 to 24 hours; EFD, embryo fetal development; FEED, fertility & early embryonic development; hr, hour; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

9. Product Quality

Approval

The proposed drug product has been formulated as an immediate-release tablet containing 750 mg of gepotidacin as gepotidacin mesylate (b) (4) The drug product, gepotidacin tablets, are yellow, film-coated, capsule-shaped tablets, debossed with 'GS GU3' on one side and plain on the other side, proposed to be packaged in a 20-count high-density polyethylene bottle (b) (4) The NDA, as amended, has provided sufficient chemistry, manufacturing, and controls information to assure the identity, strength, purity, and quality of the proposed drug product, gepotidacin tablets. That includes stability information to support the proposed 24 months expiry dating for the drug product, to be stored under controlled room temperature conditions. The manufacturing and testing facilities have been found acceptable and the Overall Manufacturing Inspection Recommendation of "Approve" was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on January 23, 2025. Therefore, this NDA

is recommended for approval by the Office of Pharmaceutical Quality; refer to the Office of Pharmaceutical Quality Integrated Assessment (dated February 20, 2025, in DARRTS).

9.1. Device or Combination Product Considerations

Not Applicable

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The Office of Scientific Investigations performed inspections at 4 study sites that participated in Study EAGLE-2 and Study EAGLE-3 as well as the Applicant (GSK). The Office of Scientific Investigations' assessment was that the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication. Please refer to the review by John Lee, for additional information. The Applicant certified that for the investigators with disclosable financial interests or arrangements, their contributions to the study enrollment were each less than 2% of the overall study total and statistically unlikely to affect the outcome of the study. Please refer to the financial disclosure form in Section 25.

11. Advisory Committee Summary

An advisory committee was not held for this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

GlaxoSmithKline Intellectual Property Development Ltd., England (Sponsor) submitted a Pre-Investigational New Drug (PIND 111885) meeting request for GSK 2140944 on April 5, 2011. A type B, PIND meeting was granted by the Division of Anti-Infectives (Division) and a May 25, 2011, teleconference held. The Sponsor did not specify a pathogen or disease-specific indication at the time of PIND submission, indicating only that GSK 2140944 was being developed for bacterial infections.

The early pre-clinical development program was discussed including the control of impurities in the drug substance, the appropriateness of non-clinical studies conducted to date, and repeat-dose animal toxicity studies. The Division also provided advice to the Sponsor on updating the Investigator's Brochure before the initial Investigational New Drug (IND) submission, and the importance of conducting *in vivo* studies, using well-established animal infection models to help further elucidate the pharmacokinetic-pharmacodynamic relationship of GSK2140944.

On August 11, 2011, the Sponsor submitted IND 111885 for GSK 2140944. The Sponsor identified the initial indications to be studied under the IND as Community-Acquired Pneumonia and Complicated Skin and Skin Structure Infections. The study proposed in the initial IND submission was titled *"A Randomized, Single Blind, Placebo Controlled Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Single Escalating Oral Doses of GSK2140944 in Healthy Adult Subjects."* In the September 9, 2011, letter, the Division informed the Sponsor that it was safe to proceed with the proposed study under IND 111885.

On June 3, 2016, the Sponsor requested a type C meeting to discuss the preclinical and phase 3 development programs for their planned uncomplicated urinary tract infection (uUTI) (b) (4) The Division provided a written response on August 15, 2016, addressing several aspects of the drug development plan.

The Division informed the Sponsor that a superiority study would provide the most reliable evidence for a favorable benefit-risk profile in uUTI but acknowledged the Sponsor's plan to demonstrate the noninferiority (NI) of GSK 2140944 to nitrofurantoin for therapeutic response (clinical and microbiological cure) at 5 to 8 days post treatment. The Division advised the Sponsor that a justification for the non-inferiority (NI) margin for this endpoint, based on the control antibacterial drug (nitrofurantoin), should be provided.

On June 29, 2016, the Sponsor submitted a request for Qualified Infections Disease Product (QIDP) designation for (b) (4) uncomplicated urinary tract infections. QIDP designation was granted on August 26, 2016, for the requested indications.

On May 16, 2017, a type C, Guidance meeting was held to discuss the Sponsor's planned phase 3 uUTI study. The Sponsor discussed their choice of comparator and endpoints and the Division indicated that the primary efficacy endpoint should be a combined clinical and microbiological endpoint.

On November 9, 2018, the Sponsor submitted a new QIDP designation request, due to a change in the product dosage form (b) (4) to a gepotidacin "mesylate salt" in a tablet. QIDP designation was granted on January 8, 2019, for the same indications granted on August 26, 2016.

On April 12, 2018, a type B, End-of-Phase 2 meeting was held to discuss the phase 3 clinical studies for gepotidacin. During the meeting, the Division noted that there had been gastrointestinal adverse events with GSK 2140944 in the current dosing regimen, expressing concern about patient compliance as the second dose was to be taken at home. The Division advised the Sponsor to carefully consider how tolerability may impact the dosing regimen and the phase 3 program. In addition, the Division and Sponsor discussed the use of a dynamic hollow-fiber infection model that might provide more data on how the proposed dosing regimen may suppress resistance and the importance of enrolling culture positive subjects for inclusion in the microbiological intent-to-treat (micro-ITT) population. The Sponsor was informed that their initial Pediatric Study Plan (iPSP) would be due within 60 days of the End-of-Phase 2 meeting.

The Sponsor submitted their iPSP on June 5, 2018. (b) (4)

The Division informed the Sponsor's in an August 31, 2018, letter that they should request a deferral for the study of pediatric patients ages 2 to less than 12 years of age with uUTI and a waiver for pediatric subjects less than 2 years old. The Division also advised the Sponsor on age-appropriate formulation development (i.e., down to 2 years) and requested information on the (b) (4) current oral formulation. The Sponsor was also asked to submit detailed information on physiologically based pharmacokinetic (PBPK) modelling and simulation in their pediatric pharmacokinetic (PK)/safety study protocol for Division review.

On October 21, 2020, the Sponsor resubmitted their iPSP. An Agreed initial Pediatric Study Plan letter was issued to the Sponsor on December 4, 2020.

An iPSP amendment was submitted on August 30, 2022, and the Division provided a Written Response letter on February 14, 2023, requesting the Sponsor provide a summary of their pharmacokinetic exposure data for the 2- to 12-year-old age group and accompanying dose rationale when these data became available. The Sponsor provided the requested information along with an Agreed Amended iPSP on February 21, 2023. On March 21, 2023, the Division issued an Amended Agreed iPSP letter. The Amended Agreed iPSP was submitted with the marketing application on July 26, 2024.

On April 2, 2021, the Sponsor submitted a request for Proprietary Name Review for their proposed name "Blujepa" and on August 27, 2024, the Division of Medication Errors and Prevention Analysis issued a Proprietary Name Request Conditionally Acceptable letter.

A pre-new drug application (NDA) meeting was held on April 21, 2023. Plans for submission of a marketing application for gepotidacin for the treatment of uUTIs were discussed. The Sponsor conveyed their plan for providing narratives for serious adverse events (SAEs) and for financial disclosure for studies conducted in Japan, which was acceptable to the Division. However, with respect to bioanalytical method performance templates, the Sponsor noted the plan to only submit these for gepotidacin. The Division noted this would not be sufficient, indicating that the bioanalytical methods for other analytes, including those done for drug-drug interaction (DDI) studies, needed to be summarized and provided in the marketing application. The content of a complete application was also discussed, and the Division and Sponsor agreed that the following components could be submitted within 30 days of the NDA submission: 10% random samples of the case report forms from the phase 3 studies, the template for in vivo pharmacology data, and bioanalytical methods for other drugs (i.e., DDI Studies).

On September 12, 2023, a type C, Guidance meeting was held to discuss the proposed control strategy for (b) (4) drug substance related impurities (b) (4) observed in gepotidacin tablets. The objective for the meeting was to reach an acceptable path forward for addressing the (b) (4) and the associated Acceptable Intake (AI). The Sponsor outlined various activities they had conducted in accordance with the guidance (Recommended Acceptable Intake Limits for (b) (4) Drug Substance-Related Impurities), August 2023 (FDA 2023) to control the (b) (4) to an AI of (b) (4) mcg/day. The Division recommended that the non-clinical data and final protocols for in vivo/in vitro and Ames testing be submitted for review.

On April 12, 2024, a follow up meeting was held to further discuss the (b) (4) issue. The in vitro pharmacology studies, pending MutaMouse transgenic gene mutation assay, and proposals for setting specifications were discussed. The Division noted that the proposed control strategy for (b) (4) in the drug substance and the information planned to be submitted appeared reasonable; the adequacy of the data would be determined after NDA submission. The Division clarified that the drug substance and drug product impurity limits for (b) (4) would not be found acceptable until an AI level was established and agreed upon. It was agreed that it would be beneficial to review the pending MutaMouse study (to be provided by the Sponsor) to gain a better understanding on the AI and additional discussion could be held after the review of the study.

On July 26, 2024, GlaxoSmithKline, limited liability company (LLC) (Applicant) submitted their NDA 218230 for gepotidacin tablets for treatment of uUTI in female adults and adolescents from 12 years of age, both weighing at least 40 kg. The NDA was granted priority review status and was filed on September 24, 2024. The NDA has a Prescription Drug User Fee Act goal date of March 26, 2025.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology

Gepotidacin (GSK2140944) is a triazaacenaphthylene bacterial Type II topoisomerase inhibitor that selectively inhibits Type II bacterial topoisomerases, namely deoxyribonucleic acid (DNA) gyrase and topoisomerase IV.

Further details regarding nonclinical efficacy of gepotidacin can be found in Section 19 from clinical microbiology.

Secondary Pharmacology

Gepotidacin was tested in an in vitro ligand screening panel, which did not show any significant activity as defined as a half maximal effective concentration of less than 1 μM, at any molecular target tested. These tests included agonist and antagonist assays for the muscarinic M1 and M2 receptors and activity as an opener or blocker of alpha-1 nicotinic acetylcholine receptor. In a separate in vitro assay, gepotidacin was tested up to 600 μM. Gepotidacin was not an M1 or M2 agonist, and was weakly active as an antagonist, with a maximum response of 88% with M1 receptor and 53% with the M2 receptor. Other receptors tested did not show substantial inhibition or activity changes.

Additional Secondary Pharmacology data, which was submitted with the NDA, is reviewed in Section 13.2.1.

13.1.2. Safety Pharmacology

Table 57. In Vitro Cardiovascular System

Study Feature and Methods	Details
Applicant study number	WD2010-00521 (V29256)
Study title	GSK2140944E: Effect on hERG Tail Current Recorded from Stably Transfected HEK-293 Cells
Validity	The positive control, E-4031 100nM, inhibited hERG tail current by 90%. The study is GLP and valid.
Findings	GSK2140944E at concentrations from 0.06-10mM were tested in HEK-293 cells and caused a concentration dependent inhibition of hERG tail current. The concentrations inhibiting the current 25%, 50% and 75% (IC_{25}, IC_{50}, and IC_{75}) were 0.551, 1.31, and 3.13mM (corresponding to 0.247, 0.588, and 1.40 mg/ml).

Source: FDA table
Abbreviations: GLP, good laboratory practice; HEK-293 cells, human embryonic kidney 293 cells; hERG, human ether-a-go-go-related gene

Table 58. In Vitro Cardiovascular System

Study Feature and Methods	Details
Applicant study number	2011 N116120
Study title	Preclinical Test of GSK2140944A for QT Prolongation and TdP Potential Using the Rabbit Left Ventricular Wedge Preparation
Validity	Non-GLP
Findings	GSK2140944A caused a concentration dependent increase in the QT interval of the cardiac wedge preparation (from female rabbits). At higher concentrations, GSK2140944A prolonged the QRS interval and decreased cardiac contractility.

Source: FDA table
Abbreviations: GLP, good laboratory practice; QRS, QRS complex; QT, interval from the start of the Q wave to the end of the T wave; TdP, torsade de pointes

Table 59. In Vivo Cardiovascular, Respiratory, and Neurobehavioral Function

Study Feature and Methods	Details
Applicant study number	G10042
Study title	GSK2140944E: Acute Effects on Cardiovascular, Respiratory, and Neurobehavioral Function Following Oral Administration in the Conscious Beagle Dog
GLP compliance	Yes
Species/strain	Dog/Beagle
Number/sex/dose group Doses Route of administration	4 male dogs in a Latin square crossover design 0 (vehicle of 1% methylcellulose), 50, 125, and 250 mg/kg/day Oral
Dosing frequency	Each dose was administered as a split dose 6 hours apart, with one week between doses to unrestrained animals

Study Feature and Methods	Details
Parameters measured	Cardiovascular function: arterial pressures, heart rate and electrocardiographic intervals and waveforms Respiratory function: tidal volume, respiratory rate and minute volume, and a measure of airway resistance (phase relation) Neurobehavioral function: spontaneous activity, body temperature and neurobehavioral observations and examinations Cardiovascular and respiratory parameters were measured for 2 hours before and 24 hours after the first dose. Neurobehavior: Each parameter was monitored for up to 24 hours following the first daily dose
Findings	Cardiovascular function: No arrhythmias No QTc prolongation Low dose: Mild increases in heart rate and cardiac contractility (decreased QA interval) Mid dose: Mild increase in cardiac workload (product of heart rate and blood pressure) High dose: Mild increases in heart rate and mean arterial pressure were observed, along with moderate increases in cardiac contractility and cardiac workload. Respiratory function: No drug-related changes Neurobehavioral function: Unsteady gait was seen at the mid and high doses Increased spontaneous activity that seemed related to agitation at the mid and high doses The high dose dogs exhibited frequent licking, slight ptosis, head shaking/bobbing and loose feces. More frequent and severe vomiting at the mid- and high doses Dose dependent increased salivation in low, mid, and high doses Small increase in body temperature (up to 0.8 ºC)

Source: FDA table
Abbreviations: GLP, good laboratory practice; QA, estimate of cardiac contractility; QTc, QT interval corrected for heart ratel

Table 60. In Vivo Cardiovascular Safety Pharmacology Study

Study Feature and Methods	Details
Applicant study number	2011N125328
Study title	GSK2140944E: Acute Effects on Cardiovascular Function Following Twice Daily Intravenous Infusion Administration in the Conscious Cynomolgus Monkey
GLP compliance	Yes
Species/strain	Monkeys/cynomolgus
Number/sex/dose group	4 males
Doses	50, 100, 250 mg/kg/day
Route of administration	IV infusion
Dosing frequency	Latin square design with the daily administration divided into two doses 6 hours apart
Parameters measured	ECG parameters, body temperature

Study Feature and Methods	Details
Findings	Emesis was reported after first and/or second dose in the 250 mg/kg/day group in 3 of 4 animals. Dose-dependent increases in heart rate, mean arterial pressure, cardiac contractility, and QTc interval, and at the high dose QRS interval. At the mid and high doses, a decrease in body temperature was also reported. Percent changes are shown in Table 61.

Table 61. Mean Percent Change From Vehicle Infusion

		mg/kg/Dose		
Parameter	**Infusion**	**25**	**50**	**125**
Heart rate	1	26%	34%	37%
	2	16%	35%	27%
Mean arterial pressure	1	10%	8%	13%
	2	13%	6%	9%
Cardiac contractility	1	11%	12%	17%
	2	11%	12%	17%
QTc interval	1	4%	5%	7%
	2	5%	6%	9%
QRS interval	1	-	-	8%
	2	-	-	6%

Source: Reviewer generated table from Applicant data
Abbreviations: QRS, QRS complex; QTc, QT interval corrected for heart ratel

Source: FDA table
Abbreviations: ECG, electrocardiogram; GLP, good laboratory practice

13.1.3. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

Absorption

- The bioavailability of gepotidacin following oral administration was found to be 16 to 72%, 45 to 100%, and 36 to 78% in monkeys, dogs, and rats, respectively. Bioavailability increased with increasing doses in monkey and dog, with only one dose tested in rat.
- Following administration of gepotidacin mesylate salt to dogs, gamma scintigraphy imaging showed primary absorption in the small intestine (and entry into the small intestine was noted to coincided with occurrence of emesis and time to maximum concentration (T_{max})).

Distribution

Transporters:

- P-glycoprotein (P-gp): Gepotidacin was shown in vitro to be substrate of P-gp with concentration dependent transport. Gepotidacin was found in vitro to inhibit P-gp with a half maximal inhibitory concentration (IC_{50}) of 2,530µM. In MDR1a (the gene encoding P-gp) knock out (KO) rats, pharmacokinetics were similar to wild type rats in one study. In a study with radiolabeled gepotidacin in MDR1a KO rats, plasma concentrations increased 1.7- to 1.8-fold. After an 8-hour infusion, central nervous system (CNS) and cerebrospinal fluid distribution of gepotidacin in the MDR1a KO rats compared to wild type increased 5-7 fold; after 24-hour infusion the distribution to the CNS and cerebrospinal fluid increase 12.5-fold.
- HBCRP: Gepotidacin is a substrate for HBCRP in vitro with an efflux concentration of 11 at 3µM. Gepotidacin inhibited transport of a HBCRP substrate in vitro with an IC_{50} of 9711µM. In HBCRP KO animals, no difference in PK was reported or distribution of radiolabeled gepotidacin, compared with WT animals.
- Gepotidacin was not a substrate or inhibitor of the OAT1, OAT3, or OATP2B1 transporters in vitro. Gepotidacin was not a substrate of OAT2 transporters in vitro.
- Gepotidacin was not a substrate of organic cation transporter 2 (OCT2) in vitro but inhibited the transporter 57% at 300µM. Gepotidacin was not a substrate of OCT3 but inhibited the transport with an IC_{50} = 356.3µM. Gepotidacin was not a substrate of OATP1B1 in vitro but inhibited the transporter 34% at 5000µM. Gepotidacin was not a substrate of OATP1B3 in vitro but inhibited the transporter 47% at 5000µM.
- Gepotidacin is a substrate of multidrug and toxin extrusion protein 1 (MATE1) in vitro and inhibited the transporter with an IC_{50} = 16.61µM. Gepotidacin is a substrate of MATE2-K in vitro and inhibited the transporter with an IC_{50} = 6.877µM.

Protein Binding:

- In vitro assays with whole blood and plasma from mouse, rat, dog, monkey, and human had mean blood/plasma concentration ratios from 0.8 to 1.2 and 35 to 44% mean percent of drug associated with blood cells across species, indicating low partitioning.
- Measured in vitro protein binding of [^{14}C]-GSK2140944 to protein in plasma of human was 40-41%, cynomolgus monkey was 26 to 28%, African Green monkey was 24 to 28%, Beagle dog was 18 to 21%, Sprague-Dawley rat was 33 to 35%, CD mouse was 21 to 27%, BALC/c mouse was 19 to 26%, and New Zealand White Rabbit was 20 to 24%.
- Using an equilibrium dialysis method, in vitro plasma protein binding of GSK2140944 in mouse, rat, dog, monkey, and human at 5µM was estimated to be 23.7%, 29.8%, 19.5%, 16%, and 11.1%, respectively.

Tissue Distribution

A quantitative whole-body autoradiography study in partially pigmented male rats (Long-Evans) used a single oral administration of [^{14}C]-GSK2140944 at 450 mg/kg to determine quantitative tissue distribution. The concentration of radioactivity in the blood was highest at 4 hours post-dose (26.535 µg equiv/g) and declined to below the level of quantification (LoQ) by 24 hours post-dose. Concentrations of radioactivity in the brain were below the LoQ at all time points. At 1 hour post-dose the radioactivity was widely distributed except in the brain and lens and the highest concentrations were in the liver and kidneys (128.271-160.447 µg equiv/g). The highest concentrations overall were measured at 4 hours post-dose and at that time the highest concentrations were reported in the kidney (367.251 µg equiv/g), liver (347.191 µg equiv/g), renal medulla (344.712 µg equiv/g), and renal cortex (323.518 µg equiv/g). At 3 days post-dose radioactivity tissues remaining with concentration above 10 µg equiv/g were the meninges, pigmented skin, and ocular uveal tract. At 7 days only the ocular uveal tract was above 10 µg equiv/g (at 125.551 µg equiv/g), and at 35 days the meninges (3.318 µg equiv/g) and ocular uveal tract (84.123 µg equiv/g) were the only tissues above the LoQ.

Tissue distribution and elimination of radiolabeled gepotidacin mesylate dihydrate was evaluated in a study of male Long Evans rats administered radiolabeled drug at 100 mg/kg by intravenous (IV) or 150 mg/kg orally. Animals were evaluated for plasma PK and liver concentrations (n = 3, IV collections at 1, 4, and 24 hours, oral collection at 2, 8 and 24 hours) and quantitative whole-body autoradiography (n = 7, single animals per time point at 1, 4, 8, 24, 72, 168, and 840 hours). Maximum concentration of radioactivity in the plasma and liver was one-hour post-dose administered by IV, the first sampling point. The liver:plasma ratio was about 5 at the 1-hour time point rising to 61 at the 24-hour time point. Following oral administration, the maximum concentration of radioactivity in the plasma and liver was two hours post-dose, the first sampling point. The liver:plasma ratio was about 10 at the 2-hour time point rising to 72 at the 24-hour time point. Following IV administration, radioactivity was widely distributed with peaks in most tissues at 1 hour, except lens of the eye (4 hours), uveal tract of the pigmented eye (168 hours), large intestine contents (8 hours), and rectum mucosa (8 hours). Concentrations in the brain and spinal column were low but quantifiable. Higher concentrations were noted in excretory tissues and contents (e.g. bile ducts, liver, gastrointestinal (GI) tract, kidney, bladder), glandular tissues of the pituitary, exorbital lachrymal, intra orbital lachrymal mucus and salivary tissue as well as the vascularized bone marrow and spleen, and in pigmented tissues. The concentrations in

pigmented tissues did decline over the course of the study indicating that the binding was present but reversible with slow elimination. By 168 hours about 75% of assessed tissues were below the level of detection, and 90% of assessed tissues were below the level of detection by 840 hours. Following oral administration, 99.7% of the radioactivity was recovered by the end of one week of dosing. Recovery via urine was about 16% and via the feces was about 82%. Plasma concentrations were below the LoQ at the one-week time point with peak elimination in the urine in the 0 to 12 hour time frame and in feces in the 0 to 24 hour time frame.

Metabolism

Metabolites are denoted with the notation "M" followed by a number. Structures of the metabolites can be found in Table 62 below. A summary of the proposed metabolic scheme is in Figure 3 below.

In Vitro

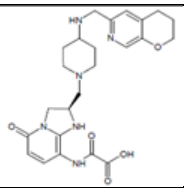
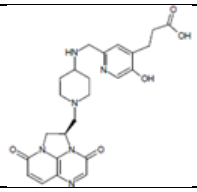
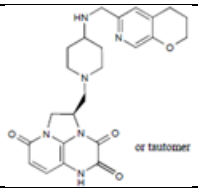
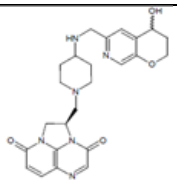
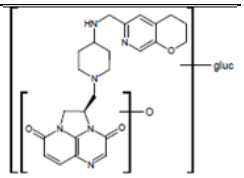
- In vitro using human liver microsomes gepotidacin was significantly metabolized to metabolites M4, M5, M13 and M15 (see Table 62). Metabolite formation was inhibited by azamulin, a cytochrome P450 (CYP)3A4 inhibitor. Incubation of gepotidacin with recombinant CYP3A4 led to formation of the same metabolites as with the human liver microsomes.
- Measured CYP450 messenger ribonucleic acids (mRNAs) (CYP1A2, CYP2BB6, and CYP3A4) were induced less than 2-fold with incubation of cultured human hepatocytes with gepotidacin.
- In human liver microsomes, gepotidacin inhibited CYP3A4/5 with calculated inhibitory concentrations that varied from 179 to 906 µM, depending on the metabolite monitored for and testing conditions. Gepotidacin inhibition of CYP3A4/5 was reversible. The IC_{50} was not calculable for gepotidacin when tested up to concentrations of 500 µM for CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 and for some substrates of CYP3A4/5.
- Gepotidacin reversibly inhibits hrCES-1 and hrCES-2 with IC_{50} values of 1675 and 1535 µM, respectively.

In Vivo

- In male CD-1 mice, following oral administration of 1000 mg/kg [^{14}C]-gepotidacin, gepotidacin accounted for 56 to 64% of radioactivity in the plasma at time points 1 to 24 hours. Other metabolites detected were M2 (4% to 5% 1 to 8 hours post-dosing), M3 (2% to 3%, 1 to 8 hours post-dosing), M5 (3% to 5%, 1 to 8 hours post-dosing), and M8 (5% to 8%, 1 to 24 hours post-dosing)
- In female CD-1 mice, following oral administration of 1000 mg/kg [^{14}C]-gepotidacin, gepotidacin accounted for 60% of measured radioactivity in the plasma. Other higher concentration metabolites detected were M4 (10%) and M8 (6%).
- In monkeys administered 125 mg/kg by IV infusion, unchanged radiolabeled gepotidacin accounted for 66% of the plasma radioactivity, and metabolite M3 accounted for 8.5%.

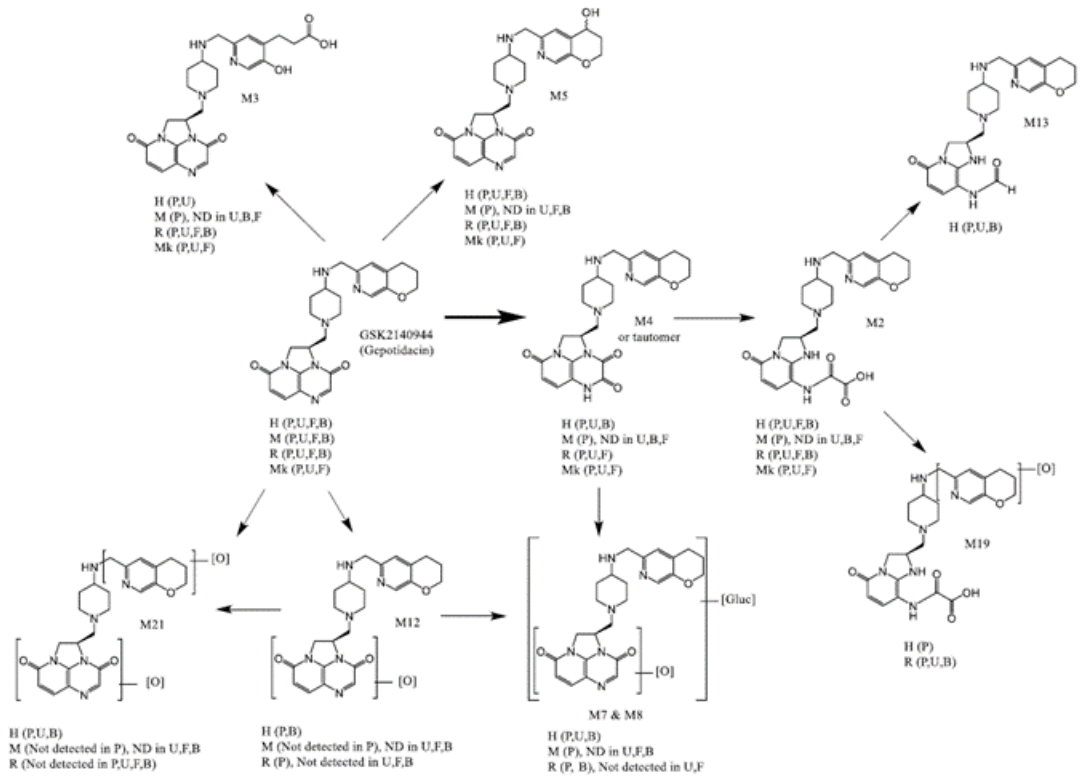
- In male Long Evans rats administered 100 mg/kg radiolabeled gepotidacin by IV injection, plasma gepotidacin was found to be 71% and 66% of the sample radioactivity at 1 and 4 hours, respectively, and M2 was found to be the major circulating metabolite at 9 and 7% of the sample radioactivity at 1 and 4 hours, respectively. Of the administered dose, 27% and 23% were excreted unchanged in feces and urine, respectively, and 19% were excreted as metabolites.
- In male Long Evans rats orally administered 150 mg/kg radiolabeled gepotidacin, plasma gepotidacin was found to be 59% and 74% of the sample radioactivity at 2 and 8 hours, respectively, and M2 was found to be the major circulating metabolite at 12% of the sample radioactivity at 2 hours, and below the lower limit of quantitation at 8 hours. About 47% of the drug was absorbed. Excretion was found to be 32% of the dose unchanged into the urine and biliary secretion of 3% of the dose. Metabolites were detected by all routes to account for about 12% of the excreted drug related substance. The most abundant component of radioactivity in liver extracts after either route of administration was the parent drug (21 to 56% at all time points) with M3 making up 3 to 11% of radioactivity up to 8 hours post-dose and M4 detected up to 4-hours post dose (3 to 6%).
- From male Long-Evans rats orally administered radiolabeled gepotidacin, a single time proportional pooled plasma sample was analyzed. Gepotidacin accounted for 65% of pool plasma radioactivity and metabolite M4 was 9.5% of the radioactivity, with the total exposure based on total radioactivity over the 24 hours found to be $AUC_{0\text{-}24}$ = 228 μg equiv*h/mL.
- In male cynomolgus monkeys administered 50 mg/kg gepotidacin, by IV and orally using a cross-over design, bioavailability was approximately 60%. At all measured time points the unchanged gepotidacin in the plasma was 40 to 60% of the radioactivity. The metabolites M3 and M5 accounted for more than 5% of the plasma radioactivity, (11 to 25% and 4 to 9%, respectively). The predominant biotransformation was predominantly via oxidation. Similar metabolite profiles were found in urine from either administration route.

Table 62. Metabolite Structures

Metabolite Designation	M2	M3	M4	M5	M8
Structure					

Source: Reviewer table constructed from Applicant data

Figure 3. Metabolic Scheme of Gepotidacin



Source: Nonclinical Overview from the Applicant, page 17
Abbreviations: B, bile; F, feces; H, human; M, mouse; Mk, monkey; P, plasma; R, rat; U, urine

Excretion

Elimination of radiolabeled gepotidacin mesylate dihydrate was evaluated in a study of intact and bile duct cannulated male Long Evans rats. The radiolabeled drug was administered as 100 mg/kg by IV or 150 mg/kg orally. Animals were evaluated for excretion balance (n=3) and biliary excretion (n=4, orally dosed only). Following IV dosing, most of the radioactivity was recovered in the first 48 hours with 98% recovered by 1 week after dosing. Mean recovery was 36% in the urine and 60% in the feces. Following oral dosing, 99.7% of administered material was recovered. Mean recovery in the urine was 16% and in the feces 82%. When the animals were euthanized at 168 hours, the radioactivity in the plasma was below the limit of detection for both the IV and oral administrations. In bile duct cannulated animals, overall mean radioactivity recovery mean was 97%, with 11% via bile, 40% via urine, and 42% in the feces.

The rate and extent of elimination of radiolabeled gepotidacin mesylate dihydrate was evaluated in intact male cynomolgus monkeys. With a single IV administration of 50 mg/kg, mean renal and fecal excretion were 37.8% and 31.2% of the administered dose, respectively. Mean total recovery of radioactivity was 73.22% at 168 hours after the start of dosing. With a single oral administration of 50 mg/kg, mean renal and fecal excretion were 24.5% and 58.3% of the administered dose, respectively. Mean total recovery of radioactivity was 85.87% at 168 hours after the start of dosing. Low recovery was noted for one of the 3 animals by both methods of administration.

Pharmacokinetics

Toxicokinetics were evaluated in good laboratory practice (GLP) repeat-dose toxicity studies; results for the toxicokinetic evaluation for those studies is described with the rest of the review of those studies.

- In mice administered the hydrochloride salt of GSK2140944 by IV (5 mg/kg), there was a high volume of distribution (2.8 L/kg) and short half-life (0.7h).
- In a ten-day oral dose range toxicity study in female mice, toxicokinetics were measured, as shown in the table below.

Table 63. Mouse Toxicokinetic Data

Study Title/Study No.	Toxicokinetic Data
General toxicology studies	
Study No: 2012N131777 Study title: GSK2140944E: 10-Day Oral Dose-Range Toxicity Study in Mice Collection times: 0.5, 1, 2, 4, 8, and 24 hours	**Table 64. Toxicokinetic Parameters in Mouse Dose-Range Finding Study**

Composite Toxicokinetic Parameters:

Parameter	Period	Dose (mg/kg/day)		
		200	500	1000
Female (n=3/timepoint)				
AUC_{0-t} (µg.h/mL)	Day 5	15.8	34.6	118
C_{max} (µg/mL)	Day 5	5.80	6.72	15.9
T_{max} (h)	Day 5	1.00	0.50	1.00

Source: Applicant study report
Abbreviations: AUC_{0-t}, area under the curve up to the last quantifiable time-point; C_{max}, maximum plasma concentration; n, number of subjects in treatment group; T_{max}, time to maximum concentration

Source: Reviewer table from Applicant data

- In rats, in single dose PK studies, with IV infusion of 3 mg/kg or oral administration of 5 to 600 mg/kg GSK2140944 (of free base), bioavailability generally increased with increasing dose, and exposure increased greater than dose-proportionally.
- In monkeys and dogs, in single dose PK studies, with IV infusion of 3 mg/kg or oral administration of 5, 20, or 50 mg/kg GSK2140944 (of free base), bioavailability increased with increasing dose, and exposure increased greater than dose-proportionally.

13.1.4. Toxicology

13.1.4.1. General Toxicology

Single Dose Toxicology/Toxicokinetic Studies

- In a non-GLP dose-ascending twice-daily oral toxicity study in dogs, doses at or above 300 mg/kg/day (150 mg/kg/dose twice daily) were not considered tolerated due to severity and frequency of emesis and diarrhea.
- In a non-GLP single dose study in female Crl:CD1 (ICR) mice, a dose of 1000 mg/kg by oral gavage was well tolerated.

Repeat Dose Toxicology/Toxicokinetic Studies

Study #CD2010-00088/GSK2140944E: 4-Week: Oral Toxicity Study in Long-Evans Rats Followed by a 2-Week Recovery Period

Key Study Findings

- 1500 mg/kg/day exceeded the maximum tolerated dose (MTD) with findings including up to 20% weight loss and loss of skin elasticity in some animals. The animals in this dose group were euthanized early on day 11.
- Tubular basophilia and dilation of proximal and distal tubules in the kidney were observed at doses ≥450 mg/kg/day, with more severe renal changes at the high dose including single cell necrosis and a few animals also exhibited tubular dilation or sloughed necrotic cells within the lumen.
- The oral no observed adverse effect level (NOAEL) for GSK2140944 in Long-Evans rats was 150 mg/kg/day when given for 4 weeks, with $AUC_{0\text{-}t}$ = 12.7 µg*h/mL, maximum plasma concentration (C_{max}) = 5.2 µg/mL (averaged between the sexes).

Table 65. Study Information #CD2010-00088

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 150, 450, 1500 mg/kg, once daily
Route of administration	Oral gavage
Formulation/vehicle	1% methylcellulose
Species/strain	Long-Evans rats (Crl:LE)
Number/sex/group	10
Age	10 weeks
Satellite groups/unique design	3/sex/group for TK 6/sex in the control and high dose groups for recovery
Deviation from study protocol affecting interpretation of results	The high dose rats received their last dose of drug on Day 10 due to intolerance. Main group high-dose animals were euthanized on Day 11. Recovery high dose animals were euthanized 5-weeks later, on Study Day 46.

Source: FDA table
Abbreviations: GLP, good laboratory practice; TK, toxicokinetics

Table 66. Observations and Results #CD2010-00088

Parameters	Major Findings
Mortality	High dose animals were euthanized early on Day 11 due to deteriorating clinical condition.
Clinical signs	Slight to moderate salivation was seen in most high dose rats pre- and post-dosing beginning on Day 7. In high dose rats, tan feces were noted in some cages and discolored/brown bedding was seen in most cages beginning on Day 8. Loss of skin elasticity was seen in most high dose rats beginning around Day 10. Hunched posture was noted in a high dose female rat on Days 10-11.
Body weights	Body weight loss (up to 20% of pre-dose weight) was observed in the high dose rats.
Feed consumption	Decreased mean cage food consumption was observed in the high dose group beginning on Day 4 and was reduced by up to 36% compared to the levels observed before the initiation of dosing.
Ophthalmoscopy	No treatment-related findings.
Hematology	No treatment-related findings.
Clinical chemistry	In the mid-dose group, increased serum urea (by about 60%) was seen in 3/8 females. One of them also had increased creatinine and inorganic phosphorus (by about 26% and 45%).
Urinalysis	No treatment-related findings.
Gross pathology	Mottled discoloration of the kidneys was observed in a high dose male rat euthanized on Day 11.
Organ weights	No treatment-related findings.
Histopathology adequate battery: Yes	Minimal to mild degeneration of the proximal and distal renal tubules was observed in the high dose rats euthanized on Day 11 (9/10 males, 3/10 females). Basophilia, with or without single cell necrosis, was observed. A few animals also exhibited tubular dilation or sloughed necrotic cells within the lumen. Kidney changes (tubular basophilia, dilation of scattered proximal and distal tubules, all rated minimal) were also observed in 3/10 female mid dose rats. Signs of necrosis were not observed in the 450 mg/kg rats, in contrast to the 1500 mg/kg group. Mild ulceration of the non-glandular and minimal erosion and/or inflammation in the glandular mucosa was observed in the stomach of a few high dose rats (3/10 males, 1/10 females). These findings may indicate irritation caused by the high concentration GSK2140944. Minimal to mild lymphoid depletion of the thymus in high dose rats appears likely to be stress-related (5/10 males, 2/10 females). At the recovery necropsy, minimal degeneration of renal tubules was observed in 1/6 female rats from the 1500 mg/kg group. The pathologist felt that the presence of mild chronic progressive nephropathy (a common background change) in this rat made it difficult to ascertain the extent of recovery from tubular degeneration (partial recovery vs. complete recovery).

Source: FDA table

Toxicokinetics

- No accumulation of gepotidacin was found in the mid and low dose animals; it could not be determined in high dose animals because of the early unscheduled euthanasia.
- At the low and mid doses there were no significant sex differences. In the high dose animals, on day 1, the area under the concentration-time curve (AUC) in females was about 2.5-fold those reported in males.

Table 67. Toxicokinetic Parameters #CD2010-00088

		Dose (mg/kg/Dose)				
		150		450		1500
Parameter	**Sex**	**Day 1**	**Day 28**	**Day 1**	**Day 28**	**Day 1**
AUC_{0-t} (µg*hr/mL)	Male	13.6	11.2	76.0	48.6	145
	Female	26.0	14.2	86.3	65.3	357
C_{max} (µg/mL)	Male	5.0	4.4	7.6	17	18
	Female	5.8	6.0	12.6	10.7	28.9
T_{max} (h)	Male	2	2	1	0.5	1
	Female	0.5	2	0.5	2	2

Source: FDA table from Applicant's study report data
Abbreviations: AUC_{0-t}, area under the curve up to the last quantifiable time-point; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Study #2010N104048/GSK2140944E: A 28-Day Twice Daily (BID) Oral Gavage Toxicity Study in the Beagle Dog Followed by a 2- or 9-Week Recovery Period

Key Study Findings

- Clinical signs at the high dose included decreased activity and partially closed eyes, and sporadic tremor, abnormal gait, and increased vocalization in a few animals. Tremor was observed once in the mid-dose. Timing of the tremors in the study report was vague and the relationship of the tremors to animals condition or to the test-article is uncertain. Emesis was observed at 125 mg/kg/day and above with increase in severity and frequency at the higher dose, though animals remained in good condition through the study, however, supplementary feed was required at the high dose. Emesis became more sporadic and less severe after the second week of dosing. No test-article related clinical signs were reported during the recovery period.
- NOAEL is 125 mg/kg/day because animals continued to eat and maintain body weights. The sex averaged exposures at this dose on the final day of dosing are with AUC_{0-t} = 144 µg*h/mL, C_{max} = 24.9 µg/mL
- Minimal dilation and slight basophilia and pigment deposits observed in scattered proximal renal tubules of one high dose male may be drug-related based on findings from previous toxicity studies.

Table 68. Study Information #2010N104048

Study Features and Methods	**Details**
GLP compliance:	Yes
Dose and frequency of dosing	0, 25, 62.5, and 125 mg/kg/dose twice daily for doses 6 hours apart leading to total daily doses of 0, 50, 125, and 250 mg/kg/day
Route of administration	Oral
Formulation/vehicle	1% methylcellulose
Species/strain	Dog/Beagle
Number/sex/group	3/sex/group
Age	Approximately 10 months
Satellite groups/unique design	2/sex/group control and high dose 2-week recovery 2/sex/group control and high dose 9-week recovery
Deviation from study protocol affecting interpretation of results	There were 1–2-day dosing holidays for 2 high dose dogs

Source: FDA table
Abbreviations: GLP, good laboratory practice

Table 69. Observations and Results #2010N104048

Parameters	Major Findings
Mortality	One control female was found dead on Day 40 of the recovery period, which was attributed to anesthetic administered before scheduled electroretinography. No cause of death was identified, and it was not considered test article related.
Clinical signs	Dose-related emesis and salivation were reported at doses 125 mg/kg/day and above and were more frequent during the first two weeks of dosing. Additional clinical signs seen occasionally in the high dose animals included tremor, abnormal gait, and increased vocalization. One mid dose female also had a single episode of tremor. On Day 2 of dosing, one high dose male exhibited an anaphylactoid reaction (periorbital swelling, red pinna, warm to touch, partially closed eyes, decreased activity). The animal was treated with an antihistamine (diphenhydramine). Red pinna and decreased activity were also noted in this dog on Days 25 and 29. Some of the high dose dogs were given electrolyte replacement to combat dehydration. The high dose would not have been tolerated for 28 days without the supplemental food and hydration.
Body weights	Most high dose female dogs and one high dose male lost 1.0-1.6 kg of body weight during the first week of dosing. These high dose dogs were offered supplemental diet for the remainder of the dosing period, and this appeared to stabilize their weight. One male in the mid dose group lost 0.8 kg over the same time period. The mid dose male's weight stabilized without food supplementation. During the 2-week recovery period, the high dose dogs gained weight.
Feed consumption	Decreased food consumption was observed in the high dose females and one high dose male during the first week of dosing. One female ate very little during this time. Supplemental diet was offered so that these animals could continue treatment. Food consumption improved or at least remained stable after supplemental diet was offered.
Ophthalmoscopy	No test-article related findings
Electroretinography	No test-article related findings
Electrocardiography	No test-article related findings
Hematology	No test-article related findings
Clinical chemistry	No test-article related findings.
Urinalysis	High dose male and mid and high dose females had 2-3-fold increases in protein excretion observed during Week 4. The investigators attributed this to the effect of GSK2140944 on the kidneys. There were no differences between treatment group after a 2-week recovery period.
Gross pathology	Small thymus was found in 1/3 females and 2/3 males in the high dose group and 1/3 females in the mid-dose group. This may be secondary to stress caused by nausea and vomiting that occurred in these dogs. Lymphoid depletion was noted upon microscopic evaluation of the thymus. One main group high dose female dog had gross changes to the gallbladder consistent with torsion.
Organ weights	Mean thymus weights in high dose males were about 60% less than controls.

Parameters	Major Findings
Histopathology Adequate battery: Yes	Slight (grade 2) basophilia of scattered proximal renal tubules was observed in 1/3 high dose males euthanized at the end of the dosing period. This was accompanied by minimal (grade 1) tubular dilation and slight pigment deposition. Minimal to slight lymphoid depletion of the thymus was seen in an animal from all treatment groups, including vehicle controls. However, moderate to marked (grade 3-4) lymphoid depletion of the thymus observed in 2/3 male and 1/3 female high dose dogs was considered related to treatment. This finding was likely associated with stress. There were microscopic lung changes (e.g., macrophage accumulation, inflammation, fibrosis of pleura) in some animals that appeared related to aspiration during emesis. Microscopic examination of the gallbladder of the high dose female that experienced torsion of this organ revealed chronic inflammation, necrosis, hemorrhage, and fibrosis. The pathologist considered that the fibrotic tissue adhesions between the gallbladder and diaphragm likely preceded the initiation of the study and may have predisposed the animal to gallbladder torsion. No test-article related microscopic findings were reported at recovery necropsies.
Stage-dependent evaluation of spermatogenesis	No test-article related findings

Source: FDA table

Toxicokinetics

- Emesis in the high dose animals did not appear to have reduced systemic exposure to GSK2140944.
- The compound was quantifiable in the blood for the 24-hour period of sampling on day 1 and day 28, each of which0 included 2 doses administered 6 hours apart.
- No apparent differences in toxicokinetic (TK) parameters between male and female dogs.
- No accumulation at the low or mid doses. There was <2-fold accumulation at the high dose.

Table 70. Toxicokinetic Parameters #2010N104048

		Dose (mg/kg/day)					
		50		125		250	
Parameter	Sex	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
AUC_{0-t} (µg*hr/mL)	Male	52.6	37.7	114	158	187	349
	Female	55.1	52.4	125	129	180	346
C_{max} (µg/mL)	Male	9.3	8.0	18.8	26.4	37.8	50.3
	Female	10.9	8.5	22.5	23.3	39.2	51.4
T_{max} (h)	Male	0.5	1	0.25	1	6.25	6.5
	Female	6.5	7	0.5	6.5	0.5	6.25

Source: FDA table
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time 0-t, C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Study #2013N160007 /GSK2140944E: A 13-week Oral (Gavage) Toxicity in Rats Followed by a 28-day Recovery Period

Key Study Findings

- The NOAEL in this study was 750 mg/kg/day, the highest dose tested, with a corresponding $AUC_{0\text{-}t}$ = 197 µg*h/mL and C_{max} = 25.8 µg/mL.

Table 71. Study Information #2013N160007

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 150, 350, or 750 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	1% (w/v) methylcellulose in water
Species/strain	Rat/Long Evans
Number/sex/group	10
Age	9-10 weeks at Day 1 of dosing
Satellite groups/unique design	6/sex/group for recovery groups control and high dose only 3/sex/group for TK groups
Deviation from study protocol affecting interpretation of results	None
Study design considerations	Doses selected based on toxicity in 4-week study at 1500 mg/kg/day

Source: FDA table
Abbreviations: GLP, good laboratory practice; TK, toxicokinetic

Table 72. Observations and Results #2013N160007

Parameters	Major Findings
Mortality	One high dose female was found dead on Day 25 due to a dosing error.
Clinical signs	Increased salivation was observed in some rats from all treated groups with increased incidence in the mid and high dose groups.
Body weights	No test-article related changes.
Feed consumption	No test-article related changes.
Ophthalmoscopy	No test-article related changes.
Hematology	No test-article related changes.
Clinical chemistry	At the high dose, 750 mg/kg/day, increased serum creatinine was observed in males at weeks 4 and 13 (1.28- and 1.34-fold greater than controls, respectively). Decreased mean serum triglycerides were observed in high dose males and females during Week 4 (0.68X, males and 0.74X, females) and at Week 13 (0.60X, males and 0.53X, females). Because these changes were minimal and no histopathological correlates were observed, the investigators did not consider them adverse.
Urinalysis	No test-article related changes.
Gross pathology	No test-article related findings.
Organ weights	No test-article related differences between groups.
Histopathology Adequate battery: Yes	No test-article related findings.

Source: FDA table

Toxicokinetics

- Levels of GSK2140944 were generally above the lower limit of quantification for at least 8 hours after dosing and frequently at 24 hours after dosing in the mid and high dose rats.
- Systemic exposure increased dose-proportionally.
- Exposure between males and females was similar (no difference greater than 2-fold) and were combined in the TK analysis shown below.

Table 73. Toxicokinetic Parameters #2013N160007

		Dose (mg/kg/Day)								
		150			350			750		
Parameter	**Sex**	**Day 1**	**Week 4**	**Week 13**	**Day 1**	**Week 4**	**Week 13**	**Day 1**	**Week 4**	**Week 13**
AUC_{0-t} (µg*hr/mL)	Combined	19.1	19.1	26.0	62.3	31.2	90.3	129	114	197
C_{max} (µg/mL)	Combined	6.8	5.9	7.0	12.1	10.7	17.5	19.5	16.5	25.8
T_{max} (h)	Combined	2	2	1.25	2	2	2	2	2	3

Source: FDA table
Abbreviations: AUC_{0-t}, area under the curve up to the last quantifiable time-point; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Key Study Findings

- At the high dose of 125 mg/kg/day a severe reduction (up to about 90%) in neutrophil count was seen in about half of the high dose females. A bone marrow smear showed an increase in granulocytic lineage cells, which suggests compensation. Recovery was reported after dosing stopped.
- A minimal to moderate increase in lymphocyte cellularity with lymphoid follicle formation was seen in the medulla of the thymus in some high dose dogs of both sexes. These microscopic findings in the thymus were not observed after the recovery period. This finding is of uncertain adversity and, therefore, uncertain clinical significance.
- NOAEL 60 mg/kg/day, which corresponds on day 91 to a sex averaged combined mean AUC = 82.3 µg*h/mL and C_{max} = 14.2 µg/mL

Table 74. Study Information #2013N160191

Study Features and Methods	**Details**
GLP compliance	Yes
Dose and frequency of dosing	0, 15, 30, and 62.5 mg/kg/dose twice daily leading to total daily doses of 0, 30, 60 and 125 mg/kg/day
Route of administration	Oral gavage

Study Features and Methods	Details
Formulation/vehicle	1% (w/v) methylcellulose in water
Species/strain	Dog/beagle
Number/sex/group	4
Age	10-11 months at initial dosing
Satellite groups/unique design	2/sex in recovery groups for the control and high dose groups only
Study design considerations	Dose was selected on 250 mg/kg/day exceeding the MTD in the 28-day study.
Deviation from study protocol affecting interpretation of results	None

Source: FDA table
Abbreviations: GLP, good laboratory practice; MTD, maximum tolerated dose

Table 75. Observations and Results #2013N160191

Parameters	Major Findings
Mortality	There were no unscheduled deaths.
Clinical signs	Excessive salivation beginning on Day 1 and throughout the dosing period was observed in most of the high dose group dogs and about half of the dogs in the mid and low dose groups. White/clear or foamy material was observed in the animals' trays throughout the study. It was seen in all dose groups, but the incidence was higher in the high dose males.
Body weights	Group mean body weights in the high dose females were 7%-8% less than controls from Week 8 to the end of dosing. Body weights at the end of recovery were similar to control animals.
Feed consumption	Feed consumption in high dose females was about 17% less than controls though most of the dosing period, which was driven by 2-3 dogs in the group. Recovery dogs in the high dose group increased their feed consumption to be similar to controls at during the recovery period.
Ophthalmoscopy	No test-article related findings were reported.
Electrocardiography	No test-article related findings were reported.
Hematology	Mean neutrophil count was reduced by about 45% in high dose females during Week 13 compared to pretreatment values, but it was primarily driven by the results of 3/6 dogs. Two of these animals had reductions in range of 30%-40%, but the third had a 90% reduction. Only one of these animals was assigned to the recovery group (it had about a 40% reduction during Week 13), and its neutrophil count returned to pretreatment levels at Week 17. Analysis of a bone marrow smear from the dog with the 90% reduction in neutrophil count did not demonstrate suppression; an increased number of cells from the granulocyte series with a slight increase in the proportion of early granulocytic precursors was observed, suggestive of compensation.
Clinical chemistry	During Week 13, mean urea was increased by about 20% in the high dose males, with reversal by the end of the recovery period. Decreased albumin was seen in 2 high dose females during Week 13, about a 40% reduction in the first animal and 14% reduction in the second. The first was not assigned to the recovery group, but the serum albumin level in the second dog returned to a pretreatment level by the end of recovery.

Parameters	Major Findings
Urinalysis	During Week 13, increased protein excretion in urine (mg/collection period) was observed in 2 high dose females (same dogs with decreased serum albumin), one 33-fold higher and the other 10-fold higher than pretreatment levels. The first animal was not assigned to the recovery group. Following recovery, urinary protein excretion in the second dog had returned to the pretreatment level
Gross pathology	Small thymus was observed in one low dose male and 2 high dose dogs (one male, one female). There was no microscopic correlated in the low dose dog. Decreased cortical lymphocyte cellularity was observed in the high dose dogs, but not considered drug related.
Organ weights	Mean absolute and relative thymus weights were decreased by 30%-40% in the mid dose male and high dose female dogs. At the end of the recovery period, mean absolute and relative thymus weights in high dose female dogs were 35%-42% higher than controls, but no macroscopic or microscopic differences were observed in this tissue.
Histopathology Adequate battery: Yes	Minimal to moderate increased lymphocyte cellularity in the medullary thymus observed in 3/4 female and 1/4 male dogs in the high dose group. Multifocal or diffuse expansion of the medulla was observed, with a pleomorphic population of small to larger lymphocytes and a variable number of lymphoid follicles with germinal centers. This change was not observed following the recovery period.

Source: FDA table

Toxicokinetics

- Levels of GSK2140944 were above the lower limit of quantification for at least 24 hours following the first daily dose.
- C_{max} occurred most frequently within an hour of the first daily dose, though C_{max} in some animals was seen an hour after the second daily dose on Days 28 and 91. In 2 different male dogs, one on Day 28 and the other on Day 91, C_{max} was seen 3 hours after the second daily dose.
- Systemic exposure increased dose-proportionally.
- Exposure between males and females was similar (no difference greater than 2-fold).

Table 76. Toxicokinetic Parameters #2013N160191

		Dose (mg/kg/Day)								
		30			60			125		
Parameter	Sex	Day 1	Week 4	Week 13	Day 1	Week 4	Week 13	Day 1	Week 4	Week 13
$AUC_{0\text{-}t}$ (µg*hr/mL)	Male	20.3	24.3	31.1	54.9	71.1	103	128	176	230
	Female	21.1	25.1	31.4	49.1	51.6	61.6	120	171	210
C_{max} (µg/mL)	Male	5.5	4.6	4.9	12.2	13.5	17.4	31.9	21.6	33.8
	Female	6.9	4.5	6.4	12.4	8.2	10.9	28.3	28.9	31.5

		Dose (mg/kg/Day)								
		30			60			125		
Parameter	**Sex**	**Day 1**	**Week 4**	**Week 13**	**Day 1**	**Week 4**	**Week 13**	**Day 1**	**Week 4**	**Week 13**
T_{max} (h)	Male	0.5	1	3.75	0.38	0.75	3.38	0.25	7	3.75
	Female	0.5	1	0.75	0.5	1	4	0.25	7	4

Source: FDA table
Abbreviations: AUC_{0-t}, area under the curve up to the last quantifiable time-point; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Study #2017N327116/GSK2140944B: A 28-Day Oral (Gavage) Impurity Qualification and Toxicity Study in Rats

Key Study Findings

- In a GLP study, Long Evans rats were administered 0, 350 or 750 mg/kg/day gepotidacin in 1% (w/v) aqueous methylcellulose in 0.1 N hydrochloric acid vehicle, by oral gavage (N = 10/sex/group in the main study groups). The study was intended to qualify impurities identified following manufacture of gepotidacin.
- Test article related findings of microscopic findings in the nasal cavity appeared related to reflux after gavage dosing, rather than specifically related to GSK2140944. Cecal dilation observed on gross necropsy has been observed with other antimicrobials as well. The reduction in serum glucose (female rats only) was of small magnitude, and the increases in urinary excretion of protein seen in high dose animals and glucose observed at both dose levels were not accompanied by any changes in serum chemistry parameters or histopathology that would suggest they are adverse.
- The NOAEL for the study was 750 mg/kg/day, the highest dose tested with exposures on the final day of dosing of AUC_{0-t} = 167 µg*h/mL, C_{max} = 25.8 µg/mL.

Toxicokinetics

- There were 6 animals/sex/group in gepotidacin groups and 3/sex/group in the vehicle control for the TK animals.
- Blood samples were collected at 0.5, 1, 2, 4, 8, and 24 hours after dosing with gepotidacin and 0.5 and 2 hours after administration of vehicle (controls).
- There were not marked sex differences in systemic exposures, so sexes were combined for toxicokinetic parameter analysis.

Table 77. Toxicokinetic Parameters

		Dose (mg/kg/dose)			
		350		750	
Parameter	**Sex**	**Day 1**	**Day 28**	**Day 1**	**Day 28**
AUC_{0-t} (µg*hr/mL)	Combined	84	64	147	167
C_{max} (µg/mL)	Combined	19.5	14.3	24.3	25.8
T_{max} (h)	Combined	2	2	2	0.5

Source: FDA table
Abbreviations: AUC_{0-t}, area under the concentration-time curve up to the last quantifiable time-point; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

13.1.4.2. Genetic Toxicology

- Gepotidacin was cytotoxic to *Salmonella typhimurium* and *Escherichia coli* and therefore an Ames assay was determined to not be a useful assay.
- An in vitro mutation assay with L5178Y mouse lymphoma cells at the TK locus was positive with a preponderance of small colonies. Small colonies have been shown to result from chromosomal breakages. A quantitative structure-activity relationship ((Q)SAR) analysis of the gepotidacin molecule did not indicate any structural alerts. A weight of evidence, therefore, indicates low risk of mutagenicity from gepotidacin.
- An in vitro micronucleus test in human peripheral blood lymphocytes was positive.
- An in vivo rat micronucleus assay and comet assay was negative for both endpoints.
- Other classes of drugs with the same target of topoisomerase inhibition (fluroquinolones) also have been seen to be positive in in vitro mammalian assays for chromosomal aberrations based on the high concentration and the mechanism of action. These classes have not been shown to cause chromosomal damage in vivo or to be carcinogenic when tested in rodents.
- Based on a weight of evidence, taking in vitro and in vivo data into consideration, gepotidacin is unlikely to pose a risk for genotoxicity to patients.

Table 78. Genetic Toxicology: In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Features and Methods	Details
Study number	8223596
Study title	GSK2140944E: Bacterial Toxicity Assay with *Salmonella typhimurium* and *Escherichia coli*
Conducting laboratory	(b) (4)
GLP compliance	Yes
Drug, lot number, % purity	GSK2140944E, Batch 2140944E-B-01P, 93% pure
Strains:	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA*
Concentrations in the definitive study/method	50-5000 µg/plate
Basis of concentration selection	Standard
Formulation/vehicle	DMSO
Results	The bacteria were completely wiped out even at 50 µg/plate. Therefore, this study design is inappropriate for this compound.
Validity	Uninterpretable

Source: FDA table
Abbreviations: DMSO, dimethyl sulfoxide; GLP, good laboratory practice

Table 79. Genetic Toxicology: In Vitro Mutation Assay With L5178Y Mouse Lymphoma Cells at the TK Locus

Study Features and Methods	Details
Applicant study number	V29136
Conducting laboratory study number	8223597
Study title	GSK2140944E: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus
Conducting laboratory	(b) (4)
GLP compliance	Yes
Drug, lot number, % purity	GSK2140944E, Batch 2140944E-B-01P, 93% pure
Cell line	L5178Y $TK^{+/-}$ mouse lymphoma cells
Concentrations in the definitive study	3-hour incubation: 300, 600, 1200, 1500, 1800, and 2220 µg/ml 24-hour incubation: 100, 200, 300, 350, 400, 450, and 500 µg/ml
Basis of concentration selection	3-hour incubation: solubility; 24-hour incubation: cytotoxicity
Negative control	DMSO
Positive control	Methyl methane sulfonate (no S9, 15 µg/ml for 3 hours and 5 µg/ml for 24 hours) Benzo[a]pyrene (with S9, 2 µg/ml)
Formulation/vehicle	DMSO
Incubation and sampling time	Cells were treated with drug (duplicate cultures) or vehicle (quadruplicate cultures) for 3 or 24 hours in the absence of metabolic activation or for 3 hours in the presence of S9 from Aroclor-treated rats. At the end of treatment, cells were washed, suspended in growth medium and incubated for a 2-day expression period. After this, cultures were aliquoted into 96 well plates + TFT in the culture medium to determine total viability and mutation frequency. Cell viability in the absence of TFT was determined after at least 3 days of incubation and mutation frequency.
Results	GSK2140944E caused a concentration-dependent increase in mutation frequency in L5178Y $TK^{+/-}$ mouse lymphoma cells regardless of treatment time (3 hours vs. 24 hours) or metabolic activation. The predominance of small colonies over large colonies suggests clastogenic activity.
Validity	Controls yielded expected results. Formulation analysis showed concentrations withing acceptable limits. Doses and mean relative total growth were acceptable. The study was valid.

Source: FDA table
Abbreviations: DMSO, dimethyl sulfoxide; GLP, good laboratory practice; TFT, trifluorothymidine; TK, thymidine kinase

Table 80. Genetic Toxicology: In Vitro Micronucleus Test in Human Peripheral Blood Lymphocytes

Study Features and Methods	Details
Applicant study number	V29137
Conducting laboratory study number	8223598
Study title	GSK2140944E: In Vitro Chromosome Aberration Assay with Cultured Human Peripheral Blood Lymphocytes
Conducting laboratory	(b) (4)
GLP compliance	Yes
Drug, lot number, % purity	GSK2140944E, Batch 2140944E-B-01P, 93% pure
Cell line	Peripheral blood lymphocytes from 3 healthy non-smoking male volunteers, stimulated with PHA
Concentrations in the definitive study	3-hour incubation: 150-2220 µg/ml; 20-hour incubation: 100-1400 µg/ml
Basis of concentration selection	3-hour incubation: solubility; 20-hour incubation: cytotoxicity
Negative control	DMSO
Positive control	4-Nitroquinoline 1-oxide (no S9, 5 µg/ml for 3 hours) Cyclophosphamide (with S9, 10, 20, and 30 µg/ml)
Formulation/vehicle	DMSO
Incubation and sampling time	Cells were treated with drug (duplicate cultures) or vehicle (quadruplicate cultures) for 3 or 20 hours in the absence of metabolic activation or for 3 hours in the presence of S9. At the end of the 3-hour treatments, cells were washed, resuspended in fresh medium and incubated for an additional 17 hours prior to harvest. Colchicine was added to the cultures 2 hours prior to harvest. All cells were harvested 20 hours after the initiation of drug or vehicle treatment. Slides were coded and scored by an evaluator blinded to treatment. At least 1000 cells per culture were scored for mitotic index. In the main study, 100 metaphase spreads per culture were scored for chromosome aberrations (total of 400 for vehicle and 200 for each drug concentration).
Concentrations evaluated in the definitive study	3-hour treatments with or without S9: 1500, 1800, and 2200 µg/ml 20-hour treatments without S9: 100, 600, and 1000 µg/ml
Results	At concentrations >600 µg/ml, GSK2140944 induced chromosome aberrations in cultured human lymphocytes after 20 hours of treatment in the absence of metabolic activation. Chromosome aberrations were not induced after 3 hours of incubation regardless of metabolic activation at concentrations up to 2220 µg/ml.
Validity	Controls yielded expected results. Formulation analysis showed concentrations within acceptable limits. Doses and reductions in mitotic indices were acceptable. The study was valid.

Source: FDA table
Abbreviations: DMSO, dimethyl sulfoxide; GLP, good laboratory practice; PHA, phytohaemagglutinin

Table 81. Genetic Toxicology: In Vivo Micronucleus Assay and Comet Assay in Rat

Study Features and Methods	Details
Applicant study number	R29138
Conducting laboratory study number	8223599
Study title	GSK2140944E: Oral Combined Liver Comet and Bone Marrow Micronucleus Assay in Rats
Conducting laboratory	(b) (4)
GLP compliance	Yes
Drug, lot number, % purity	GSK2140944E, Batch 2140944E-B-01P, 93% pure
Species/strain	Rat/ Sprague Dawley
Number/sex/group	6 males/dose group; 3 satellite animals for TK to confirm exposure
Doses in the definitive study	1000 or 2000 mg/kg/day
Basis of dose selection	Recommended limit for assay
Negative control	Vehicle (1% methylcellulose)
Positive control	200 mg/kg/day EMS
Formulation/vehicle	1% methylcellulose
Results	At doses up to 2000 mg/kg (given orally once daily for 3 days), GSK2140944 did not induce micronuclei in polychromatic erythrocytes in rat bone marrow and did not induce DNA damage in hepatocytes harvested from rats.
Validity	Adequate doses of test article were administered and there was shown to be systemic circulation. Adequate animals were available for analysis. Excessive cytotoxicity was not observed in bone marrow or liver single cell suspensions. Vehicle controls were within historical control ranges for both assays and positive controls showed clear positive responses. Formulation analysis showed concentrations that were within the expected ranges.

Source: FDA table
Abbreviations: DMSO, dimethyl sulfoxide; EMS, ethyl methanesulfonate; GLP, good laboratory practice; TK, thymidine kinase

13.1.4.3. Carcinogenicity

No studies were available.

13.1.4.4. Reproductive Toxicology

2014N217705 /GSK2140944E: Oral Male and Female Fertility and Early Embryonic Development Study in Rats

Key Study Findings:

- The NOAEL for GSK2140944E on male and female fertility and early embryonic development in rats was the highest dose tested, 750 mg/kg/day.

Table 82. Method of Fertility and Early Embryonic Development (FEED) in Rats

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 150, 350, and 750 mg/kg/day expressed as free base, once daily
Dosing days	15 days prior to cohabitation, cohabitation (1-6 days), and until gestation day (GD) 6 (females) or day 46 (males); On GD 20, litters were delivered by cesarean section and dams were euthanized.
Route of administration	Oral gavage
Formulation/vehicle	1% (w/v) aqueous methylcellulose
Species/strain	Rat/Long Evans (Crl:LE)
GLP compliance	Yes
Number/sex/group	22
Study design	Estrus cycle data was collected daily for females for 14 days prior to the initiation of dosing and for 14 days beginning after the initiation of dosing and ending when there was evidence of copulation. Rats were dosed for 15 days prior to 1:1 cohabitation, during cohabitation (all pair copulated within 1-6 days), and until GD 6 for mated females and the day prior to euthanasia dosing Day 46 for males. On GD 20, litters were delivered by cesarean section and dams were euthanized. Doses were chosen based on results of previous repeat dose rat studies.
Deviation from study protocol affecting interpretation of results	None

Source: FDA table
Abbreviations: DMSO, dimethyl sulfoxide; GLP, good laboratory practice

Table 83. FEED Observations and Results

Parameters	Major Findings
Mortality	No test-article related mortality
Clinical signs	Excess salivation was observed in male and female rats that received ≥ 350 mg/kg/day of GSK2140944E. In most animals, it was seen on only 1 or 2 days, but the investigators considered it drug-related based on previous repeat-dose toxicity studies in rats with this compound. At the high dose of 750 mg/kg/day, urine staining of abdominal fur was observed primarily in female rats during the initial period of cohabitation (study Days 16-18) and resolved shortly after mating was completed
Body weights	No treatment related effects on male body weights. In females, an increase in mean body weight gain during dosing days 1-15 in all drug-treated groups (1.29X, 1.39X and 1.64X of control at 150, 350, and 750 mg/kg/day, $p<0.05$) was reported. Mean body weight gain during pregnancy was similar between control and drug-treated dams, however.
Fertility parameters	There were no effects on the reproductive performance in the male or female animals. The mean frequency of estrus was similar between groups. Other measured parameters were similar between groups.
Necropsy findings	No test article related findings were reported at necropsy.
Cesarean section data	Mean numbers of corpora lutea, implantation sites, resorptions, live/dead fetuses, fetal body weights, gravid uterine weights, and sex ratio of offspring were similar between groups. No differences in placental morphology or external fetal malformations were reported.

Source: FDA table
Abbreviations: DMSO, dimethyl sulfoxide; FEED, fertility and early embryonic development

2012N139462 / GSK2140944E: Oral Embryo-Fetal Development Study in Rats (GlaxoSmithKline Study No.: G12101) Amended Report

Key Study Findings:

- The NOAEL was 150 mg/kg/day, based on slight reduction in mean fetal body weights observed in both male and female fetuses at ≥450 mg/kg/day.
- No malformations or variations that appeared related to GSK2140944E were observed at 450 or 750 mg/kg/day, the mid and high doses in this study.
- Maternal toxicity was not observed, but the high dose was acceptable based on results of a 1 month repeat dose oral toxicity study in Long-Evans (LE) rats where unscheduled mortality was observed at 1500 mg/kg/day.

Table 84. Method of Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 150, 450, or 750 mg/kg/day, expressed as free base Once daily, GD 6-17
Route of administration	Oral gavage
Formulation/vehicle	1% aqueous methylcellulose
Species/strain	Rat/ Long-Evans (Crl:LE)
GLP compliant	Yes
Number/sex/group	22 mated
Satellite groups	None
Study design	High dose selection based on 1500 mg/kg exceeding the MTD in a 4-week study. The study included two vehicle control groups as there are limited amounts of historical control data. Rats were euthanized on GD 21, and fetuses delivered by cesarean section. A total of 10 male and 10 female fetuses from each treatment group (each from a different litter) were decapitated and heads preserved for possible microscopic examination of the eyes.
Deviation from study protocol affecting interpretation of results	No

Source: FDA table
Abbreviations: GD, gestational day; GLP, good laboratory practice; MTD, maximum tolerated dose

Table 85. Observations and Results of Embryo-Fetal Developmental Study in Rats

Parameters	Major Findings
Mortality	There were no drug related deaths. One control rat was found dead on GD 8 due to a dosing accident.
Clinical signs	No clinical signs of toxicity were reported.
Body weights	Maternal weight gain was not different between groups.
Feed consumption	Transient reductions in food consumption were observed at the mid and high doses during GD 6-9 (9% and 12%, respectively). Thereafter, the groups treated with GSK2140944E tended to eat slightly more food than controls.
Maternal necropsy findings	No treatment related findings were reported.
Cesarean section data	One high dose female delivered one pup just prior to scheduled euthanasia, with the rest of the litter delivered by cesarean section. Uterine weight was not recorded but otherwise the pups/fetuses were examined as scheduled.
Offspring terminal observations	Mean fetal body weights were statistically significantly reduced compared to control group 1 for the mid-dose (4% reduced for males and 5% for females) and high dose (7% reduction for males, 6% for females). Compared to control group 2, the high dose was statistically significantly reduced (5% for males and 3% for females), at the mid-dose both males and females were 3% lower in weight, which was not statistically significant.
Offspring necropsy finding	There were no test-article related external, visceral, or skeletal malformations or variations.

Source: FDA table
Abbreviations: GD, gestational day

2012N139463 / GSK2140944E: Oral Embryo-Fetal Development Study in Mice

Key Study Findings:

- The increase in late resorptions at the high dose of 1000 mg/kg/day may also be indicative of fetal toxicity, although it was at the high end of the historical control range for this strain of mouse, as the concurrent control carries greater weight, and the increase was statistically significant compared to the control group ($p<0.01$).
- No malformations or variations that appeared related to GSK2140944E were observed at 500 or 1000 mg/kg/day, the mid and high doses in this study.
- The NOAEL is the low dose of 200 mg/kg/day, based on slight reduction in mean fetal body weights observed in both male and female fetuses at ≥ 500 mg/kg/day.

Table 86. Method of Embryo-Fetal Developmental Study in Mice

Parameter	Method Details
Dose and frequency of dosing:	0, 200, 500, and 1000 mg/kg/day, expressed as free base. Dosed once daily GD 6-15
Route of administration:	Oral gavage
Formulation/vehicle:	1% aqueous methylcellulose
Species/strain:	CD-1 (Crl:CD-1[Icr])
GLP compliant	Yes
Number/sex/group:	26 mated females (phase 1) 15 mated females (phase 2)
Study design:	Dose selection was based on nonpregnant female CD-1 mice receiving oral GSK2140944E at doses of 200, 500, or 1000 mg/kg/day for 10 days and showing no signs of clinical toxicity, including decreases in body weight gain or food consumption. A dose of 1000 mg/kg is generally considered an adequate limit dose. Data from naturally delivered litters was excluded from analysis which included 4, 8, 5, and 3 litters in the vehicle, low, mid, and high dose groups, respectively. During phase 2, only one high dose dam delivered naturally.
Deviation from study protocol affecting interpretation of results:	The study was conducted in 2 phases because many animals in phase 1 were determined not to have been pregnant after termination and several delivered their litters prior to scheduled euthanasia. This occurred across treatment groups and did not appear related to drug. Reviewer wonders if the supplier of the pregnant mice was mistaken about the date of conception of a significant number of animals in the phase 1 shipment. Excessive feed crumbing was noted and may have caused inaccurate feed consumption measurements for up to 6, 6, 3, and 10 dams in the control, low, mid, and high dose groups over both phases.

Source: FDA table
Abbreviations: GD, gestational day

Table 87. Observations and Results of Embryo-Fetal Developmental Study in Mice

Parameters	Major Findings
Mortality	There was no test-article related mortality.
Clinical signs	No signs of maternal toxicity were reported.
Body weights	No test-article related body weight changes were reported.
Feed consumption	Feed consumption was increased in the mid and high dose groups, of 15% and 24%, respectively, with statistical significance at the GD 12-16 interval.
Necropsy findings	No test-article related findings in the dams was reported in the gross necropsy.
Cesarean section data	The mean number of late resorptions was greater in high dose litters compared to vehicle control; the high dose at the outer limit of the historical control range for this strain of mouse. Mean % post-implantation loss was greater at the high dose of 1000 mg/kg (7.24% vs. 10.79%). As fetal body weights in the mid and high dose groups were statistically significantly lower than controls, the investigators considered the increases in late resorptions at the mid dose and the increases in late resorptions and post-implantation loss at the high dose possibly indicative of fetal toxicity.
Necropsy findings Offspring	Mean fetal body weights were reduced by 4% and 5% in male and female fetuses in the 500 mg/kg (mid dose) group compared to control ($p<0.05$) and by 7% at 1000 mg/kg (high dose) ($p<0.01$). There were no treatment related external, visceral, or skeletal malformations or variations.

Source: FDA table
Abbreviations: GD, gestational day

2019N408359 / GSK2140944E: Oral Critical Window Embryo-Fetal Development Study in Mice

Key Study Findings:

- GSK2140944 was not associated with an increase in late resorptions when administered only from GD 6 to 9 (early critical period).
- A similar reduction (7-8 %) in mean fetal body weight compared to control was observed as with longer dosing from GD 6 to 15.
- There was no evidence of maternal toxicity.

Table 88. Method of Critical Window Embryo-Fetal Developmental Study in Mice

Parameter	Method Details
Dose and frequency of dosing	0 and 1000 mg/kg/day, expressed as free base Once daily from GD 6-15
Route of administration	Oral gavage
Formulation/vehicle	1% aqueous methylcellulose
Species/strain	Mouse/CD-1 (Crl:CD-1[Icr])
GLP compliant	Yes

Parameter	Method Details
Number/sex/group	22 mated females/group
Study design	The study was designed to determine whether early embryonic exposure (GD 6-9 dosing) could produce late resorptions as had been observed in the definitive developmental toxicity in mice where the dams were dosed from GD 6-15. Mice were euthanized on GD 18 and fetuses delivered by cesarean section. Body weights of live fetuses were recorded and sex was determined. They were not examined further.
Deviation from study protocol affecting interpretation of results	There were no deviations from the study protocol that would be expected to affect the outcome.

Source: FDA table
Abbreviations: GD, gestational day; GLP, good laboratory practice

Table 89. Observations and Results in Critical Window Embryo-Fetal Developmental Study in Mice

Parameters	Major Findings
Mortality	No drug related mortality. One dam delivered naturally prior to scheduled cesarian section; this was within the historical control range of the laboratory.
Clinical signs	No signs of maternal toxicity.
Body weights	No differences in maternal body weights or body weight gains between groups.
Feed consumption	No treatment-related changes.
Necropsy findings	No treatment-related maternal gross pathology.
Cesarean section data	GSK2140944E did not have any effects on numbers of implantation sites, live fetuses per litter, or late resorptions (or the percentage of late resorptions). No effects were seen on sex ratio, gravid uterine weight, or placental morphology. The mean number of late resorptions per litter did not differ significantly between the control and 1000 mg/kg groups and both were within the historical control range. This contrasts with the pivotal mouse developmental toxicity study (above) where an increase in the mean number of late resorptions was seen in mice dosed with 1000 mg/kg/day from GD 6-15.
Necropsy findings Offspring	Mean fetal body weights were reduced by 7%-8% at 1000 mg/kg ($p<0.01$), similar to what was observed at this dose level in the pivotal mouse developmental toxicity study (above) and considered indicative of GSK2140944E-related fetotoxicity.

Source: FDA table
Abbreviations: GD, gestational day

2020N438276 / GSK2140944E: Oral Developmental and Perinatal/Postnatal Reproduction Study in Mice, Including a Postnatal Behavioral/Functional Evaluation

Key Study Findings:

- Oral administration of GSK2140944 at doses up to 1000 mg/kg/day given to mouse dams from GD 6- LD 20 did not result in maternal toxicity (F0) or adverse effects on their offspring (F1).
- There were no drug related adverse effects in the F1 including survival, growth, early physical development, neurological development, sexual maturation, learning and memory, or reproductive capacity.

- Plasma TK data from the F1 confirmed their exposure to the drug via milk during the lactation period.
- In addition, no adverse effects were observed in the F2 generation up to postnatal day 7.
- The NOAEL was 1000 mg/kg/day, the highest dose tested.

Table 90. Method of Pre- and Postnatal Development Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0 (vehicle), 200, 500 or 1000 mg/kg/day (expressed as free base) Once daily from GD 6 to LD 20
Route of administration	Oral gavage
Formulation/vehicle	1% (w/v) aqueous methylcellulose
Species/strain	Mouse/ Crl:CD-1[ICR]
GLP compliant	Yes
Number/sex/group	24 dams/F_0 group
Study design	Dams that did not deliver a litter by GD 23 were euthanized. On PND 10, 3 pups/sex/group/timepoint were selected for blood collection at 3, 8, and 22 hours after maternal dosing to determine plasma concentration of GSK2140944. On PND 21, pups were weaned and F_0 dams were euthanized and necropsied. Two F_1 pups/sex/litter were assigned to subset 1 or subset 2 for postweaning evaluation. Subset 1 was evaluated for acoustic startle (PND 60-62), estrous cycle, and reproductive capacity (beginning PND 80-90). Subset 2 was evaluated for acoustic startle (PND 27-29), FOB (PND 50±2 days), motor activity (PND 54-61), and Morris water maze (beginning PND 62-80). For reproductive capacity testing of F1, males and females from different litters in the same dose group were cohabited 1:1 for up to 14 days beginning around PND 80-90. Estrus cycle was evaluated in females for at least 14 days prior (alternate male could be provided after 7 days without mating, pending availability). The day a vaginal plug or vaginal smear containing sperm was seen was considered GD 0. Mated F_1 females were allowed to deliver naturally, and the dams and their litters were evaluated until PND 7.
Deviation from study protocol affecting interpretation of results:	No deviations that would be expected to affect study results.

Source: FDA table
Abbreviations: FOB, functional observational battery; GD, gestational day; LD, lactation day; PND, postnatal day

Table 91. Study Findings (F_0 Generation)

Parameters	Major Findings
Mortality	No test-article related deaths. One control dam was euthanized on LD 7 due to an eye injury. One control female delivered 10 stillborn pups on GD 17 and was subsequently euthanized.
Clinical signs	No test-article related clinical signs or effects on nesting or nursing behaviors.
Body weights	No test article related effects.
Feed consumption	No test article related effects.
Pregnancy status	1, 1, 4, and 3 females in the control, 200, 500, and 1000 mg/kg groups that were not pregnant. No effects on gestation length, number of pups/litter, viable pups/litter, or stillborn pups/litter were observed.
Necropsy findings	No test article related gross changes.

Source: FDA table
Abbreviations: GD, gestational day; LD, lactation day

Table 92. Study Findings (F_1 Generation)

Parameters	Major Findings
Mortality	Post-weaning mortality was not associated with the drug. On PND 27 or 30, one female in the low dose group, and one male and female in the mid-dose group were found dead, but no clinical signs were noted, and no gross findings were reported on necropsy. On PND 101, one 200 mg/kg male was euthanized due to adverse clinical signs including thin fur and scabbing in different areas of the body and an ulcerated abrasion on the neck with severe dermatitis.
Clinical signs	No differences between groups.
Body weights	Body weights and body weight gains were similar across groups.
Physical development	No drug-attributable adverse changes were reported.
Sexual maturation	Vaginal patency in mid and high dose females was significantly later than concurrent controls, but all were within the historical controls, with the control group in the early part of the range. The difference was therefore not considered toxicologically significant.
Behavior and activity	Early attainment of startle response to auditory stimuli and normal pupil constriction response were similar across groups. No significant differences were seen in the functional observational battery, in locomotor activity tasks or in learning and memory tasks.
Toxicokinetics	Plasma samples were collected from F_1 pups on PND 10. Gepotidacin was detectable in the serum at all the dose levels and time points (3, 8 and 22 hours), with the exposure to the F_1 animals only through milk. **Table 93. Combined Male and Female F_1 pup Toxicokinetic Parameters** Combined Male and Female F_1 Pup Mean Concentration of GSK2140944 at 3, 8, and 22 Hours Post Maternal Dose on PND 10 (ng/mL) 3 Hour: Mean / Standard Deviation; 8 Hour: Mean / Standard Deviation; 22 Hour: Mean / Standard Deviation 200 mg/kg/day: 31.6 / 9.64; 53.3 / 13.9; 9.46 / 3.28 500 mg/kg/day: 300 / 340; 263 / 190; 363 / 705 1000 mg/kg/day: 443 / 303; 720 / 629; 313 / 160 Source: Study report page 46. Abbreviation: PND, postnatal day
Mating, fertility, and pregnancy parameters	No effects of gepotidacin on fertility were reported. No changes in gestation, parturition, or lactation were observed in the F_1 dams. All pregnant animals delivered litters that appeared healthy and well cared for.

Source: FDA table
Abbreviation: PND, postnatal day

Table 94. Study Findings (F_2 Generation)

Parameters	Major Findings
Malformations	No malformations were reported.
Litter size	Litter size was similar across groups.

Parameters	Major Findings
Survival	Survival was similar across groups.
Pup weights	Pup weights were similar across groups.

Source: FDA table

2012N141031 / GSK2140944E: Oral Investigative Tolerability/Dose Range Study in Juvenile Long-Evans Rats

Key Study Findings:

- No juvenile-specific toxicities were observed. Based on previous detection of effects on joints from fluoroquinolones, the juvenile rats were examined and found not to have lesions in the cartilage or bone of weight-bearing joints (femoro-tibial joints from hindlimbs) in LE rats treated from postnatal Days 4 through 35 at doses approaching an MTD.
- The highest dose completed was 300 mg/kg/day from postnatal days 4 through 21, escalated to 1250 mg/kg/day for postnatal days 22 through 35.

Table 95. Method of Juvenile Dose-Range Finding Study in Rats

Parameter	Method Details
Dose and frequency of dosing	Round 1 (tolerability): 1, 10, 100, and 1000 mg/kg/day. Doses selected based on results of a 4-week repeat dose toxicity study in adults of the same species/strain. Round 2 (dose ranging/escalation): 0 (vehicle control), 30/300, 300/1000, and 1000/1500 mg/kg/day. Increased doses were given starting on postnatal Day 22 because TK data from Round 1 showed reduced exposure on postnatal Day 21 compared to postnatal Day 13. Round 3 (second escalation): 0 (vehicle control), 100/1000, and 300/1250 mg/kg/day. Doses selected due to excessive toxicity at the high dose in Round 2. Dosing: once daily
Dosing days	Round 1: Postnatal Days 4-21 Rounds 2 and 3: Postnatal Days 4-35/32
Route of administration	Oral gavage
Formulation/vehicle	1% aqueous methylcellulose
Species/strain	Rat/Long Evans
GLP compliance	No
Number/sex/group	Main study:12 (from the 3 litters assigned to each dose group) in Rounds 1 and 3, 20 in Round 2 TK: 2 per timepoint for Round 1 and 2-3 per timepoint for Rounds 2 and 3

Parameter	Method Details
Study design	Pups came from time-mated 10-week-old females. To reduce maternal stress, there were no disruptions during active littering and pups were not examined until postnatal Days 3-4 . Litters containing more than 8 pups were culled to 8 pups, 4 of each sex when possible. There was no fostering. Litters were randomly assigned to a dam through the lactation period ending at weaning on postnatal Day 21 and as a group until postnatal Day 28, then housed 2-3 per box until the end of the study. Round 2 dose groups had an inadvertent dosing holiday (due to bad weather conditions) on either postnatal Days 32-33 or 32-34. All animals in treatment Rounds 2 and 3 were euthanized on the last day of dosing (Day 35 or 32, respectively) and underwent necropsy and tissues (eyes/optic nerves, femoro-tibial joints of hindlimbs, and femoral heads with cartilage) were removed from designated pups (6/sex) in each group at the end of the study treatment group and housed together.

Source: FDA table
Abbreviations: GLP, good laboratory practice; TK, toxicokinetic

Table 96. Round 1 Observations and Results

Parameters	Major Findings
Mortality	No treatment related mortality
Clinical signs	1000 mg/kg: loose feces/fecal stained fur.
Body weights	1000 mg/kg: mean pup body weight gain was reduced during postnatal Days 4-7 compared to other groups
Gross examinations of eyes/optic nerve and cartilage and bone of weight bearing joints	No adverse test article related findings.
Microscopic exam of cartilage and bone of weight bearing joints	No adverse test article related findings.

Source: FDA table

Table 97. Round 2 Observations and Results

Parameters	Major Findings
Mortality	1000 mg/kg/day: 5 males/8 females from 4 litters were found dead or missing on postnatal Days 5-9 and the dose group was terminated on postnatal Day 21 due to excessive toxicity. 300/1000 mg/kg/day group: 3 pups from a single litter were missing or found partially cannibalized, but attributed to poor maternal behavior and not the test article
Clinical signs	1000 mg/kg: Loose feces/fecal stained fur.
Body weights	1000 mg/kg: mean pup body weights were reduced postnatal Days 4-21 30/300 mg/kg and 300/1000 mg/kg: increased weight gain compared to controls during postnatal Days 4-21

Parameters	Major Findings
Gross examinations of eyes/optic nerve and cartilage and bone of weight bearing joints	Gross necropsy of the premature decedents during Round 2 did not reveal any visceral abnormalities. No adverse test article related findings.
Microscopic exam of cartilage and bone of weight bearing joints	No adverse test article related findings.

Source: FDA table

Table 98. Round 3 Observations and Results

Parameters	Major Findings
Mortality	300/1250 mg/kg/day: a single female pup found cannibalized on postnatal Day 13, which was not considered test article related
Clinical signs	No treatment related adverse effects
Body weights	No treatment related effects
Gross examinations of eyes/optic nerve and cartilage and bone of weight bearing joints	No adverse test article related findings.
Microscopic exam of cartilage and bone of weight bearing joints	No adverse test article related findings.

Source: FDA table

Toxicokinetics

- At the maximum tolerated dose of 300/1250 mg/kg/day, for postnatal days 13, 22, and 32, the AUCs were 252, 128 and 107 µg*hr/mL, and C_{max} values were 29.2, 18.6 and 14.5 µg/mL, respectively.

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13.1.4.6. Other Toxicology

Study # 2012N149232/ Evaluation of in vitro phototoxicity on Balb/c 3T3 fibroblasts using the Neutral Red Uptake assay

Key Study Findings

- Mouse fibroblasts (Balb/c 3T3 clone A31) were treated with GSK2140944 E at concentrations of 0.316 to 1000 μg/mL (as free base) in phosphate-buffered saline. Cultures were incubated with test article for 60 minutes at 37°C in the dark, following which one plate was irradiated with ultraviolet-A (UV-A) light for 100 minutes, 14 seconds to achieve a dose of 5 J/cm^2 and the other plate was wrapped in foil and kept in the dark. Following additional incubation and treatment with neutral red, a photo-irritation factor or mean photo effect was calculated.
- In the absence of UV-A light, gepotidacin was not cytotoxic, so the IC_{50} and photo-irritation factor were not calculated. In the presence of UV-A light neutral red uptake was decreased and permitted a calculation of IC_{50} and mean photo effect, indicating a phototoxic response.

Study # 2014N208368/ GSK2140944E: 7-Day Phototoxicity Study in the Female Long-Evans Pigmented Rat

Key Study Findings

- In a GLP study, 9-week-old Long-Evans rats were administered gepotidacin (150, 350 and 750 mg/kg/day by oral gavage in 1% methylcellulose once daily for 7 days) or 8-methoxypsoralen administered once 50 mg/kg on day 7 one hour before UV radiation exposure. On day 7 the mice were exposed to 10.3 J/cm2 of UV-A and 145 mJ/cm2 UV-B and over a period of 42 minutes on an area of the back that had the hair removed.
- No phototoxicity was observed up to the highest dose tested of 750 mg/kg/day for 7 days. Skin lesions (grade 1 erythema and grade 1 edema) were observed in animals administered 8-methoxypsoralen .

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Pharmacology

Secondary Pharmacology

In an in vitro functional assay, gepotidacin did not act as an M3 agonist, and 50% inhibition of activity was not reached in an antagonist activity (#2013N15814). Gepotidacin, at concentrations up to 1 mM, was tested in vitro for acetylcholinesterase enzyme inhibition. The mean IC_{50} for gepotidacin against acetylcholinesterase was 10.7 μM. Maximal inhibition was reported from 100 μM to the top concentration tested in the assay, 1mM (#2013N172406). Inhibition of acetylcholinesterase in a fluorescent assay showed that the inhibition was reversible (#2013N172400).

13.2.2. Safety of Impurities

Article I. Specified impurities were adequately qualified using levels in nonclinical toxicology studies or using risk assessment read-across to gepotidacin.

Article II. 13 potential impurities that were identified by (Q)SAR as potentially mutagenic will be sufficiently purged during processing.

Article III. Four chemicals were identified as (Q)SAR positive for which bacterial reverse mutation (Ames) assays were provided that demonstrate that they are not mutagenic.

Article IV. Impurities were found not to be of concern at the levels expected to be present.

Article V. Inactive ingredient, metals and solvent levels are within reasonably safe concentrations.

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14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Protein Binding and Blood-to-Plasma Ratio

An equilibrium dialysis method was used to evaluate gepotidacin plasma protein binding (study report 12GSKUMP10R2) and protein binding to alpha-1-glycoprotein (AAG) (study report 13GSKUMP1R1). At [^{14}C]-gepotidacin concentrations of 9, 18, and 36 µM, plasma protein binding in human, monkey, dog, rat, and mouse was 40 to 41%, 24 to 28%, 18 to 21%, 33 to 35%, and 21 to 27%, respectively. Additionally, a [^{14}C]-gepotidacin concentration of 30 µM exhibited a binding range of ~25 to 33% to AAG plasma groups (AAG content: 56 to 300 mg/dL). Although the plasma protein binding appeared to be concentration independent to gepotidacin, AAG protein binding appeared to show a trend towards reduced protein binding with increasing concentrations. Elevated free drug concentrations are likely to be seen in infected patients.

Blood-to-plasma concentration ratios and red blood cell partitioning were evaluated in vitro in pooled human donor blood at gepotidacin concentrations of 0.77 to 23 µg/mL. Blood-to-plasma ratio was 0.95, and blood cell partitioning was ~40% (study report 2012N131922_00).

14.1.2. Metabolism

The enzymes responsible for the oxidative metabolism of gepotidacin were investigated in human liver microsomes (HLM), cytosol, S9 fraction, and recombinant cytochrome P450 (CYP) enzymes (Study 2014N210367). Overall, the study findings showed that CYP3A4 is the primary CYP enzyme involved in the oxidative metabolism of gepotidacin.

The Applicant performed an additional study evaluating if gepotidacin undergoes glutathione metabolism in HLM but found no evidence for glutathione adduct formation (study report RH2010/00041/00).

14.1.3. Potential for CYP Enzyme-Mediated Drug-Drug Interactions

The Applicant conducted in vitro enzyme-mediated DDI studies evaluating CYP enzyme inhibition and induction potential of gepotidacin.

In vitro studies were conducted to evaluate the potential time- and metabolism-dependent inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and CYP3A4/5 enzymes in HLM (Study 2013N158000). Gepotidacin directly inhibited CYP3A4/5 (nifedipine oxidation) with a calculated IC_{50} value of 340 µM. For CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 (atorvastatin ortho-hydroxylation and midazolam 1'-hydroxylation), IC_{50} values were ≥500 µM. The reversible and metabolism-dependent inhibition of CYP3A4 was further investigated in HLM (Study 2020N429708). Gepotidacin was shown to be a reversible inhibitor of CYP3A4 with calculated IC_{50} values of 773, 906, and 179 µM for atorvastatin, midazolam, and nifedipine

probe substrates, respectively. There was no evidence of metabolism-dependent inhibition of CYP3A4.

The potential for gepotidacin to induce expression of CYPs 1A2, 2B6, and 3A4 was evaluated in cryopreserved human hepatocytes (n = 3 donors) (Study 2017N324049). Treatment with gepotidacin caused concentration-dependent decreases in CYP mRNA expression at concentrations ≥600 µM in different donor incubations, likely due to cytotoxicity. A 2.37-fold increase in CYP3A4 mRNA was observed in one donor incubation treated with 300 and 600 µM gepotidacin (≤3% compared to positive control rifampin). Treatment with up to 300 µM of gepotidacin caused little to no induction of CYPs 1A2, CYP2B6 or CYP3A4 mRNA expression (i.e., <2-fold expression change and/or <20% positive control). The induction potential of gepotidacin at higher concentrations could not be determined due to cytotoxicity.

Clinical DDI studies were conducted to further evaluate gepotidacin as an object (CYP3A4 induction: rifampin, CYP3A4 inhibition: itraconazole) and precipitant (CYP3A4 substrate: midazolam) (see Section 14.2.1.6).

The Applicant also investigated reversible inhibition of human carboxylesterase enzymes (hCES) by gepotidacin (Study 2020N442536). Although gepotidacin was shown to be a reversible inhibitor of hCES-1 and hCES-2 with calculated IC_{50} values of 1675 and 1535 µM, respectively, this finding is not clinically relevant.

14.1.4. Potential for Transporter-Mediated Drug-Drug Interactions

The Applicant performed in vitro transporter mediated DDI studies and a rat P-gp and breast cancer resistance protein (BCRP) knockout study evaluating cell membrane transporter substrate and inhibition potential of gepotidacin.

The following studies (2015N235182, 2020N436056, 2015N235181, 2013N159502, 2013N158519, 2011N124110) evaluated gepotidacin as a substrate or inhibitor of P-gp, BCRP, OAT1, OAT2, OAT3, OCT2, OCT3, OATP1B1, OATP1B3, OATP2B1, MATE1, MATE2-K using MDCK2, HEK293, S2, or HEK293-MDCK2 transfected cells in membrane vesicle, bidirectional, and uptake assays (Table 110). The results showed that gepotidacin is a substrate of P-gp, BCRP, MATE1, and MATE2-K as net efflux/uptake ratio was ≥2 and the ratio was reduced by 50% with the probe inhibitors of the given transporters; meanwhile, gepotidacin showed inhibitory potential for MATE1 (IC_{50} = 16.6 µM), MATE2-K (IC_{50} = 6.9 µM), OCT3 (IC_{50} = 356.3 µM), P-gp (IC_{50} = 2530 µM), and BCRP (IC_{50} = 9731 µM).

Study 2020N440839 evaluated the impact of oral bioavailability and renal clearance of gepotidacin (a potential substrate of P-gp and BCRP transporters) in rats with P-gp, BCRP, P-gp and BCRP (double) knockout versus wild-type (no knockout). Rats were administered a single gepotidacin IV dose of 125 mg/kg over 4 hours and 2 days later a single gepotidacin oral gavage dose of 250 mg/kg. The Applicant notes that BCRP and P-gp do not affect gepotidacin systemic absorption or clearance, as the knockouts when compared to wild-type did not exhibit marked increases in plasma C_{max} or AUC, or marked decreases in total clearance and renal clearance, or increase in half-life.

Clinical studies were conducted to further evaluate gepotidacin as a substrate of P-gp, MATE1, and MATE2-K and as an inhibitor of P-gp (see Section 14.2.1.6 for additional information).

Table 110. In Vitro Assessment of Gepotidacin as Substrate or Inhibitor of Human Efflux and Uptake Transporters

	In Vitro Findings		In Vivo Potential Predictions		
Transporter	Max Flux Rate Ratio	IC_{50} (µM)	Recommended Ratio and Cutoff Values* (Reviewer Analysis)	Interpretation (Substrate/Inhibitor)	Clinical Study Conducted
P-gp	15.6	2530	S: ≥2 fold I: <10 cutoff (6.8)	Substrate	Yes (substrate and inhibitor)
BCRP	11.0	9731	S: ≥2 fold I: <10 cutoff (1.8)	Substrate	No
OATP1B1	<2	ND	S: <2 fold I: ND	---	
OATP1B1	<2	ND	S: <2 fold I: ND	---	
OATP1B1	<2	ND	S: <2 fold I: ND	---	
OAT1	<2	ND	S: <2 fold I: ND	---	
OAT2	<2	ND	S:† I:†	---	
OAT3	<2	ND	S: <2 fold I: ND	---	
OCT2	<2	ND	S: <2 fold I: ND	---	
OCT3	<2	356.3	S:† I:†		
MATE1	5.0	16.6	S: ≥2-fold and 50% reduction I: >0.02 cutoff (0.46)	Substrate, Inhibitor	Yes (substrate only)
MATE2-K	11.5	6.9	S: ≥2-fold and 50% reduction I: >0.02 cutoff (1.2)	Substrate, Inhibitor	Yes (substrate only)

Source: Reviewer's analysis of study reports (2015N235182, 2020N436056, 2015N235181, 2013N159502, 2013N158519, 2011N124110) and 2024 M12 Drug Interaction Studies (DDI) Guidance for Industry (Table 1).
Substrate (P-gp and BCRP): net efflux ratio ≥2; (SLC transporters): uptake ratio ≥2 and 50% uptake inhibited by transporter inhibitor probe
Inhibitor (P-gp and BCRP): Dose/250mL/IC_{50},u<10; (OATP1B1/OATP1B3):C_{max},inlet,u/IC50,u <0.1; OAT1,OAT3,OCT2 (C_{max},u/IC_{50},u <0.1); MATE1/MATE2-K (C_{max},u/IC_{50},u<0.02) :
† Not specified in the M12 DDI Guidance
Abbreviations: ND, not determined; u, unbound of 0.6, Molecular weight 580.7 g/mol

Reviewer's Comments:

Although the in vitro studies referenced were mostly conducted as recommended in the 2024 M12 DDI guidance, there were a few noteworthy instances where the studies deviated from the guidance.

- *Gepotidacin was only evaluated as a substrate of OAT1 and OAT3 at one concentration (1µM or ~0.6 mcg/mL) near or within the unbound minimum concentration of the proposed oral dosage and displayed an uptake ratio ~1.5; it is not clear if higher concentrations would demonstrate gepotidacin to be a concentration dependent OAT substrate.*
- *Although it appears that gepotidacin was evaluated as an inhibitor of OATP1B1 and OATP1B3 following preincubation, the study only displayed the inhibition results following incubation (30 to 50% inhibition of substrate probe). It is not clear if preincubation would have increased the inhibition potency to provide IC50 values. This is unlikely to be a significant clinical concern.*
- *A clinical study evaluating gepotidacin as a BCRP substrate was not performed despite in vitro study results demonstrating gepotidacin as a BCRP substrate. In addition, the Applicant performed a BCRP and P-gp knockout study in rats, and they noted that BCRP and P-gp did not affect gepotidacin systemic absorption or clearance. However, the findings from the rat model were deemed untranslatable for three reasons. First, rodents express more BCRP in the kidneys than humans, so it is not clear how to translate the BCRP clearance findings from rodent to human. Second, there were study design concerns, as no inhibitor or substrate probes were used to evaluate the functionality of the knockouts. Third, the results specific to BCRP were questionable and inconsistent for an efflux transporter located on the apical side of enterocytes. Instead of exhibiting the same or higher gepotidacin exposures, the T_{max} was 2-fold longer, and AUC, C_{max} and bioavailability were ~30-50% lower in BCRP knockout rats than wild-type given the same dose of gepotidacin.*
- *The Applicant did not perform a clinical study and did not provide a reason for not performing the study to evaluate gepotidacin as a possible inhibitor to MATE1 and MATE2-K. A clinical study was not requested by the review team as it is not considered a clinical issue for the uUTI indication due to the short duration of treatment. However, the likelihood of a drug-drug interaction effect cannot be ruled out given the in vitro results indicating gepotidacin as a potential inhibitor and PBPK simulated results exhibiting an AUC ratio beyond 1.25 for metformin (MATE substrate) (see Sections 8.2.2 – Summary of DDI Studies and 14.5.5- Physiologically-Based Pharmacokinetics).*

14.1.5. Nonclinical Pharmacokinetic-Pharmacodynamic Studies

14.1.5.1. Identification of PK-PD Index and Target

In vivo PK-PD Model

Gram-negative bacteria

In Study 2021N489444, pharmacokinetic-pharmacodynamic (PK-PD) index and target were evaluated using a neutropenic mouse thigh infection model with 17 strains of *E. coli* (MICs of 0.25 to 16 µg/mL) and 7 strains of *K. pneumoniae* (MIC of 2 to 16 µg/mL). For the pharmacodynamic (PD) studies, mice were given gepotidacin subcutaneous (SC) at doses ranging from 1 to 600 mg/kg every 6 hours for 24 hours. Mice were euthanized at 25 hours postinfection. Results identified area under the area under the free-drug concentration-time curve from 0 to 24 hours to MIC ratio (*f*AUC/MIC) as the PK-PD index that best correlated (based on r^2 and AIC) with bactericidal activity; however, the other two PD parameters (%*f*T>MIC, *f*Cmax/MIC) evaluated were comparable to *f*AUC/MIC (Table 111). Of note, the murine free drug estimate was 0.763. An Emax model was used to determine the best index and calculate the gepotidacin *f*AUC/MIC values associated PK-PD endpoints of net bacterial stasis, 1-$\log_{10}$ and 2-$\log_{10}$ bacterial reduction (kill) for both *E. coli* and *K. pneumoniae*. The results are presented in Table 112.

Table 111. Diagnostics for PK-PD Index Selection Based on Co-Modeling Data Across All *Escherichia coli* and *Klebsiella pneumoniae* Strains in Neutropenic Murine Infection Thigh Model

	***E. coli* (n=17)**		***K. pneumoniae* (n=7)**	
PK-PD Index	**AIC**	**r^2**	**AIC**	**r^2**
*f*AUC/MIC	3363.9	0.61	849.6	0.80
fC_{max}/MIC	3395.5	0.60	873.2	0.78
%*f*T>MIC	3480.7	0.56	888.7	0.77

Source: Adapted from Table 5 in study report 2021N489444_00
Abbreviations: AIC, Akaike information criterion; r^2, coefficient of determination; n, number of bacterial strains; *f*AUC/MIC, free area under-the-curve to minimum inhibitory concentration; *f*C_{max}/MIC, free maximum concentration to MIC; %*f*T>MIC, percentage of time the free drug concentration is above the MIC; PK-PD, pharmacokinetic-pharmacodynamic

Reviewer's Comment:

PK-PD index was determined by dose-ranging methods as opposed to dose-fractionation. Among the 17 E. coli strains and 7 K. pneumoniae strains used for evaluating the PK-PD index and target, five E. coli strains and one K. pneumoniae strain exhibited an average less than 1 $\log_{10}$ of growth in the 24-hour vehicle control (saline). The Applicant performed the PK-PD analysis with and without the strains with vehicle controls that exhibited poor growth at 24 hours. For our review of the PK-PD targets, we excluded the strains with vehicle controls that exhibited poor growth at 24 hours.

We did not review the kidney infection model part of the study for two reasons: 1) the kidney is the relevant site of infection for complicated UTI (e.g., pyelonephritis), while the bladder is the relevant site of the infection for the proposed indication, uUTI (cystitis); and 2) only one strain was evaluated in the model.

Gram-Positive Bacteria

Study 2013N171797 evaluated the gepotidacin PK-PD index and target for *S. aureus* and *S. pneumoniae* strains utilizing a neutropenic murine thigh infection model. To determine the PK-PD index, mice were infected with either one strain of *S. aureus* (gepotidacin MIC of 1 µg/mL) or *S. pneumoniae* (gepotidacin MIC of 0.25 µg/mL) and two hours later administered gepotidacin SC doses of 2, 8, 32, 128, and 512 mg/kg/day evenly divided every 3, 6, 12, or 24 hours. For the PK-PD target determination, mice were initially infected with five additional strains of *S. aureus* (gepotidacin MIC 0.5 to 2 µg/mL) or five additional strains of *S. pneumoniae* (gepotidacin MIC 0.125 to 1 µg/mL) and administered gepotidacin SC doses ranging from 2 to 2048 mg/kg/day (evenly divided every 6 hours). Among the three PK-PD indices correlated with bacterial reduction in *S. aureus* and *S. pneumoniae*, area under the free-drug concentration-time curve from 0 to 24 hours (*f*AUC)/MIC and %*f*T>MIC were similar for both *S. aureus* and *S. pneumoniae* at r^2 of ~0.90. The coefficient of determination for fC_{max}/MIC was ~0.67 for *S. aureus* and ~0.78 for *S. pneumoniae*. Despite similar PK-PD indices, *f*AUC/MIC was selected over %*f*T>MIC because gepotidacin has a similar mechanism of action as fluoroquinolones (i.e., bacterial type II topoisoisomerase inhibitor). This is consistent with the known PK-PD index of fluoroquinolones (*f*AUC/MIC). The PK-PD target values of each of the three endpoints (net bacterial stasis, 1-$\log_{10}$ and 2-$\log_{10}$ bacterial reduction from baseline to 26-hour postinfection) for both *S. aureus* and *S. pneumoniae* are presented in Table 112.

Reviewer's Comments:

It is acceptable to use fAUC/MIC as the PK-PD index for gepotidacin given that this parameter has consistently shown to be the best index correlated for efficacy in multiple models and bacterial species. In addition, gepotidacin has a similar mechanism of action as fluoroquinolones which uses a PK-PD index of fAUC/MIC. However, %fT>MIC was also shown to be highly correlated with bacterial killing in another murine thigh model. This suggests that gepotidacin dosing could be optimized by a loading dose to maximize the early part of the AUC, especially for bacterial organisms with high gepotidacin MICs.

Overall, the interpretation of the findings is not clear in two areas: 1) how PK-PD plasma targets from the neutropenic thigh infection model relate to urinary PK-PD targets for uUTI; and 2) if gepotidacin PK-PD targets of S. aureus (four methicillin-resistant and two methicillin-susceptible) can represent the Staphylococcus saprophyticus. Therefore, it is the opinion of the clinical pharmacology review team that this model is not appropriate for determining PK-PD targets for uUTIs.

Table 112. Summary Statistics of Gepotidacin Unbound Plasma AUC to MIC Targets Associated With PK-PD Endpoints for Enterobacterales (*Escherichia coli, Klebsiella pneumoniae), Staphylococcus aureus,* and *Streptococcus pneumoniae* in a Neutropenic Thigh Infection Model

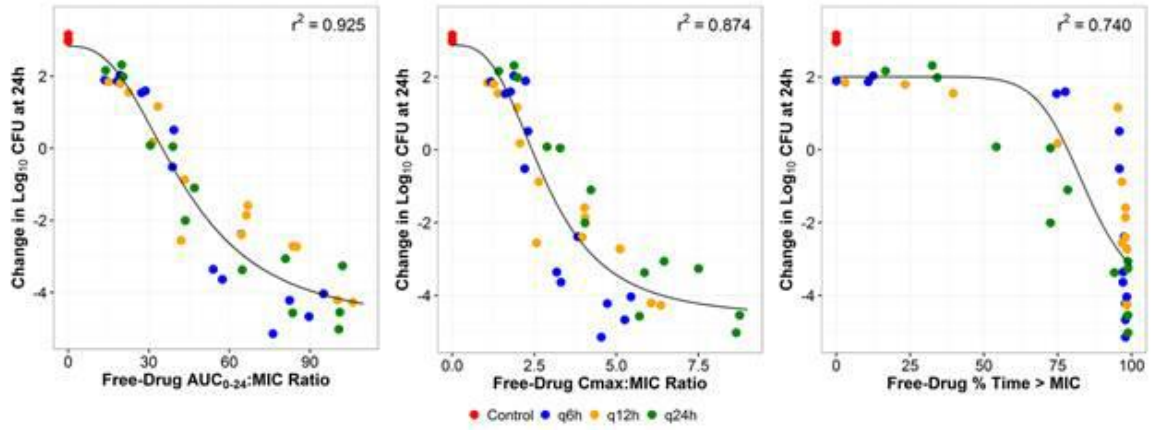
	PK-PD Endpoints at Free[a] AUC/MIC Targets		
Bacterial Species	**Stasis**	**1-log_{10} Kill**	**2-log_{10} Kill**
Enterobacterales (n)	18[b]	18[b]	18[b]
Mean, median	7.0, 4.2	12.0, 8.1	22.0, 15.0
75th percentile	11.0	20.0	38.0
Min to max	0.6 to 23.0	1.4 to 37.0	2.9 to 63.0
E. coli (n)	12[b]	12[b]	12[b]
Mean, median	8.6, 5.3	15.0, 13.0	25.0, 24.0
75th percentile	16.0	27.0	39.0
Min to max	0.6 to 23.0	1.4 to 37.0	2.9 to 63.0
K. pneumoniae (n)	6[b]	6[b]	6[b]
Mean, median	3.8, 4.2	7.4, 7.6	14.0, 14.0
75th percentile	5.7	10.0	20.0
Min to max	1.1 to 5.9	2.8 to 10.0	6.6 to 21
S. aureus (n)	6	6	4
Mean, median	15.3, 13.4	52.0, 58.9	430.0, 257.2
75th percentile	24.8	74.3	925.8
Min to max	4.0 to 35.5	12.6 to 103.2	103.8 to 1102.0
S. pneumoniae (n)	6	6	6
Mean, median	10.8, 7.9	23.8, 16.9	95.1, 69.8
75th percentile	15.1	33.2	139.8
Min to max	1.1 to 35.3	2.6 to 78.8	16.0 to 286.1

Source: Adapted from study reports 2013n171797_00 (Tables 4 and 5) and 2021N489444_00 (Tables 6 to 8)
n = bacterial strains
[a]. Value of 76.3% unbound gepotidacin was used based on in vitro protein binding assay in mice.
[b]. Subset analysis excludes 5 *E. coli* and 1 *K. pneumoniae* strains with vehicle-treated control group exhibiting a 24-hour growth that was <1 log_{10} CFU/mL.
Abbreviations: AUC, area under-the-curve; max, maximum; MIC, minimum inhibitory concentration; min, minimum; PK-PD, pharmacokinetic-pharmacodynamic

In Vitro PK-PD Model

In Study 2018N371065, the PK-PD index and target were evaluated using a one-compartment (chemostat) dynamic infection model in *E. coli*. Dose-fractionation studies were carried out over 24 hours with seven doses from 3 to 20 g (representing *f*AUC_{0-24} values from 29.6 to 197 µg*h/mL) that were divided evenly over 6, 12, or 24 hours with one *E. coli* strain (*E. coli* 13441, gepotidacin MIC = 2 µg/mL) at a starting inoculum of ~10^6 colony-forming unit (CFU)/mL. The unbound gepotidacin concentration-time profile used in the in vitro model was based on the plasma PK profiles of healthy subjects administered oral gepotidacin (T_{max} of 2 hours and terminal half-life of 7 hours). *f*AUC/MIC was the PK-PD index that best described efficacy of gepotidacin from baseline to 24 hours, based on an r^2 of 0.93 and dispersion of data across the fitted line (Figure 9). To determine the PK-PD target, a dose ranging study was performed with 9 to 11 gepotidacin doses from 0.125 to 32 g that were evenly divided over 12 hours and infused over two-hours (representing *f*AUC_{0-24} values from 2.46 to 632 µg*h/mL) against four *E. coli* strains (gepotidacin MICs of 1 to 4 µg/mL). The magnitudes of gepotidacin *f*AUC/MIC values associated PK-PD endpoints of net bacterial stasis, 1-log_{10} and 2-log_{10} bacterial reduction (kill) from baseline to 24 hours were pooled from all four *E. coli* strains and it is presented in Table 113.

Figure 9. Correlation of Gepotidacin PK-PD Indices With Bactericidal Activity Against *Escherichia coli* Strain 13441



Source: Figure 5 in study report 2018N371065_00
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h; C_{max}, maximum plasma concentration; MIC, minimum inhibitory concentration; PK-PD, pharmacokinetic-pharmacodynamic

Table 113. Summary Statistics of Gepotidacin Unbound Plasma AUC/ MIC Targets Associated With PK-PD Endpoints of *Escherichia coli* in In Vitro One-Compartment (Chemostat) Infection Model

	PK-PD Endpoint at Free Plasma AUC/MIC Targets		
Bacterial Species	**Stasis**	**1-log_{10} Kill**	**2-log_{10} Kill**
E. coli (n)	4	4	4
Pooled [a]	34.5	41.3	49.7
Mean, median	32.4, 33.9	45.5, 43.7	63.3, 60.7
Range	26.8 to 34.9	41.2 to 53.4	48.8 to 83.0

Source: Adapted from report ICPD00434-1 (Table 5), and ICPD00434-1, version: Addendum 1, Final (Table 1)
[a]. Represents the parameter estimates for the Hill-type model based on analysis of the data for all strains pooled.
n = bacterial strains
Abbreviations: AUC, area under-the-curve; max, maximum; MIC, minimum inhibitory concentration; PK-PD, pharmacokinetic-pharmacodynamic

Reviewer's Comments:

The Applicant used the PK-PD target from the chemostat model for probability of target attainment (PTAs) analyses. The gepotidacin 1-log kill PK-PD target for E. coli in the chemostat model was nearly 3-fold higher than the gepotidacin PK-PD target for E. coli in the neutropenic murine thigh model. No rationale was provided for this PK-PD target discrepancy between the two models. Of note, one of the E. coli strains (ATCC25922) was evaluated in both models; the PK-PD target in the chemostat model at net bacterial stasis was comparable to the 2-log target in the murine model at ~33 and ~38, respectively.

It should be noted that the chemostat model was designed to emulate drug effects in the blood and not the urine. In addition, the model does not account for the urodynamics and pH differences between urine and blood, as some antimicrobials are heavily pH-dependent and have reduced activity due to pH (Yang et al. 2014; Abbott et al. 2021). Therefore, it is the opinion of the review team that this model is not appropriate for determining PK-PD targets for uUTIs.

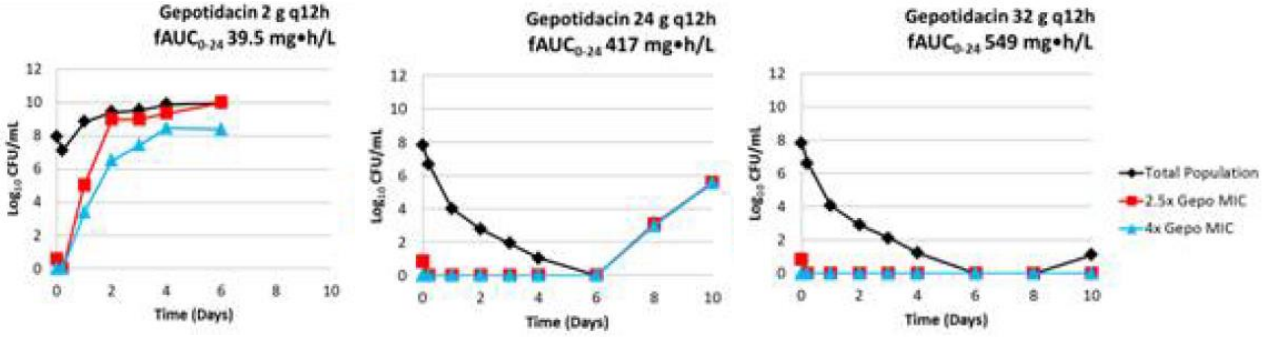
14.1.6. Hollow-Fiber Infection Model Evaluating Clinically Relevant Drug Exposures

Study 2018N371065 evaluated humanized exposures of gepotidacin in a hollow-fiber infection model (HFIM) to assess activity (bacterial burden reductions determined from drug-free agar plates) and suppression of treatment emergent resistance (bacterial growth on agar plates containing 2.5x and 4x MIC the baseline MIC of gepotidacin). The HFIM was performed over 10 days using one *E. coli* strain (NCTC 13441, gepotidacin MIC of 2 µg/mL) against gepotidacin doses of 0.5 to 48 g every 12 hours (representing *f*$AUC_{0\text{-}24}$ values from 9.7 to 811 µg*h/mL). An initial inoculum of 10^8 CFU/mL was used in the model. The gepotidacin free drug plasma concentration time profiles used for each of the dosages were designed to simulate human free-drug plasma concentration profiles in healthy subjects from phase 1 studies administered an oral dosage of 1.5 g every 12 hours (terminal half-life of 7 hours, T_{max} of 2 hours). All gepotidacin treatments were compared to no treatment or meropenem unbound exposures matching a 1 g IV every 8-hour dosage. PK assessments were performed utilizing a qualified bioanalytical method (data not submitted) to confirm the gepotidacin and meropenem PK profile. The study showed that meropenem sterilized the *E. coli* strain by Day 2. Gepotidacin 0.5 g to 24 g every 12 hours were not able to prevent drug resistant subpopulations; however, gepotidacin dosages ≥32 g every 12 hours were able to prevent the amplification of resistant subpopulations (Figure 10).

Reviewer's Comments:

For the following reasons the HFIM results were difficult to translate to the findings for a uUTI: 1) gepotidacin exposures were simulating plasma concentrations instead of drug concentrations in the urine; 2) the pH of the system was simulating blood (pH of 7.2) and not urine (pH of 6 to 6.5); and 3) only one E. coli strain was evaluated in the HFIM.

Figure 10. HFIM Dose-Range Study Results for *E. coli* 13441 (MIC of 2 mcg/mL) Exposed to Gepotidacin $AUC_{0\text{-}24h}$ That Represent Dosages of 2 g, 24 g, and 32 g Every 12 Hours, Over a 10-Day Period



Source: Adapted from Figure 18 in study report 2018N371065
Abbreviations: $AUC_{0\text{-}24h}$, area under the concentration-time curve from time 0 to 24 h; *f*$AUC_{0\text{-}24}$, free-drug area under the plasma concentration curve from time 0 to 24 h; HFIM, hollow fiber infection model; MIC, minimum inhibitory concentration

14.2. In Vivo Studies

Overall, the various formulations (except high shear wet granulation [HSWG] tablet free base tablet) employed in the clinical studies were found to be equivalent to each other based on

relative bioavailability studies and the in vitro dissolution study. Although HSWG tablet was not equivalent to the reference formulation, it was only evaluated in the relative bioavailability part (Part 1) of Study 117351 and was not used in pivotal clinical studies.

Table 114. Individual Clinical Pharmacology Reports Reviewed and Formulation

Study	Title	Type of Study	Formulation
BTZ114595	A Randomized, Single Blind, Placebo Controlled Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Single Escalating Oral Doses of GSK2140944 in Healthy Adult Subjects	SAD, FE	Capsule
BTZ115198	A Two Part Study To Evaluate Safety, Tolerability, and Pharmacokinetics of Single and Repeat IV Doses of GSK2140944 in Healthy Adult Subjects	SAD, MAD	Capsule, IV
BTZ115774	An Open-Label, Non-Randomized, Two-Period, Cross-Over, Mass Balance Study to Investigate the Recovery, Excretion and Pharmacokinetics of [^{14}C]-GSK2140944 Administered as a Single Intravenous and Single Oral Dose to Healthy Adult Male Subjects (BTZ115774)	MB	Capsule, IV
BTZ116778	A Randomized, Single Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Repeat Escalating Oral Doses of GSK2140944 in Healthy Adult Subjects (BTZ116778)	SAD, MAD	Capsule
BTZ116849	A phase I, Open-Label, Single-Dose, Multi-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Subjects with Varying Degrees of Renal Impairment and in Matched Control Subjects with Normal Renal Function	Renal impairment	IV
BTZ117349	A Single-Center, Three-Part, Open Label Study to Evaluate the Relative Bioavailability of Two Formulations, Food Effect, and Interaction with Itraconazole Following Single Dose of GSK2140944 in Healthy Subjects and Effect of Food on Safety, Tolerability, and Pharmacokinetics Following Multiple Doses of GSK2140944 in Healthy Elderly Subjects	geriatric, BA/BE, DDI	Mesylated tablet (part 1,2, 3), capsule (part 1)
BTZ117351	A phase I; Multi-Center; Open-Label (Parts 1 and 2); Randomized, Double-Blind, Placebo-Controlled (Part 3); Single-Dose; 3-Part Study to Evaluate the Relative Bioavailability of Three Formulations in Healthy Subjects, Food Effect on Tablet Formulation in Healthy Subjects, and Pharmacokinetics of Gepotidacin (GSK2140944) in Japanese Subjects in Fasted and Fed States	FE, BA/BE, race	Capsule (part 1), HSWG tablet (part 1), RC tablet (parts 1-3)

Study	Title	Type of Study	Formulation
BTZ117352	A phase I, Open-Label, Single-Dose, Two-Part Study to Assess the Pharmacokinetics of Gepotidacin in Male and Female Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function	Hepatic impairment	RC tablet
EAGLE-2	A phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)	Phase 3	To be marketed tablet
206899	A phase IIa Single-Center, Open-Label Study Evaluating the Pharmacokinetics of Repeat Oral Doses of Gepotidacin in Adult Female Participants With Uncomplicated Urinary Tract Infection (Acute Cystitis)	Phase 2a	RC tablet
209611	A phase I, Double-Blind, Two-Part, Sequential Study to Evaluate the Pharmacokinetics of Gepotidacin Tablets in Healthy Adult and Adolescent Participants	Pediatric	To be marketed tablet
213678	A Pharmacokinetic, Multi-Cohort Study in Healthy Adult Subjects to Assess Gepotidacin as Victim and as Perpetrator of Drug-Drug Interactions via CYP450, Renal and Intestinal Transporters, and to Assess Gepotidacin Pharmacokinetics in Japanese Healthy Adults	Race, FE, DDI	To be marketed tablet

Source: module 2.7.1, clinical study reports (BTZ114595, BTZ115198, BTZ115774, BTZ116778, BTZ116849, BTZ117349, BTZ117351, BTZ117352, EAGLE-2, 206899, 209611, 213678)
Abbreviations: BA/BE, bioavailability/bioequivalence; DDI, drug-drug interaction; FE, food-effect; HSWG, high shear wet granule tablet free base (884.7B/T); IV, intravenous; MAD, multiple ascending dose; MB, mass balance;; RC, roller compacted free base tablet (b) (4) SAD, single ascending dose

14.2.1. Healthy Subjects

14.2.1.1. Single Ascending Dose

Study BTZ114595

BTZ114595 was a randomized, single-blind, placebo-controlled, single-dose, dose-escalation study that evaluated the safety, tolerability, and PK of oral gepotidacin in 48 healthy adult subjects (completed: n=48, sex: n=38 men/n=10 women, age: 21 to 59 years, body weight: 50-104 kg).

There were 6 cohorts (100 mg, 800 mg, 1500 mg, 2300 mg, 2300 mg fed/moderate fat-moderate calorie meal, 3000 mg), each consisting of 8 subjects (n=6 gepotidacin, n=2 placebo) who were administered a single dose of gepotidacin capsule(s) or placebo on Day 1. Sentinel dosing was

employed for all dose levels except for the food effect cohort; 3 subjects were dosed initially and the remaining 5 subjects were dosed if no safety issues were observed within 48 hours.

Blood and urine PK samples were collected pre-dose and up to 72 hours post-dose; blood was collected at all doses while urine was collected at 2300 mg and 3000-mg doses only. Gepotidacin and three circulating metabolites (GSK1653580, GSK2682068, GSK2007900) were quantified in blood, plasma, and urine using a validated bioanalytical method. GSK1653580, GSK2682068, and GSK2007900 were measured in plasma and urine from the highest dose only while GSK2007900 was also measured in blood at all doses. Blood and urine PK parameters were derived by non-compartmental methods (Table 115, Table 116). The resultant gepotidacin blood exposure estimates (C_{max} and $AUC_{0-\infty}$) were evaluated for dose proportionality using a power model (Table 117).

Table 115. Summary of Gepotidacin Blood Pharmacokinetic Parameters Following Single Oral Administration in Healthy Subjects

Treatment	N	AUC(0-∞) (µg·hr/mL)	AUC(0-t) (µg·hr/mL)	Cmax (µg/mL)	tmax[2] (hr)	t1/2[2] (hr)
100 mg GSK2140944	6	0.596 (27.6)[3]	0.423 (31.3)	0.100 (70.2)	3.0 (1.50 - 4.00)	5.97 (3.45 – 8.64)[3]
800 mg GSK2140944	6	7.44 (14.7)	7.20 (15.0)	1.94 (41.8)	1.75 (1.00 - 3.00)	12.4 (9.19 – 13.7)
1500 mg GSK2140944	6	25.0 (15.2)	24.6 (15.3)	6.92 (14.0)	1.50 (1.50 - 2.00)	16.1 (10.4 – 24.3)
2300 mg GSK2140944 (fasted)	6	27.5 (25.6)[4]	26.9 (25.1)[4]	6.00 (30.0)	1.00 (0.50 - 2.00)	19.2 (12.3 – 32.2)[4]
2300 mg GSK2140944 (fed)	6	25.7 (18.0)	25.3 (17.9)	5.06 (38.9)	3.50 (2.00 - 6.00)	18.9 (9.5 – 22.4)
3000 mg GSK2140944	6	38.3 (28.6)	37.9 (28.7)	9.79 (45.5)	1.25 (1.00 - 2.00)	15.3 (8.1 – 23.2)

Source: Clinical Study Report BTZ114595 – Table 13
[1] Geometric mean (CVb%)
[2] Median (range)
[3] n=4
[4] n=5
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; C_{max}, maximum concentration; N, number of subjects; t_{max}, time to maximum concentration; $t_{1/2}$, half-life

Table 116. Summary of Gepotidacin Urine Pharmacokinetic Parameters Following Single Oral Administration in Healthy Subjects[1]

Treatment	N	Ae (mg)	CLr (L/hr)	Fe (%)
2300 mg GSK2140944 (fasted)	6	363 (295 - 703)[2]	15.4 (11.8 - 21.7)[2]	15.8 (12.8 - 30.6)[2]
3000 mg GSK2140944	6	722 (418 - 819)	16.7 (15.1 - 26.5)	24.1 (13.9 - 27.3)

Source: Clinical Study Report BTZ114595 – Table 15
[1] Median (range)
[2] n=5
Abbreviations: Ae, amount of drug excreted in urine or feces; CLr, renal clearance; Fe, fraction of dose excreted unchanged into urine; N, number of subjects

Table 117. Summary of Results of Statistical Analysis for Gepotidacin Dose Proportionality (Blood)

Parameter (units)	N	Slope	90% Confidence Interval
AUC(0-∞) (µg·hr/mL)	27[1]	1.25	(1.17, 1.33)
	23[2]	1.19	(0.989, 1.39)
Cmax (µg/mL)	30[1]	1.36	(1.24, 1.48)
	24[2]	1.11	(0.825, 1.40)

Source: Clinical Study Report BTZ114595 – Table 18
[1] Excludes 2300 mg (fed) group
[2] Excludes 100 mg and 2300 mg (fed) groups
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; C_{max}, maximum concentration; N, number of subjects

Gepotidacin AUC and C_{max} values increased in a greater than dose proportional manner over the dose range of 100 to 3000 mg. Median T_{max} ranged from 1 to 3.5 hours and median half-life ranged from 6 to 19 hours. The mean AUC and C_{max} plasma:blood ratios after a single oral dose of 3000 mg ranged from 0.86 to 0.92, suggesting gepotidacin is moderately associated with red blood cells.

Plasma AUC and C_{max} of the cleavage amine (GSK2007900) were less than 1% of the parent compound. Plasma concentrations of the aldehyde (GSK1653580) and the carboxylic acid (GSK2682068) metabolites were below the limit of quantitation.

Approximately 16 to 24% of the absorbed gepotidacin dose was excreted unchanged in urine following doses of 2300 and 3000 mg.

Food had minimal effect on AUC (6 to 7% decrease) and C_{max} (16% decrease) of gepotidacin and delayed T_{max} from 1 hour (fasted) to 3.5 hours (fed) (Table 118).

Table 118. Effect of Moderate-Fat, Moderate-Calorie Meal on Gepotidacin Blood Pharmacokinetic Parameters in Healthy Subjects

Comparison	Parameter (units)	Geometric LS Mean Test (Fed)	Geometric LS Mean Ref (Fasted)	Ratio	90% Confidence Interval
2300 mg GSK2140944 Fed: 2300 mg GSK2140944 Fasted	AUC(0-∞) (µg·hr/mL)	25.7[1]	27.5[2]	0.93	(0.74, 1.18)
	AUC(0-t) (µg·hr/mL)	25.3[1]	26.9[2]	0.94	(0.74, 1.19)
	Cmax (µg/mL)	5.06[1]	6.00[1]	0.84	(0.59, 1.20)
	tmax (hr)	3.5[3]	1.0[3]	2.3[4]	(1.5, 3.5)

Source: Clinical Study Report BTZ114595 – Table 17
[1] n-6
[2] n=5
[3] Median
[4] Estimated Median Difference
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; C_{max}, maximum concentration; LS, least squares; t_{max}, time to maximum concentration

14.2.1.2. Multiple Ascending Dose

Study BTZ116778

BTZ116778 was a randomized, single-blind, placebo-controlled, multiple-dose, dose-escalation study that evaluated the safety, tolerability, and PK of oral gepotidacin in 72 healthy adult

subjects (completed: n=67, sex: n=59 men/n=13 women, age: 20 to 58 years, body weight: 55.7 to 93.9 kg).

There were 7 cohorts (400 mg twice daily (BID), 800 mg BID, 1500 mg BID, 2300 mg BID, 1500 mg three times daily (TID), 2000 mg TID, 1500 mg BID fasted), each consisting of 8 or 16 subjects (n=6 or 12 gepotidacin, n=2 or 4 placebo) who were administered a single dose of gepotidacin capsule(s) or placebo on Day 1 followed by BID or TID dosing on Days 3 through 16 (14 days). Doses were administered under fed conditions (moderate-fat meal) except for the 1500 mg BID cohort.

For BID dosing, blood PK samples were collected pre-dose through 12 hours post dose on Day 1 and Day 16, and four additional timepoints (16, 24, 36, and 48 hours post dose) on Day 1 only. For TID dosing, blood PK samples were collected pre-dose through 8 hours post dose on Day 1 and Day 16, and five additional timepoints (12, 16, 24, 36, and 48 hours post dose) on Day 1 only. Single pre-dose trough samples were collected on Day 14 and Day 15. Gepotidacin was quantified in plasma using a validated bioanalytical method and PK parameters were derived by non-compartmental methods (Table 119).

Table 119. Summary of Gepotidacin Plasma PK Parameters Following Repeat Oral Administration in Healthy Subjects[a]

Treatment	N	Visit[b]	n	AUC(0-24) (µg·h/mL)	AUC(0-t) (µg·h/mL)	AUC(0-∞) (µg·h/mL)	AUC(0-τ) (µg·h/mL)[c]	Ro	Cmax (µg/mL)	t1/2 (h)	Effective t1/2 (h)	Tmax (h)[d]
GSK2140944 400 mg single dose Day 1 and BID Days 3-16	6	Day 1	6	2.60 (21.5)	2.73 (21.6)	2.94 (19.6)	2.22 (23.3)	NA	0.602 (18.4)	11.2 (17.9)	NA	2.01 (1.50 - 4.00)
		Day 16	6	NA	NA	NA	3.00 (43.0)	1.35 (25.5)	0.868 (104)	NA	7.48[g] (11.0)	1.75 (1.50 - 4.02)
GSK2140944 800 mg single dose Day 1 and BID Days 3-16	12	Day 1	12	7.38 (38.0)	7.91 (36.4)	8.20[f] (37.0)	6.60 (40.5)	NA	1.86 (53.2)	14.7[f] (17.9)	NA	1.76 (1.00 - 4.00)
		Day 16	12	NA	NA	NA	8.40 (40.1)	1.27 (37.4)	2.28 (85.4)	NA	7.20[g] (42.9)	2.00 (1.50 - 4.05)
GSK2140944 1500 mg single dose Day 1 and BID Days 3-16 (fed)	12	Day 1	12	18.9 (22.6)	19.7 (21.9)	20.1 (21.5)	17.3 (23.7)	NA	4.08 (40.3)	12.0 (17.9)	NA	2.00 (1.50 - 4.02)
		Day 16	12	NA	NA	NA	22.4 (29.6)	1.30 (34.9)	5.41 (31.1)	NA	6.56[h] (56.4)	2.00 (1.50 - 4.00)
GSK2140944 2300 mg single dose Day 1 and BID Days 3-16	6	Day 1	6	26.1 (22.2)	27.2 (22.1)	27.5 (21.8)	23.9 (21.5)	NA	6.73 (30.2)	11.4 (14.5)	NA	1.75 (1.50 - 6.00)
		Day 16	6	NA	NA	NA	36.0 (11.7)	1.50 (24.4)	7.85 (7.4)	NA	7.27 (42.3)	2.00 (1.50 - 4.00)
GSK2140944 1500 mg single dose Day 1 and TID Days 3-16	6	Day 1	6	18.9 (23.9)	19.7 (23.6)	20.0 (23.4)	15.2 (21.6)	NA	4.80 (22.3)	11.8 (13.8)	NA	2.50 (1.98 - 4.00)
		Day 16	4	NA	NA	NA	24.1 (29.4)	1.69 (17.5)	6.04 (25.0)	NA	6.12 (28.9)	2.00 (2.00 - 3.00)
GSK2140944 2000 mg single dose Day 1 and TID Days 3-16	6	Day 1	6	23.2 (14.6)	24.3 (13.5)	24.8 (12.4)	18.6 (14.2)	NA	5.49 (16.4)	13.6 (21.5)	NA	2.50 (1.50 - 3.07)
		Day 16	3	NA	NA	NA	30.3 (14.4)	1.72 (8.8)	8.64 (24.7)	NA	6.37 (13.8)	1.50 (1.50 - 3.00)
GSK2140944 1500 mg single dose Day 1 and BID Days 3-16 (fasted)	6	Day 1	6	14.3 (25.2)	15.1 (25.8)	15.5 (26.1)	13.0 (24.9)	NA	5.07 (20.3)	12.3 (25.3)	NA	1.25 (1.00 - 1.50)
		Day 16	6	NA	NA	NA	19.8 (31.5)	1.52 (25.7)	6.50 (35.9)	NA	8.96[e] (21.2)	1.50 (1.50 - 2.00)

Source: Clinical Study Report BTZ116778 – Table 6
[a] Geometric mean (CVb%)
[b] Visit on Day 16 corresponded to steady-state PK Day 14
[c] τ=12 hours for BID dosing and τ=8 hours for TID dosing
[d] Median (range)
[e] n=5
[f] n=11
[g] n=9
[h] n=10
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; $AUC_{0-\tau}$, area under the concentration-time curve during the dosing interval; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h; AUC_{0-t}, from time 0 to last quantifiable timepoint; BID, twice daily; C_{max}, maximum plasma concentration; N, number of subjects in treatment group; NA, not applicable; LS, least squares; PK, pharmacokinetic; Ro, accumulation ratio; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; TID, three times daily

Gepotidacin AUC and C_{max} values increased in a greater than dose proportional manner over the dose range of 400 to 2300 mg following single or repeat BID or TID oral dosing. Day 16/Day 1 AUC ratio ranged from 1.27 to 1.72 following BID and TID dosing.

Median T_{max} ranged from 1.25 to 2.5 h on Day 1 and 1.5 to 2 hours on Day 16 following single or repeat BID or TID dosing. Geometric mean elimination half-life ranged from 11.2 to 14.7 hours across all dose levels and were dose-independent. After 14 days of repeat BID or TID dosing, geometric mean effective half-life values ranged from approximately 6 to 9 hours across all dose levels and were generally dose-independent. Steady-state was achieved by the 12th day of repeat oral BID or TID dosing (i.e., earliest time point at which PK data were available to assess steady-state).

Time invariance analysis showed a ratio of approximately 1 for AUC values on Day 16 and Day 1, indicating gepotidacin PK is not time-dependent and remained unaltered after repeated oral dose administration.

14.2.1.3. Bioavailability and Food Effect

Study BTZ115198

BTZ115198 was a two-part (A and B), randomized, placebo-controlled, single-blind, dose-escalation study that evaluated the safety, tolerability, and PK of single and multiple dose IV gepotidacin in 86 healthy adult subjects. Part A included a crossover evaluation of the absolute bioavailability (capsule vs. IV) of a single 1800-mg dose of gepotidacin. Serial PK samples were collected through 48 hours post-dose or after the start of infusion. Gepotidacin was quantified in blood using a validated bioanalytical method and PK parameters were derived by non-compartmental methods (Table 120).

Table 120. Assessment of Absolute Bioavailability for Gepotidacin in Part A

Parameter	Treatment	Geometric LS Mean		Ratio	90% C.I.
		Oral Dose	IV Dose		
AUC(0-∞)	GSK2140944 1800 mg single dose Day 1	21.6	47.8	0.45	(0.37, 0.55)

Source: Clinical Study Report BTZ115198 – Table 36
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; CI, confidence interval; IV, intravenous; LS, least squares

The mean absolute bioavailability following a single 1800 mg oral dose compared with a single 1800 mg IV dose was estimated to be 45%.

Study BTZ117349 (Part 1)

BTZ117349 was a 3-period, randomized, open-label, single-center, crossover (only period 1 and 2) study that evaluated the relative bioavailability and food-effect of gepotidacin in healthy subjects. The study enrolled 15 healthy subjects (80% male, 19 to 62 years of age, and 69.4 to

105.5 kg), who participated in three treatment periods (at least a 3-day washout window between periods):

- Periods 1 and 2 (crossover): Single 1500 mg oral dose of gepotidacin test formulation (2x 750 mg mesylated salt tablet) or reference capsule formulation (3x 500 mg capsule) in fasted state
- Period 3: Single 1500 mg oral dose of gepotidacin tablet formulation in the fed state (moderate fat meal)

Serial plasma PK was collected over 48 hours and concentrations were quantified using a validated bioanalytical method and PK parameters were derived by noncompartmental analysis.

Gepotidacin AUC, C_{max}, and T_{max} between the two formulations were comparable under fasted conditions (Table 121). Gepotidacin tablet under fed vs. fasted conditions met the 90% confidence interval (CI) for AUC but the C_{max} was marginally outside the 90% CI of 0.80 to 1.25, and median T_{max} increased from 1.75 hours to 3 hours (Table 122). Therefore, a minimal food effect was observed with the gepotidacin tablet.

Table 121. Statistical Assessment of Gepotidacin Relative Bioavailability

	Geometric LS Mean			
	Test Tablets/Fasted N=14	Reference Capsules/Fasted N=15	Ratio Test/Ref	90% Confidence Interval
AUC(0-inf) (ng*h/mL)	15089.27	13978.38	1.079	(1.019, 1.144)
AUC(0-t) (ng*h/mL)	14798.33	13634.42	1.085	(1.017, 1.158)
Cmax (ng/mL)	3919.12	3781.55	1.036	(0.932, 1.152)

Source: Table 28 in clinical study report 2014N199850_00
Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; C_{max}, maximum plasma concentration; LS, least square; N, number of subjects in treatment group; Ref, reference

Table 122. Statistical Assessment of Food Effect on Gepotidacin

Part		N		Geometric LS Mean		Ratio Test/Ref	90% Confidence Interval
		Test	Ref	Test Tablets/Fed	Reference Tablets/Fasted		
1	AUC(0-inf) (ng*h/mL)	13	14	16888.14	15784.44	1.070	(0.979, 1.170)
	AUC(0-t) (ng*h/mL)	13	14	16592.98	15470.87	1.073	(0.980, 1.173)
	Cmax (ng/mL)	13	14	3812.44	4374.14	0.872	(0.782, 0.972)

Source: Adapted from Table 29 in clinical study report 2014N199850_00
Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; C_{max}, maximum plasma concentration; LS, least square; N, number of subjects in treatment group; Ref, reference

Reviewer's Comments:

The gepotidacin mesylated salt tablet formulation (b) (4)) that was found to be bioequivalent to the capsule formulation in this study, is similar to the to-be-marketed mesylated salt tablet formulation (b) (4). The minor differences between the tablet formulations did not affect the in vitro dissolution profiles.

In addition, it is not clear if the FDA guidance recommended high fat-meal would alter the PK of gepotidacin. The Applicant did not provide information regarding the total calorie count and fat calories in a moderate fat meal.

Study BTZ117351 (Part 1)

BTZ117351 was a 3-period, randomized, cross-over study that assessed the relative bioavailability of a single 1500-mg dose of gepotidacin in two free base tablet formulations (2x 750 mg Roller Compacted [RC] and HSWG tablets) compared with the reference capsule formulation of gepotidacin (3 × 500 mg capsule) under a fasted state. The study enrolled 26 healthy subjects (80.8% males, 24 to 58 years of age, and 54.5 to 115.0 kg) that received all 3 treatments according to their assigned treatment sequence that was separated between sequences by at least a 3-day washout window.

Serial blood and urine PK were collected over 48 hours post dose and gepotidacin concentrations were quantified using a validated bioanalytical method.

Gepotidacin capsule and tablet formulations under fasted conditions were rapidly absorbed with a median T_{max} value ranging from 1.0 to 1.5 hours. Statistical analysis found that gepotidacin RC tablet formulation was equivalent to the reference capsule, while the HSWG tablet formulation was not equivalent to the reference capsule (Table 123).

Table 123. Bioequivalence Analysis of Plasma Gepotidacin Pharmacokinetic Parameters by Treatment of Three Formulations (Capsule, RC Tablet, and HSWG Tablet)- Part 1

Parameter	Treatment	LS Geometric Mean	LS Geometric Mean Ratio (Test/Reference)	90% CI of the LS Geometric Mean Ratio
AUC(0-t) (h*ng/mL)	Reference	16480		
	RC 1500 mg	17152	1.0408	(0.9792, 1.1062)
	HSWG 1500 mg	18356	1.1138	(1.0479, 1.1838)
AUC(0-∞) (h*ng/mL)	Reference	16815		
	RC 1500 mg	17516	1.0417	(0.9809, 1.1063)
	HSWG 1500 mg	18679	1.1108	(1.0459, 1.1797)
Cmax (ng/mL)	Reference	4676		
	RC 1500 mg	4483	0.9586	(0.8440, 1.0888)
	HSWG 1500 mg	5372	1.1487	(1.0113, 1.3047)

Source: Table 23 in clinical study report 2017N322476_00
A mixed effects model with treatment, sequence, period as fixed effects and subject within sequence as random effect was performed on the natural log-transformed parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; C_{max}, maximum plasma concentration; CI, confidence interval; HSWG, high shear wet granulation; LS, least squares; RC, roller compacted

Reviewer's Comments:

The free base RC tablet was used in the Japanese healthy subject PK and dose-response study (Study BTZ 117351 part 2 and 3) and hepatic impairment study (Study BTZ117352).

Although HSWG tablet was not equivalent to the reference formulation, it was only evaluated in the relative bioavailability part of Study 117351 (Part 1), and it was not used in any other clinical studies. (For additional information about formulations, see Table 114- Individual Clinical Pharmacology Reports Reviewed and Formulation.)

14.2.1.4. Mass Balance

BTZ115774 was a phase 1, open-label, non-randomized, two-period, crossover mass balance study in 6 healthy male subjects (31 to 51 years of age and 67.6 to 89.0 kg) that were administered a single [^{14}C]-gepotidacin IV dose of 1000 mg (infused over 2 hours) and single oral capsule dose of 2000 mg with a minimum 8-day washout period. Both formulations were administered after a 10 hour fast. The IV dose contained approximately 22.5 µCi (~0.8 MBq) of radioactivity and oral dose contained approximately 45 µCi (~1.7 mBq) of radioactivity. The absolute bioavailability was determined to be 43.8%.

Blood and Plasma Sample Analysis

The parent compound following oral and IV dose accounted for ~60% and 75% of the total plasma radioactivity contained in the plasma pool, respectively. A notable metabolite formed by oxidation, M4, accounted for ~9% and ~11% of drug-related material in plasma following IV and oral dose, respectively. The remaining eight detected metabolites each accounted for 5.4% or less of the total radioactive material recovered in plasma following oral or IV dose.

The mean blood-to-plasma total radioactivity concentration ratio over 168 hours ranged from 0.77-to-1.32 and 0.75-to-1.03 by the oral and IV routes, respectively. Mean terminal half-life for gepotidacin in plasma, total radioactivity in plasma and total radioactivity in whole blood was approximately 12 hours, 77 hours, and 62 hours, respectively by the oral route and approximately 13 hours, 95 hours, and 70 hours, respectively by the IV route (Table 124).

Duodenal Bile Qualitative Assessment

Entero-test device was used to collect a duodenal bile sample up to 2 hours post dose of IV infusion. Of the ~95% total radioactive material assigned from the pooled human bile extract across subjects using Entero-Test™ strings, the relative % sample radioactivity consisted of ~51% parent drug, ~30% M4, and the remaining metabolites were <10%.

Excreta Sample Analysis

The mean radioactive recoveries in total excreta (urine + feces) following the oral and IV dose were 83.7% (predominately in feces at 52.5%), and 92.4% (predominately in urine, 59.6%), respectively. For both oral and IV, over 90% of total radioactivity recovered in the excreta occurred within the first 24 hours in urine and 72 hours in feces. The total radioactivity recovered in the urine and feces was ≤1% of administered dose over a 24-hour period on 2 consecutive sample days starting at 72 hours in urine and 120 hours in feces.

The mean recovery of radioactivity following centrifugation of individual pooled urine and extraction and reconstitution of individual pooled feces was >80% in the excreta following IV dose and >80% for urine only (feces was 75%) following oral dose. Unchanged parent was identified as the major radioactive component in excreta for both routes of administration at ~50% (~20% in urine and ~30% in feces) of oral dose and ~57% (~43% in urine and ~14% in feces) of the IV dose. It is to be noted that the percentages did not add up to total excreta for each formulation (oral- 83.7% and IV- 92.4%) due to losses specific to sample processing and radioactivity recovery. Elimination of metabolites in excreta accounted for ~19% (~11% in urine and ~8% in feces) and 13% (~8% in urine and ~5% in feces) of recovered dose by the IV and oral routes, respectively. All metabolites in urine or feces were minor with no single metabolite exceeding ~8%.

Table 124. Summary of Plasma and Blood Total Radioactivity and Plasma Gepotidacin PK Parameters

Treatment	Analyte	Matrix	N	AUC(0-∞) (µg.h/mL)	AUC(0-t) (µg.h/mL)	Cmax (µg/mL)	tmax (h)[b]	t1/2 (h)	CL (L/h)	Vdss (L)
[14C]-GSK2140944 1000 mg IV single dose	GSK2140944	Plasma	6	25.8 (9.2)	25.5 (9.3)	7.08 (15.2)	1.98 (1.98-2.0)	12.6 (13.5)	38.8 (9.2)	188.7 (22.0)
	Total radioactivity	Plasma	6	40.7 (8.0)	38.5 (8.7)	8.53 (16.8)	1.98 (1.98-2.0)	94.5 (51.3)	NA	NA
	Total radioactivity	Blood	6	34.6 (10.5)	33.2 (9.9)	7.21 (19.8)	1.98 (1.0-2.0)	70.1 (40.1)	NA	NA
[14C]-GSK2140944 2000 mg Oral single dose	GSK2140944	Plasma	6	22.6 (23.4)	22.2 (24.1)	5.28 (31.9)	1.01 (1.0-2.0)	12.1 (24.6)	NA	NA
	Total radioactivity	Plasma	6	45.7 (18.4)	41.6 (17.3)	6.54 (28.2)	2.00 (1.0-2.0)	77.2 (112)	NA	NA
	Total radioactivity	Blood	6	40.5 (15.6)	37.9 (17.3)	5.96 (22.2)	2.00 (1.0-6.0)	61.8 (60.2)	NA	NA

Source: Table 4 in clinical study report 2014N189951_00
[a] Geometric Mean (CVb%)
[b] Median (range)
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; CL, clearance; C_{max}, maximum plasma concentration; N, number of subjects in treatment group; NA, not applicable; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; Vd_{ss}, volume of distribution at steady state

Reviewer's Comments:

No rationale was provided for both the mean drug recovery over the 168-hour collection time for the oral dose being lower than 90%, or the radioactivity recovered in the excreta (i.e., feces) being lower than 80% (FDA clinical mass balance guidance recommended mean drug recovery). The Applicant notes in the study report that feces samples from 48-72- and 72-96-hour collections times were sent at ambient temperature in error instead of cold packs. Therefore, it is not clear if this affected the stability of the sample, and possibly been the cause of the lower mean recovery of drug.

Additionally, the parent compound was co-eluted with metabolite (M12), but when plasma PK of parent and M12 were compared in another clinical PK study the data suggested that M12 contribution to the total peak was likely negligible.

An information request was sent to the Applicant if the M4 metabolite was an active moiety and if the PK of M4 was assessed in any of the clinical studies. The Applicant noted that they were not able to assess the M4 moiety's pharmacological activity since they were not able to chemically synthesize it due to instability. This lack of chemically synthesized M4 reference standard prevented them from developing a bioanalytical assay to quantify M4 clinical concentrations. Therefore, it is not clear if M4 is an active moiety and the safety risk associated with M4 in situations when a patient is co-administering gepotidacin with a strong inducer is also not clear.

14.2.1.5. Intrinsic Factors

Age- Pediatric (Adolescents)

Study 209611 was a double-blind, two-part, sequential, study that evaluated the pharmacokinetics of gepotidacin in healthy adults in 3-periods and adolescents in 2-periods. Part 1 of the study enrolled 16 healthy adult subjects (56% male, 27 to 64 years of age, and 47 to 103 kg) that received three different oral doses of gepotidacin. Part 2 of the study enrolled 17 healthy adolescent subjects (71% male, 12 to 17 years of age, and 41 to 88 kg) that received two different oral doses of gepotidacin. All subjects received the to-be-marketed mesylated tablet (b) (4) with food (standard meal).

- Part 1 (healthy adults)- subjects were randomized (13:3) to receive all three periods (separated by at least 4 days) in a fixed sequence:
    - Period 1- single dose gepotidacin 1500 mg or matching placebo
    - Period 2- two gepotidacin 3000 mg separated by 12 hours or matching placebo
    - Period 3- two gepotidacin 3000 mg separated by 6 hours or matching placebo
- Part 2 (healthy adolescents)- subjects were randomized (14:3) to receive gepotidacin all two periods (separated by at least 7 days) in a fixed sequence:
    - Period 1-single dose of gepotidacin 1500 mg or matching placebo
    - Period 2-two gepotidacin 3000 mg separated by 6 hours or matching placebo.

Plasma and urine PK were collected up to 48 hours post-dose for Period 1, and up to 60 hours post-dose for Period 2 and 3 (adults only).

Gepotidacin plasma and urine PK parameters from the five cohorts are in Table 125 and Table 126, respectively. The results of the study show that adolescent gepotidacin plasma exposures were ~30-35% higher than adults when comparing the same doses (1500 mg × 1 or 3000 mg × 2 at 6-hour interval). Plasma $t_{1/2}$ was shorter, and apparent volume of distribution was lower by nearly 2-fold for adolescents compared to adults in cohorts administered two 3000-mg doses at 6-hour intervals.

Reviewer's Comments:

Seven subjects (2 adults and 5 adolescents) experienced emesis after study drug administration of the two 3000-mg dose. One adult and adolescent experienced emesis on first dose of 3000 mg, while seven subjects experienced it after the second dose. The time in which emesis occurred ranges from ~1 to 4.5 hours. Data was not excluded from the PK summaries, as the maximum observed concentrations were within the range of non-emesis subjects.

Table 125. Summary of Gepotidacin Plasma Pharmacokinetic Parameters of Single 1500 mg and Two 3000 mg (6- and 12-Hour Interval) in Adults and Adolescents (12 to 17 Years of Age)

Parameter	Single Dose 1500 mg Adults (N=14)	Two 3000 mg Doses 12-hour Interval Adults (N=13)		Two 3000 mg Doses 6-hour Interval Adults (N=13)		Single Dose 1500 mg Adolescents (N=13)	Two 3000 mg Doses 6-hour Interval Adolescents (N=12)	
		Dose 1*	Dose 2*	Dose 1*	Dose 2*		Dose 1*	Dose 2*
AUC(0-t) (µg•h/mL)	19.7 (17.6)	91.2 (22.6)	–	87.1 (26.3)	–	23.3 (21.6)	116 (23.8)	–
AUC(0-∞) (µg•h/mL)	20.2 (16.8)	–	–	–	–	23.8 (20.9)	–	–
AUC(0-24) (µg•h/mL)	18.7 (19.5)	83.5 (22.7)	–	82.4 (27.3)	–	22.1 (22.6)	111 (23.8)	–
AUC(0-48) (µg•h/mL)	19.7 (17.6)	90.5 (22.7)	–	86.5 (26.4)	–	23.3 (21.6)	116 (23.8)	–
AUC(0-τ) (µg•h/mL)	–	38.2 (24.3)	44.4 (22.8)	24.1 (33.6)	40.1 (29.5)	–	32.4 (22.0)	53.9 (26.7)
Cmax (µg/mL)	3.57 (38.1)	9.94 (24.2)	11.0 (28.1)	8.42 (41.8)	13.0 (28.6)	4.52 (29.5)	10.9 (26.8)	14.3 (29.5)
Tmax (h)	3.00 (0.50, 6.00)	2.00 (1.00, 4.00)	1.57 (1.00, 4.00)	2.63 (0.50, 5.42)	1.50 (1.00, 3.28)	3.00 (1.50, 6.00)	2.75 (1.00, 4.00)	1.50 (1.00, 3.00)
Tlag (h)	0.00 (0.00, 1.50)	0.00 (0.00, 0.00)	–	0.00 (0.00, 0.00)	–	0.50 (0.00, 1.50)	0.00 (0.00, 0.50)	–
t1/2 (h)	11.5 (36.2)	–	11.0 (27.3)	–	12.0 (14.6)	13.0 (16.6)	–	6.98 (19.7)
CL/F (L/h)	74.4 (16.8)	65.3 (22.3)	–	68.4 (26.2)	–	63.1 (20.9)	51.6 (23.6)	–
Vz/F (L)	1239 (39.3)	1033 (41.9)	–	1186 (30.8)	–	1181 (32.9)	520 (36.6)	–
RO Cmax	–	–	1.11 (30.6)	–	1.54 (25.9)	–	–	1.32 (32.8)
RO AUC(0-τ)	–	–	1.16 (12.7)	–	1.67 (25.9)	–	–	1.66 (18.3)

Source: Table 16 in clinical study report 2019N422403_00
Only PK parameters $AUC_{0-\tau}$, C_{max}, and T_{max} were estimated separately by dose where 2 doses were administered. Otherwise, parameters were estimated using the full profile while the terminal elimination was characterized based on samples following the second dose.
Values are presented as geometric mean (%CVb) except for T_{max} and T_{lag} which are presented as median (minimum, maximum).
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; $AUC_{0-\tau}$, area under the concentration-time curve during the dosing interval; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h; AUC_{0-48}, area under the concentration-time curve from time 0 to 48 h; AUC_{0-t}, from time 0 to last quantifiable timepoint; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; N, number of subjects in the treatment group; PK, pharmacokinetics; RO, accumulation ratio (Dose 2/Dose1); $t_{1/2}$, half-life; T_{lag}, time prior to the first measurable concentration; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Table 126. Summary of Gepotidacin Urine Pharmacokinetic Parameters of Single 1500 mg and Two 3000 mg (6- and 12-Hour Interval) in Adults and Adolescents (12 to 17 Years of Age)

Parameter	Single Dose 1500 mg Adults (N=14)	Two 3000 mg Doses 12-hour Interval Adults (N=13)	Two 3000 mg Doses 6-hour Interval Adults (N=13)	Single Dose 1500 mg Adolescents (N=13)	Two 3000 mg Doses 6-hour Interval Adolescents (N=12)
Concentration (8-12h) (µg/mL)	147 (153)	–	–	155 (60.9)	–
AUC(0-τ) (µg•h/mL)	–	6300 (61.2)	3040 (86.7)	–	4520 (74.5)
AUC(0-24) (µg•h/mL)	2750 (69.4)	15000 (62.4)	11000 (69.9)	3660 (87.2)	19200 (63.1)
AUC(0-48) (µg•h/mL)	2980 (67.0)	16400 (62.4)	12000 (68.9)	4070 (84.7)	21400 (63.4)
Ae total (mg)	322 (19.7)	1440 (15.3)	1240 (31.7)	352 (25.5)	1670 (25.3)
fe% (%)	21.5 (19.7)	24.0 (15.3)	20.7 (31.7)	23.4 (25.5)	27.9 (25.3)
CLr (L/h)	16.4 (19.6)	15.8 (13.0)	14.3 (33.3)	15.1 (25.9)	14.5 (26.4)

Source: Table 19 in clinical study report 2019N422403_00
Values are presented as geometric mean (%CVb), except for concentration, arithmetic mean (%CV). Fe% accounts for both doses for treatments where 2 doses were administered. CLr was calculated as Ae total/AUC_{0-t}
Abbreviations: Ae, Ae, amount of drug excreted in urine or feces; $AUC_{0-\tau}$, area under the concentration-time curve during the dosing interval; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h; AUC_{0-48}, area under the concentration-time curve from time 0 to 48 h; CLr, renal clearance; Fe, percentage of dose excreted in urine; N, number of subjects in the treatment group

Age- Geriatric

BTZ117349 (Part 3) was a 2-period, multiple dose, crossover study of gepotidacin to evaluate the effect of food on PK in healthy elderly subjects. The study enrolled 16 healthy subjects (56% male, 64 to 78 years of age, and 53 to 98 kg), who participated in two treatment periods (at least a 7-day washout window between periods) then crossed over to receive the other state:

- Period 1: 1500 mg oral dose of gepotidacin mesylate (2 × 750 mg (b) (4) tablet) twice daily in either fasted or fed state (moderate fat meal) for 5 consecutive days.
- Period 2: 1500 mg oral dose of gepotidacin mesylate (2 × 750-mg tablet) twice daily in either fasted or fed state (standard meal) for 5 consecutive days.

Serial plasma PK samples for gepotidacin were collected through 48 hours post dose for Periods 1 and 2, respectively, and the drug concentrations were evaluated using a validated bioanalytical method.

Gepotidacin AUC and C_{max} were approximately 15% and 7% higher with food, while the median T_{max} was 2.5 hours longer with food (T_{max} = 4 hours) (Table 127). Statistical assessment show that the ratio of geometric LS mean point estimates for gepotidacin exposures under fed conditions were comparable to fasted conditions, but both $AUC_{0\text{-}tau}$ and C_{max} 90% CI were marginally above 0.80 to 1.25 (Table 128).

As noted by the Applicant, gepotidacin steady-state exposures (which were achieved by Day 3) in healthy elderly subjects from this study were comparable to healthy non-elderly subjects in other studies administered the same dosage 1500 mg twice daily for 14 days with or without food (i.e., Study BTZ116778).

Table 127. Healthy Elderly Population Plasma Pharmacokinetic Parameters Under Fasted and Fed State

	GSK2140944 1500 mg Tablet/Fasted BID N=13	GSK2140944 1500 mg Tablet/Fed BID N=13
AUC(0-T) (µg.h/mL)	21.1 (28.8)	25.6 (35.5)
Cmax (µg/mL)	4.89 (33.8)	5.25 (38.2)
tmax (h)[b]	1.5 (1.0 – 3.0)	4.0 (1.5 – 6.0)
t1/2 (h)[c]	8.11 (15.7)	8.34 (12.8)
C_T (µg/mL) (Day 3)	0.661 (24.7)	0.805 (39.6)[d]
C_T (µg/mL) (Day 4)	0.722 (46.2)	0.632 (66.9)[d]
C_T (µg/mL) (Day 5)	0.761 (49.1)	0.743 (47.7)[e]

Source: Table 27 in clinical study report 2014N199850_00
[a] Geometric mean (CVb%)
[b] Median (range)
[c] Arithmetic mean (CVb%) and n=12
[d] n=15
[e] n=14
Abbreviations: $AUC_{0\text{-}T}$, area under the concentration-time curve during the dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; C_T, plasma concentration at the end of the dosing interval; N, number of subjects in the treatment group; $t_{1/2}$, half-life

Table 128. Statistical Assessment of Food Effect on Gepotidacin in Healthy Elderly Population

Statistic	Test	Reference	Geometric LS Mean		Ratio Test/Ref	90% CI
			Test Tablets/Fed	Reference Tablets/Fasted		
$AUC_{0\text{-}tau}$ (µg*h/mL)	13	13	25.76	22.31	1.155	(1.049, 1.271)
C_{max} (µg/mL)	13	13	5.33	4.99	1.068	(0.887, 1.287)

Source: Adapted from Table 29 in clinical study report 2014N199850_00
Abbreviations: $AUC_{0\text{-}tau}$, area under the concentration-time curve during the dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; Ref, reference

Race- Japanese

Study 213678 (Part 4)

Part 4 of the study was a double blind, placebo controlled, three period, randomized sequence (Periods 1 and 2 only) in Japanese healthy subjects. The primary objectives were 2-fold: 1) evaluate the effect of food on PK at a single 1500-mg dose and 2) evaluate the PK of two 3000 mg doses given 12 hours apart. Both objectives were evaluated for the mesylate to-be-market oral tablet formulation (b) (4)). An exploratory objective compared gepotidacin PK in Japanese subjects and non-Japanese subjects from other parts of study 213678 (see Section 8.1.4). The study enrolled 14 healthy subjects (57% male, 30 to 48 years of age, and 47 to 81 kg) who were randomized (10 active: 2 placebo) to each of the 2 sequences (1:1 ratio): HIJ versus IHJ. The washout period was at least 3 days between treatments.

- Treatment H: single 1500 mg oral dose of gepotidacin mesylate (2 × 750-mg tablet) or placebo under fed state (Japanese standard meal-total calories 875 kcal, 40% fat, 49% carbohydrate, 11% protein)
- Treatment I: single 1500 mg oral dose of gepotidacin mesylate (2 × 750-mg tablet) or placebo under fasted state
- Treatment J: two doses (given 12 hours apart) of 3000 mg oral dose of gepotidacin mesylate (4 × 750-mg tablet) or placebo under fed conditions (Japanese standard meal)

Serial plasma and urine PK samples for gepotidacin were collected up to 48 hours (period 1 and 2) 60 hours (period 3) post-dose for all treatments and concentrations were evaluated using a validated bioanalytical method and the parameters are reported in Table 129.

Gepotidacin AUC and C_{max} were approximately 10% and 5% higher with food, while the median T_{max} was 0.5 hours longer with food (T_{max} = 2 hours). As shown in Table 130, statistical assessment show that gepotidacin tablet under fed conditions met the 90% CI for AUC but the C_{max} was marginally above 0.80 to 1.25. Additionally, it appears that C_{max} had moderate within-subject variability (% coefficient of variation of ~30).

Table 129. Summary Statistics of Gepotidacin Plasma and Urine Pharmacokinetics Under Fed State

Statistic	Single dose 1500 mg (N=11)	Two 3000-mg Doses (N=11)	
		Dose 1	Dose 2
$AUC_{0\text{-}inf}$ (µg*h/mL)	22.3 (15.5)	NC	NC
$AUC_{0\text{-}12h}$ (µg*h/mL)	NC	37.3 (25.4)	46.7 (23.1)
C_{max} (µg/mL)	5.4 (27.8)	11.2 (45.0)	12.4 (21.3)
T_{max} (h)	2.0 (1.5, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)
$T_{1/2}$ (h)	12.8 (28.5)	12.6 (36.6)	NC
Fe (%)	19.6 (29.0)		22.2
CLr (L/h)	13.4 (31.9)		14.6 (19.3)

Source: Clinical Study report TMF-14741177 in tables 48, 49
Geometric mean (CV%b), T_{max} is median (range)
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve estimated to infinity; $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0 to 12 h; CLr, renal clearance; C_{max}, maximum plasma concentration; Fe, percentage of dose excreted in urine; N, number of subjects in the treatment group; NC, not calculated; $T_{1/2}$, half-life; T_{max}, time to maximum concentration

Table 130. Statistical Analysis of Gepotidacin Plasma Pharmacokinetic Parameters: Food Effect in Japanese Subjects, Parametric Analysis- Cohort 4

Parameter Treatment	N	n	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90% CI of the Ratio	Within-subject %CV
AUC(0-t) (µg•h/mL)							
Gepotidacin 1500 mg Fasted	11	11	20.0				
Gepotidacin 1500 mg Fed	11	11	21.9	Gepotidacin 1500 mg Fed/ Gepotidacin 1500 mg Fasted	1.09	(0.987, 1.21)	13.1
AUC(0-∞) (µg•h/mL)							
Gepotidacin 1500 mg Fasted	11	11	20.4				
Gepotidacin 1500 mg Fed	11	11	22.3	Gepotidacin 1500 mg Fed/ Gepotidacin 1500 mg Fasted	1.10	(0.991, 1.21)	12.7
Cmax (µg/mL)							
Gepotidacin 1500 mg Fasted	11	11	5.16				
Gepotidacin 1500 mg Fed	11	11	5.42	Gepotidacin 1500 mg Fed/ Gepotidacin 1500 mg Fasted	1.05	(0.824, 1.34)	31.7

Source: Table 46 in clinical study report TMF-14741177
A linear mixed-effect model with treatment and period as fixed effects and participant as a random effect was performed on the natural ln-transformed plasma parameters $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, and C_{max}
Abbreviations: $AUC_{0\text{-}\infty}$, area under the concentration-time curve estimated to infinity; $AUC_{0\text{-}t}$, from time 0 to last quantifiable timepoint; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; LS, least squares; N, number of participants in the treatment; n, number of participants with evaluable values

Reviewer's Comment:

The effect of food on PK was designed similarly to the other food effect studies (BTZ117349-part1, BTZ114595, and BTZ117349-part 3) in which the subjects were not given a high fat meal as recommended in the 2022 FDA Food Effect Guidance (FDA 2022a) (total calories- 800-1000, fat calories-500 to 600, 50% of calories are fat).

BTZ117351 (Parts 2 and 3)

Part 2 of the study was a 2-period, fixed sequence study that evaluated the PK of two single dose levels (1500 mg [750 mg × 2] and 3000 mg [750 mg × 4]) of gepotidacin RC free base tablet formulation in Japanese healthy subjects under fasted conditions. The study enrolled 10 healthy subjects (20% male, 44 to 64 years of age, and 50.1 to 73.7 kg), who participated in both treatment periods (at least a 3-day washout window between periods).

1. Treatment B: gepotidacin 1500-mg (2 × 750 mg) RC tablets – fasted
2. Treatment F: gepotidacin 3000-mg (4 × 750 mg) RC tablets – fasted

Part 3 of the study was a 3-period, randomized, double blind, placebo-controlled, fixed-sequence study that evaluated the PK of single ascending doses of 1500, 2250, 3000 mg gepotidacin oral tablet formulation (free base RC tablet) in Japanese healthy subjects under a fed state (standard Japanese meal). The study enrolled 12 healthy subjects (50% male, 28 to 56 years of age, and 50.1 to 79.8 kg) who participated in all three treatment periods or placebo (5:1 randomization) with at least a 3-day washout window between periods.

- Treatment E: gepotidacin 1500-mg (2 × 750 mg) RC tablets – fed
- Treatment G: gepotidacin 2250-mg (3 × 750 mg) RC tablets – fed
- Treatment H: gepotidacin 3000-mg (4 × 750 mg) RC tablets – fed
- Treatment I: placebo tablets - fed

Serial plasma and urine PK samples for gepotidacin were collected up to 48 hours post-dose for all treatments in Parts 2 and 3. Concentrations were evaluated using a validated bioanalytical method. The C_{max} and $AUC_{0\text{-}inf}$ for the 1500-mg dose was ~7 µg/mL and ~21 to 23 µg*hr/mL (Table 131). Two subjects (n = 1 on 1500 mg, and n = 1 on 3000 mg) were determined to be outliers based on Grubbs statistical test.

Dose proportionality was evaluated in two ways: 1) statistical analysis by Analysis of Variance was used for Part 2 and Part 3 data alone and pooled with geometric mean ratios and 90% CI for the ratios of dose-normalization of AUC and C_{max} for the doses of 1500 and 3000 mg, and 2) a power model was performed for dose-proportionality of Part 3 data only.

When evaluating Part 2 (excluding the 2 subjects identified as outliers) and Part 3 separately, the point estimates of the AUC and C_{max} were dose-proportional, but the C_{max} for both Part 2 (Table 132) and Part 3 (Table 133) was slightly outside of 90% CI range; however, when Parts 2 (removed outliers) and 3 were pooled together dose-proportionality was observed for AUCs and C_{max} (Table 134).

Table 131. Summary Statistics of Gepotidacin Plasma PK Parameters by Treatment of Three Dose Levels Under Fasted and Fed States (Parts 2+3)

	Part 2 (Fasted)		Part 3 (Fed)		
Parameter	**1500 mg (N=9)***	**3000 mg (N=9)***	**1500 mg (N=10)**	**2250 mg (N=10)**	**3000 mg (N=9)**
$AUC_{0\text{-}inf}$ (µg*h/mL)	21.4 (23.0)	44.1 (12.6)	22.9 (19.9)	37.2 (17.2)	50.2 (21.9)
C_{max} (µg/mL)	7.3 (36.1)	15.0 (29.3)	6.5 (27.7)	9.8 (21.1)	12.9 (21.1)
T_{max} (hr)	1.0 (0.5-1.5)	0.5 (0.5-2.5)	2.3 (1.0-4.0)	2.1 (1.5-4.0)	2.0 (1.0-3.0)
$T_{1/2}$ (hr)	10.7 (11.5)	8.9 (7.4)	9.2 (9.7)	8.2 (7.2)	7.9 (10.6)

Source Data: Adapted from Tables 17 and 18 in clinical study report 2017N322476
Values are presented as geometric mean (%CVb), except for T_{max} which is median (min, max)
*Subject (b) (6) 3000 mg) and Subject (b) (6) (1500 mg) were excluded as outliers based on the Grubbs' test of PK parameters
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; max, maximum; min, minimum; N, number of subjects in the treatment group; PK, pharmacokinetic; $T_{1/2}$, half-life; T_{max}, time to maximum concentration

Table 132. Dose-Proportionality Analysis of Plasma Gepotidacin Pharmacokinetic Parameters by Treatment- Part 2

Parameter	Treatment	LS Geometric Mean	LS Geometric Mean Ratio	90% CI of the LS Geometric Mean Ratio
All Subjects				
DNAUC(0-t) (h*ng/mL/mg)	RC 1500 mg	15.186		
	RC 3000 mg	15.387	1.013	(0.835, 1.229)
DNAUC(0-∞) (h*ng/mL/mg)	RC 1500 mg	15.423		
	RC 3000 mg	15.520	1.006	(0.831, 1.219)
DNCmax (ng/mL/mg)	RC 1500 mg	6.120		
	RC 3000 mg	5.112	0.835	(0.542, 1.287)
Outliers Excluded				
DNAUC(0-t) (h*ng/mL/mg)	RC 1500 mg	14.027		
	RC 3000 mg	14.624	1.043	(0.892, 1.218)
DNAUC(0-∞) (h*ng/mL/mg)	RC 1500 mg	14.258		
	RC 3000 mg	14.746	1.034	(0.885, 1.209)
DNCmax (ng/mL/mg)	RC 1500 mg	4.859		
	RC 3000 mg	4.994	1.028	(0.790, 1.338)

Source: Table 25 in clinical study report 2017N322476_00
A mixed effects model with treatment as fixed effect and subject within sequence as random effect was performed on the natural log-transformed parameters $DNAUC_{0\text{-}t}$, $DNAUC_{0\text{-}\infty}$, and DNC_{max} in Japanese subjects for Part 2 only.
Subject (b) (6) for RC 3000 mg and Subject (b) (6) or RC 1500 mg were excluded as outliers based on Grubbs' test of PK parameters.
Abbreviations: $AUC_{0\text{-}\infty}$, area under the concentration-time curve estimated to infinity; $AUC_{0\text{-}t}$, from time 0 to last quantifiable timepoint; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; PK, pharmacokinetic; RC, roller compacted

Table 133. Analysis of Dose Proportionality of Plasma Gepotidacin Pharmacokinetic Parameters for Fed Japanese Subjects- Part 3

Dose Range	Parameter	Estimated Slope of ln(dose)	Standard Error	90% CI (lower, upper)	p-value
1500 mg, 2250 mg, 3000 mg	AUC(0-t) (h*ng/mL)	1.152	0.054	(1.058, 1.246)	0.0119
	AUC(0-∞) (h*ng/mL)	1.146	0.054	(1.052, 1.239)	0.0149
	Cmax (ng/mL)	0.990	0.150	(0.730, 1.250)	0.9460

Source: Table 27 in clinical study report 2017N322476
To assess dose proportionality on Japanese subjects, the power model, ln(parameter)=ln(a)+b*ln(dose), was used to estimate the slope, corresponding 90% CI, and the p-value testing dose proportionality (b=1)
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; CI, confidence interval; C_{max}, maximum plasma concentration

Table 134. Analysis of Dose-Normalized Plasma Gepotidacin Pharmacokinetic Parameters for Pooled Japanese Subjects- Parts 2 and 3

Parameter	Treatment	LS Geometric Mean	LS Geometric Mean Ratio	90% CI of the LS Geometric Mean Ratio
All Subjects				
DNAUC(0-t) (h*ng/mL/mg)	RC 1500 mg	15.157		
	RC 3000 mg	16.014	1.057	(0.957, 1.166)
DNAUC(0-∞) (h*ng/mL/mg)	RC 1500 mg	15.348		
	RC 3000 mg	16.126	1.051	(0.952, 1.159)
DNCmax (ng/mL/mg)	RC 1500 mg	5.150		
	RC 3000 mg	4.736	0.919	(0.737, 1.146)
Outliers Excluded				
DNAUC(0-t) (h*ng/mL/mg)	RC 1500 mg	14.603		
	RC 3000 mg	15.751	1.079	(1.000, 1.163)
DNAUC(0-∞) (h*ng/mL/mg)	RC 1500 mg	14.794		
	RC 3000 mg	15.858	1.072	(0.994, 1.156)
DNCmax (ng/mL/mg)	RC 1500 mg	4.592		
	RC 3000 mg	4.671	1.017	(0.875, 1.182)

Source: Table 26 in clinical study report 2017N322476
A mixed effects model with treatment as fixed effect and subject within sequence as random effect was performed on the natural log-transformed parameters $DNAUC_{0-t}$, $DNAUC_{0-\infty}$, and DNC_{max} in Japanese subjects pooled for Part 2 and 3.
Subject (b) (6) for RC 3000 mg and Subject (b) (6) for RC 1500 mg were excluded as outliers based on Grubbs' test of PK parameters.
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; AUC_{0-t}, from time 0 to last quantifiable timepoint; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; PK, pharmacokinetic; RC, roller compacted

Reviewer's Comments:

Based on the data presented above, dose proportionality was demonstrated for both AUC and C_{max} of Japanese healthy subjects administered gepotidacin oral RC tablet for 3 single doses ranging from 1500 to 3000 mg. The findings were marginally different than Study 114595 which showed greater than dose proportionality, with C_{max} and AUC increasing over the dose range of 100 to 3000 mg. It is important to note that the two studies had several differences that most likely contributed to the different results. These differences include- population demographic (~80% Caucasian and ~80% male versus 100% Japanese and ~20% male), number of single

doses (5 versus 3), dose range (1500-3000 mg versus100-3000 mg), meal type (moderate fat meal vs. standard Japanese meal), gepotidacin matrix analyzed (whole blood vs. plasma), and formulation (oral capsule vs. RC tablet).

Hepatic Impairment

BTZ117352 was a phase 1, open label, two-part study that evaluated the PK of a single oral dose of gepotidacin 1500 mg (750 mg × 2 free base (b) (4) tablets) under a fed state (standard meal) in subjects with varying degrees of hepatic function. Among the 25 subjects (92% male, 84% Caucasian, 51 to 72 years of age, 73.7 to 115.8 kg, and 24 to 37 kg/m^2) enrolled in the study, eight had moderate hepatic impairment (Child Pugh 7 to 9) and eight had severe hepatic impairment (Child Pugh 10 to 15) with the remainder being healthy matched controls. The match was based on sex, age (approximately ± 10 years), and body mass index (approximately ± 20%).

Serial plasma and urine PK samples for gepotidacin were collected up to 48 hours post-dose for all groups and gepotidacin concentrations were evaluated using a validated bioanalytical method and the parameters are reported in Table 135.

When compared statistically to normal hepatic function, gepotidacin plasma AUC and C_{max} was numerically higher at 1.2-fold for moderate hepatic impairment (HI) and significantly higher at 1.7 and 1.9-fold for severe HI (Table 138). Although half-life and T_{max} were similar among the three populations of hepatic functions at ~8 to 9 hours and 2.25 to 3 hours, both apparent oral clearance and apparent volume of distribution decreased by 1.2-fold in moderate hepatic impairment and 1.6 and 1.8-fold in severe hepatic impairment as compared to normal hepatic function.

Approximately, 7.5%, 11%, and 20% of gepotidacin dose was eliminated in urine of subjects with normal hepatic function, moderate HI, and severe HI, respectively, with majority of drug elimination in urine by 12 hours post-administration. The mean renal clearance was >7.2 L/h (or 120 mL/min) for all degrees of hepatic functions; however, moderate HI and severe HI exhibited ~1.2-fold and 1.6-fold increased renal clearance compared to normal hepatic function, respectively (Table 136).

Reviewer's Comment:

Protein binding of gepotidacin was not evaluated in a clinical study. Considering gepotidacin binds to AAG and AAG has shown to be significantly reduced in patients with hepatic impairment (Verbeeck 2008), an understanding of the impact of gepotidacin binding to AAG in this population would have been important information. Primarily, severe hepatic impairment would have been the population to evaluate for unbound gepotidacin levels, as this population is most affected by alterations in AAG concentrations. However, the Applicant has proposed, and we agree, to avoid gepotidacin in patients with severe hepatic impairment.

Of note, the renal clearance and urine exposures from subjects with normal hepatic function was ~2-fold lower than other phase 1 studies that evaluated urine PK. One reason for this appears to be a possible issue with the 0–2-hour time point collection for normal subjects as the total amount of gepotidacin excreted in urine at 2 hours was 5% (based on arithmetic mean). This is 10x lower than the amount excreted by subjects with normal renal function in the clinical study BTZ116849-Renal impairment study, which had ~50% of the total amount excreted in urine by2 hours.

Table 135. Summary of Gepotidacin Plasma and Urine Pharmacokinetic Parameters by Hepatic Group

Parameter	Normal Hepatic Function (N=9)	Moderate Hepatic Impairment (N=8)	Severe Hepatic Impairment (N=8)
AUC_{inf} (µg*hr/mL)	15.9 (44.1)	19.5 (42.6)	25.4 (30.1)
C_{max} (µg/mL)	3.2 (85.0)	3.9 (64.1)	5.5 (42.7)
T_{max} (hr)	3.0 (1.5, 6.0)	2.8 (2.5, 4.0)	2.3 (0.5, 4.0)
$T_{1/2}$ (hr)	9.1 (14.9)	8.5 (12.3)	8.2 (15.2)
CL/F (L/hr)	94.4 (44.1)	76.9 (42.6)	59.0 (30.1)
Vz/F (L)	1235 (57.5)	945 (50.3)	699 (41.7)
CL_r (L/hr)	7.6 (46.6)*	9.1 (32.8)*	11.8 (38.7)*
Fe%	7.5 (61.9)*	11.2 (70.9)*	19.9 (52.2)*
Ae total (mg)	113 (61.9)*	168 (70.9)*	299 (52.2)*

Source: Adapted from Tables 12 and 15 from clinical study report 2018N388749_00
*n=6 subjects in each cohort. The Applicant noted that there were protocol deviations among several subjects due to missed assessments or procedures occurring within the 48-hour urine PK collection. Therefore, the subject's data were excluded from the summary table.
Values are presented as geometric mean (%CVb), except for T_{max} which is presented as median (min, max)
Abbreviations: Ae, amount of drug excreted in urine or feces; AUC_{inf}, area under the curve from 0 h extrapolating to infinity; CL/F, apparent oral clearance (Dose/AUCinf); CL_r, renal clearance (total amount excreted/AUC0-t); C_{max}, maximum concentration; Fe, fraction of the dose administered excreted unchanged in urine; GMCV, geometric coefficient of variation; N, number of subjects in the hepatic function group; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; T_{max}, time to maximum concentration Vz/F, apparent volume of distribution (CL/terminal phase rate constant)

Table 136. Analysis of Variance of Gepotidacin Plasma Pharmacokinetic Parameters by Hepatic Function

Parameter	Hepatic Function Group	N	n	Geometric LS Means	Ratio of Geometric LS Means (Relative to Normal)	90% CI of the Ratio
AUC(0-∞) (ng•hr/mL)	Moderate	8	8	19506	1.2272	(0.8614, 1.7482)
	Normal	9	9	15895		
	Severe	8	8	25416	1.7189	(1.2704, 2.3257)
	Normal	8	8	14786		
Cmax (ng/mL)	Moderate	8	8	3914	1.2243	(0.6911, 2.1688)
	Normal	9	9	3197		
	Severe	8	8	5542	1.8720	(1.1003, 3.1848)
	Normal	8	8	2960		

Source: Table 13 from clinical study report 2018N388749_00
Analysis of variance with hepatic function group as a fixed effect was performed on the natural In-transformed parameters $AUC_{0-\infty}$ and C_{max}
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; LS, least squares; N, number of participants in the hepatic function group; n, number of participants with evaluable data

Renal Impairment

BTZ116849 was a phase 1, open label, parallel group, two-part, match paired study that evaluated the PK of a single IV dose of gepotidacin 750 mg over 2 hours in healthy subjects with varying degrees of renal impairment who were enrolled in the following groups according to renal function, and matched to normal renal function based on sex, age (approximately ± 10 years), and body mass index (approximately ±20%).

- Group A: normal renal function (estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m^2 or creatinine clearance ≥90 mL/min)
- Group B: subjects with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2)
- Group C: subjects with severe renal impairment and subjects with end stage renal disease (ESRD) not on hemodialysis (eGFR <30 mL/min/1.73 m^2)
- Group D: subjects with ESRD on intermittent hemodialysis (IHD)

The study enrolled 32 subjects (8 per group) of which 72% were male, with ages that ranged from 38 to 79 years and a body mass index (BMI) that ranged from 21 to 39 kg/m^2. Of note, Modification of Diet in Renal Disease (MDRD) equation was used to calculate the estimated glomerular filtration rate (eGFR) for subjects with renal impairment, and the renal function for subjects with normal renal function was calculated either with MDRD equation for eGFR or Cockcroft-Gault (total body weight) equation for creatinine clearance. For subjects with ESRD on IHD, gepotidacin was administered either 2 hours before initiation of the last IHD (Period 1-ESRD before hemodialysis) and started 2 hours after completion of the last IHD (Period 2-ESRD after hemodialysis).

Serial plasma and urine PK samples for gepotidacin were collected up to 48 hours post-dose for all groups and dialysate fluid collection for PK in Group D was collected on Day 1 after dosing (Period 1 only) hourly after the start of the hemodialysis session (~4 hours). Gepotidacin concentrations were evaluated using a validated bioanalytical method and the parameters are reported in Table 137.

Gepotidacin exposures increased with the increase in the degree of renal impairment. Differences in C_{max} and AUC_{inf} were <2-fold for eGFR ≥30 mL/min compared to normal renal function. $AUC_{0\text{-}inf}$ in subjects with eGFR <30 mL/min or subjects with ESRD on IHD were ~2 to 4.5-fold higher when compared to subjects with normal renal function (Table 138). Of note, mean gepotidacin $t_{1/2}$ were similar among the various renal classifications at ~10 to 11 hours.

Approximately 20% and 40% of gepotidacin dose was eliminated in urine for eGFR ≥30 to 60 and eGFR ≥60 mL/min, respectively, with the majority of the drug in urine by 6 hours post-administration; meanwhile, renal clearance was >7.2 L/h (or 120 mL/min) for subjects with eGFR >30 mL/min, which indicates that gepotidacin undergoes renal tubular secretion in these subjects. The hemodialysis clearance at ≤ 4 hours was comparable to the renal clearance seen in moderate renal impairment; however, only ~6% of the gepotidacin dose was removed by intermittent hemodialysis.

Reviewer's Comments:

The clinical pharmacology review team sent an information request recommending the Applicant to align with the 2024 Renal Impairment Guidance for Industry (FDA 2024) and reassess the PK parameters and exposures based on individualized (de-indexed) MDRD calculated eGFR (mL/min) instead of indexed MDRD calculated eGFR (mL/min/1.73m^2) for all subjects. As detailed in Table 137, using the de-indexed eGFR to reclassify renal function status only impacted one subject in normal renal function group (now classified as mild renal impairment) and one subject in severe/ESRD not on IHD that was reclassified as moderate renal impairment.

Table 137. Summary of Gepotidacin NCA Plasma, Urine, Dialysis PK Parameters for Subjects Classified Based on Indexed eGFR/CLcr and De-Indexed eGFR

	Normal Renal Function		Mild Renal Impairment	Moderate Renal Impairment		Severe/ESRD (Not on IHD)		ESRD on IHD (Before IHD)	ESRD on IHD (After IHD)
Parameter	De-indexed eGFR (N=7)	Indexed eGFR or CrCl (N=8)	De-indexed eGFR (N=1)	De-indexed eGFR (N=9)	Indexed eGFR (N=8)	De-indexed eGFR (N=7)	Indexed eGFR (N=8)	De-indexed, indexed, CrCl (N=8)	De-indexed, indexed, CrCl (N=8)
$AUC_{0\text{-inf}}$ (µg*hr/mL)	14.3 (19.0)	14.8 (20.7)	19.4	22.2 (16.1)	22.4 (17.0)	29.9 (18.3)	28.5 (21.4)	35.2 (95.0)	60.5 (140.5)
C_{max} (µg/mL)	4.3 (14.2)	4.5 (16.3)	5.7	5.2 (16.2)	5.3 (16.0)	7.6 (14.1)	7.1 (23.3)	10.1 (216.3)	26.8 (797.1)
$T_{1/2}$ (hr)	11.5 (12.9)	11.5 (11.9)	11.7	11.0 (15.2)	10.9 (16.1)	11.0 (14.3)	11.1 (13.4)	9.5 (8.4)	10.8 (16.4)
CL (L/hr)	52.5 (19.0)	50.6 (20.7)	38.7	33.8 (16.1)	33.5 (17.0)	25.1 (18.3)	26.3 (21.4)	21.3 (95.0)	12.4 (140.5)
CL_r (L/hr)	19.9 (17.4)	19.2 (18.8)	15.2	7.4 (42.4)	7.6 (44.3)	1.9 (73.7)	2.1 (84.3)	0.3* (101.7)	0.1* (277.5)
Fe%	37.0 (16.2)	37.4 (15.2)	40.3	21.3 (38.7)	22.1 (39.4)	7.2 (65.6)	7.9 (68.3)	1.1* (96.4)	1.5* (64.7)
CL_d (L/hr)	NC	NC	NC	NC	NC	NC	NC	6.6 (15.8)	NC
Frem% (0-4)	NC	NC	NC	NC	NC	NC	NC	5.9 (26.2)	NC

Source: Adapted from Table 2 of the information request sequence 32 (12/19/2024), Table 19 from study report 2016N307631_00, and BTZ116849 ADPP dataset (7/26/2024)
Values presented as geometric mean (%CVb)
*n=3 subjects
Abbreviations: AUC_{0-}inf, area under the curve from 0 h extrapolating to infinity; CL, total body clearance; CL_d, dialysis clearance (total amount recovered in dialysate/partial AUC); CL_r, renal clearance (total amount excreted/AUC0-t); CrCl, creatinine clearance; C_{max}, maximum concentration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Fe, fraction of the dose administered excreted unchanged in urine; Frem%(0-4), fraction(%) of the dose removed by hemodialysis from 0 to 4 hours (or end of dialysis if <4 hours) after the start of intermittent hemodialysis GMCV, geometric coefficient of variation; IHD, intermittent hemodialysis; N, number of subjects; NC, data not calculated; NCA, Noncompartmental analysis; PK, pharmacokinetic; $T_{1/2}$, terminal half-life

Table 138. Comparison of Geometric Mean AUC_{0-inf} in Subjects With Varying Degree of Renal Impairment to Subjects With Normal Renal Function (eGFR ≥90 mL/min)

		Fold Increase From Normal Renal Function (eGFR ≥90 mL/min)	
Group (Based eGFR, mL/min)	**N**	**C_{max}**	**AUC_{0-inf}**
Mild impairment (≥60 to <90)	1	1.3	1.4
Moderate impairment (≥30 to <60)	9	1.2	1.6
Severe impairment and ESRD not on IHD (<30)	7	1.7	2.1
ESRD, dosed before IHD	8	2.3	2.5
ESRD, dosed after IHD	8	6.2	4.2

Source: Reviewer's Analysis of Table 2 of the information request sequence 32 (12/19/2024)
Abbreviations: AUC_{0-inf}, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; IHD, intermittent hemodialysis; N, number of subjects for each renal group

14.2.1.6. Extrinsic Factors

Effect of Itraconazole on Gepotidacin Pharmacokinetics

Part 2 of study BTZ117349 was a single center, open label, fixed sequence DDI study that evaluated the effect of itraconazole (a known strong CYP3A4 and a P-gp inhibitor) on gepotidacin (a suspected CYP3A4 and P-gp substrate) PK. The study enrolled 15 healthy subjects (87% male, 20 to 61 years of age, and 60.7 to 108.0 kg) in the following treatment schematic:

- Day 1: Single 1500 mg oral dose of gepotidacin (2 × 750 mg mesylate tablet) with a standard meal.
- Day 4-6: Oral itraconazole 200 mg once daily.
- Day 7: Oral itraconazole 200 mg × 1 then 1 hour later a single dose of 1500 mg oral tablet of gepotidacin with a standard meal.
- Day 8-9: Oral itraconazole 200 mg once daily

Serial plasma PK samples for gepotidacin were collected through 48- and 72-hours post-dose for Day 1 and Day 7, respectively. The gepotidacin concentrations were evaluated using a validated bioanalytical method and PK parameters were compared based on geometric mean ratios (between the dosing period 2 [test] and dosing period 1 [reference] and associated 90% CI. The findings are reported in Table 139.

Following co-administration of itraconazole with gepotidacin, gepotidacin plasma AUC and C_{max} significantly increased by ~48% and ~42%, respectively.

Reviewer's Comments:

It is not clear from the clinical study if the magnitude of the interaction was mainly due to CYP3A4 inhibition, P-gp inhibition, or both.

Table 139. Statistical Analysis of Selected Gepotidacin Plasma Pharmacokinetic Parameters After Coadministration With Itraconazole (Part 2)

Plasma Parameter	Geometric LS Means		Ratio of Geometric LS Means Test/Reference	90% CI of the Ratio
	Test	Reference		
	Gepotidacin 1500 mg + Itraconazole 200 mg N=15	Gepotidacin 1500 mg N=15		
AUC(0-inf) (µg.h/mL)	26.8	18.1	1.48	1.40, 1.57
Cmax (µg/mL)	5.58	3.93	1.42	1.25, 1.62
tmax (h)[a]	2.00 (1.00, 4.00)	3.00 (1.00, 4.00)	–	–

Source: Table 25 of Applicant's Summary of Clinical Pharmacology Studies
[a] Median (range)
Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; LS, least squares; N, number of subjects in the treatment group; T_{max}, time to maximum concentration

Effect of Rifampicin on Gepotidacin Pharmacokinetics

Study 213678 (Cohort 2) was a single center, open label, fixed sequence DDI study that evaluated the effect of rifampin (a known strong CYP3A4 inducer) on gepotidacin (a suspected CYP3A4 substrate) PK. The study enrolled 17 healthy subjects (76% male, 25 to 51 years of age, and 59.3 to 105.6 kg) who participated in two treatment periods (at least a 3-day washout window between periods) as follows:

- Period 1: Single 1500 mg oral dose of gepotidacin (2x 750 mg to-be-marketed mesylate tablet) with a standard meal.
- Period 2: Nine consecutive nights (Days 1 to 9) of oral rifampicin 600 mg once daily in the evening and a single dose of 1500 mg oral tablet of gepotidacin administered in the morning on Day 8 with a standard meal.

Serial plasma and urine PK samples for gepotidacin were collected through 48 hours post-dose for Periods 1 and 2. The gepotidacin concentrations were evaluated using a validated bioanalytical method and PK parameters were compared based on geometric mean ratios (between the dosing period 2 [test] and dosing period 1 [reference] and associated 90% CI. The findings are reported in Table 140.

Following co-administration of rifampicin (evening on Day 7) with gepotidacin (morning on Day 8), gepotidacin plasma AUC and C_{max} significantly decreased by ~52% and ~27%, respectively

Table 140. Statistical Analysis of Selected Gepotidacin Plasma and Urine Pharmacokinetic Parameters After Coadministration With Rifampicin (Cohort 2)

Matrix Parameter	Geometric LS Means Test Gepotidacin 1500 mg + Rifampicin 600 mg N=14	Geometric LS Means Reference Gepotidacin 1500 mg N=17	Ratio of Geometric LS Means Test/Reference	90% CI of the Ratio
Plasma				
AUC(0-inf) (µg.h/mL)	9.30	19.3	0.478	0.435, 0.526
Cmax (µg/mL)	2.73	3.74	0.730	0.635, 0.840
tmax (h)[a]	2.00 (1.00, 4.00)	2.50 (1.00, 6.00)	–	–
Urine				
AUC(0-24) (µg.h/mL)	1350	3080	0.439	0.370, 0.521
Ae total (mg)	156	313	0.499	0.441, 0.565
CLr (L/h)	17.1	16.5	1.04	0.950, 1.13

Source: Table 24 of Applicant's Summary of Clinical Pharmacology Studies
[a] Median (range)
Abbreviations: Ae, amount of drug excreted in urine or feces; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h; AUC_{0-inf}, area under the curve from 0 h extrapolating to infinity; CI, confidence interval; CL_r, renal clearance (total amount excreted/AUC0-t); C_{max}, maximum concentration; LS, least squares; N, number of subjects in the treatment group; T_{max}, time to maximum concentration

Reviewer's Comments:

Rifampicin significantly decreased gepotidacin urine AUC_{0-24} by 56%; this led to an average urine concentration of 56 µg/mL. As mentioned in Sections 5.1 and 6.1, the interpretation of urine drug concentrations in relation to the plasma MIC is not clear.

Effect of Cimetidine on Gepotidacin Pharmacokinetics

Study 213678 (Cohort 1) was a single center, open label, fixed sequence DDI study that evaluated the effect of cimetidine (a known nonspecific inhibitor of OCT and MATE) on gepotidacin (a suspected MATE1 and MATE2-K substrate) PK. The study enrolled 14 healthy subjects (50% female) with mean (range) age of ~39 (25 to 51) years of age who participated in two treatment periods (at least a 3-day washout window between periods) as follows:

- Period 1: Single 1500 mg oral dose of gepotidacin (2 × 750 mg to-be-marketed mesylate tablet) with a standard meal.
- Period 2: Four consecutive days (Days 1 to 4) of oral cimetidine 400 mg four times daily. On Day 2, a single dose of 1500 mg oral tablet of gepotidacin with a standard meal was co-administered 1 hour after the first dose of cimetidine.

Serial plasma and urine PK samples for gepotidacin were collected through 48 hours post-dose for Periods 1 and 2. To assess if the MATE transporter was fully inhibited based on clinical exposures and half-maximal inhibitory concentration from in vitro data, three cimetidine plasma concentrations were collected 1 hour after the first dose on Days 2 to 4. Gepotidacin and cimetidine drug concentrations were evaluated using a validated bioanalytical method and gepotidacin PK parameters were compared based on geometric mean ratios (between the dosing

period 2 [test] and dosing period 1 [reference] and associated 90% CI. The findings are reported in Table 141.

Following co-administration of cimetidine with gepotidacin, gepotidacin plasma AUC significantly increased by ~16%, while the gepotidacin plasma C_{max} was decreased by 6%. The results suggest that there is no DDI between gepotidacin and cimetidine. In addition, the gepotidacin urine PK was not affected when co-administered with cimetidine; this suggests that MATEs, OCT2/OAT1 and OAT3 are likely not contributing to the renal tubular secretion of gepotidacin.

Table 141. Statistical Analysis of Selected Gepotidacin Plasma and Urine Pharmacokinetic Parameters After Coadministration With Cimetidine (Cohort 1)

Matrix Parameter	Geometric LS Means Test Gepotidacin 1500 mg + Cimetidine 400 mg N=13	Geometric LS Means Reference Gepotidacin 1500 mg N=14	Ratio of Geometric LS Means Test/Reference	90% CI of the Ratio
Plasma				
AUC(0-inf) (µg.h/mL)	23.9	20.6	1.16	1.06, 1.26
Cmax (µg/mL)	4.55	4.82	0.944	0.753, 1.18
tmax (h)[a]	2.50 (1.00, 4.00)	2.50 (1.00, 4.00)	–	–
Urine				
AUC(0-24) (µg.h/mL)	3610	3290	1.10	0.948, 1.27
Ae total (mg)	410	338[b]	1.21	1.00, 1.47
CLr (L/h)	17.6	16.1[b]	1.10	0.930, 23.0

Source: Table 23 of Applicant's Summary of Clinical Pharmacology Studies
a Median (range)
b n=12
Abbreviations: Ae, amount of drug excreted in urine or feces; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h; AUC_{0-inf}, area under the curve from 0 h extrapolating to infinity; CI, confidence interval; CLr, renal clearance (total amount excreted/AUC_{0-t}); C_{max}, maximum concentration; LS, least squares; N, number of subjects in the treatment group; t_{max}, time to maximum concentration

Reviewer's Comments:

Given that gepotidacin is a P-gp substrate (a transporter found in the apical side of the renal tubule which contributes to the secretion of drugs in the urine), it is possible that P-gp is confounding the above results. Therefore, despite the no observed effect of cimetidine on urinary excretion of gepotidacin inhibiting MATEs, gepotidacin plasma and urine exposures and renal clearance (CLr) would possibly be similar with or without cimetidine.

Effect of Gepotidacin on Midazolam and Digoxin Pharmacokinetics

Study 213678 (Cohort 3) was a single center, open label, two-period, two-sequence, randomized (1 of 2 treatment sequence in a 1:1 ratio), crossover DDI study that evaluated the effect of gepotidacin (a suspected P-gp and CYP3A4 inhibitor) on digoxin (a known P-gp substrate) and midazolam (a known CYP3A4 substrate) PK. The study enrolled 19 healthy subjects (58% male) with mean (range) age of ~37 (24 to 50) years of age who were randomized to one of two treatment sequence groups (at least 9 subjects/group) in a 1:1 ratio to receive Sequence 1 (treatment F, washout, and treatment G) or Sequence 2 (treatment G, washout, and treatment F). Of note, there was at least a 10-day washout period between each treatment.

- Treatment F: Digoxin 0.5 mg (tablet) plus midazolam 2 mg (2 mg/mL syrup) on Day 1
- Treatment G: Two doses of 3000 mg gepotidacin (12 hours apart, each with a standard meal) co-administered with digoxin 0.5 mg (tablet) plus midazolam 2 mg, with the 2 probe drugs administered with the second daily dose of gepotidacin only on Day 1.

Serial plasma PK samples for gepotidacin, digoxin, and midazolam were collected through 60-, 96-, and 48-hours post-dose, respectively, and concentrations for each drug were evaluated using a validated bioanalytical method. The findings for each substrate are reported in Table 142 and Table 143.

Following administration with gepotidacin, midazolam plasma AUC_{inf} was significantly increased by 90%. This suggests that gepotidacin is a weak CYP3A4 inhibitor. In addition, the molecular weight adjusted metabolite to parent ratio based on AUC_{inf} (i.e., 1'-hydroxymidazolam: midazolam) was significantly decreased by ~40%; this indicates that gepotidacin contributed to the inhibition of metabolite production.

When gepotidacin was co-administered with digoxin, digoxin plasma AUC_{inf} increased by 1.12-fold and C_{max} increased by 1.53-fold. Digoxin AUC does not support that gepotidacin is a clinically relevant P-gp inhibitor; however, the digoxin C_{max} increase is a potentially clinically significant interaction due to digoxin being a narrow therapeutic index drug.

Table 142. Statistical Analysis of Selected Midazolam and 1'-Hydroxymidazolam Plasma Pharmacokinetic Parameters After Coadministration With Gepotidacin (Cohort 3)

Analyte Plasma Parameter	Geometric LS Means Test Gepotidacin 2 × 3000 mg + Digoxin 0.5 mg + Midazolam 2 mg N=18	Geometric LS Means Reference Digoxin 0.5 mg + Midazolam 2 mg N=19	Ratio of Geometric LS Means Test/Reference	90% CI of the Ratio
Midazolam				
AUC(0-inf) (ng.h/mL)	47.4	24.9	1.90	1.62, 2.23
Cmax (ng/mL)	6.51	5.24	1.24	1.05, 1.48
tmax (h)[a]	0.50 (0.50, 4.00)	0.65 (0.50, 2.50)	–	–
1'-Hydroxymidazolam				
AUC metabolite/parent	0.184	0.299	0.617	0.526, 0.723

Source: Table 27 of Applicant's Summary of Clinical Pharmacology Studies
[a] Median (range)
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-inf}}$, area under the curve from 0 h extrapolating to infinity; CI, confidence interval; C_{max}, maximum concentration; LS, least squares; N, number of subjects in the treatment group; t_{max}, time to maximum concentration

Table 143. Statistical Analysis of Selected Digoxin Plasma PK Parameters After Coadministration With Gepotidacin, Cohort 3, Study 213678

Plasma Parameter	Geometric LS Means Test Gepotidacin 2 × 3000 mg + Digoxin 0.5 mg + Midazolam 2 mg N=18	Geometric LS Means Reference Digoxin 0.5 mg + Midazolam 2 mg N=19	Ratio of Geometric LS Means Test/Reference	90% CI of the Ratio
AUC(0-inf) (pg.h/mL)	34500	30700	1.12	0.983, 1.28
Cmax (pg/mL)	2380	1550	1.53	1.27, 1.85
tmax (h)[a]	1.28 (0.50, 4.00)	2.00 (0.50, 4.00)	–	–

Source: Table 26 of Applicant's Summary of Clinical Pharmacology Studies
[a] Median (range)
Abbreviations: $AUC_{0\text{-inf}}$, area under the curve from 0 h extrapolating to infinity; CI, confidence interval; C_{max}, maximum concentration; LS, least squares; N, number of subjects in the treatment group; PK, pharmacokinetic; t_{max}, time to maximum concentration

14.2.2. Infected Subjects

Study 206899

Study 206899 was a phase 2a, single-center, open label study that determined the PK parameters in both plasma and urine of adult female subjects with cystitis that received gepotidacin oral free base tablets (b) (4) at 1500 mg twice daily for 5 days (standardized meal or snacks).

Serial plasma and urine PK samples for gepotidacin were collected up to 12 hours post-dose for the first dose on Day 1 and the time-matched dose on Day 4. Predose plasma PK samples were collected before each time-matched dose on Days 1 through 5. Predose urine PK samples were collected 0 to 2 hours before each time-matched dose on Days 1 through 5. Only 1 sample was collected when serial and predose samples overlapped.

A total of 22 female subjects (19 to 60 years of age and 50 to 106 kg) were enrolled in the study. Statistical analysis of gepotidacin predose plasma concentrations from Days 1 to 5 showed that steady state was achieved by Day 3. The PK for plasma and urine of gepotidacin based on noncompartmental analysis are shown in Table 144.

Overall, gepotidacin geometric mean and between subject variability systemic exposures and CLr in infected subjects were generally comparable to values observed in healthy subjects in the phase 1 studies. Meanwhile, the amount of dose excreted in urine over the 12-hour dosing interval on Day 1 was slightly higher than healthy subjects with normal or mild renal function in Study BTZ117352 (20% versus 7%).

Table 144. Summary Statistics of Derived Gepotidacin Plasma and Urine Pharmacokinetic Parameters in Adult Female Subjects With uUTI

Parameter	Day 1	Day 4
Plasma		
$AUC_{0\text{-}12h}$ (µg*h/mL)	20.2 (28.6) n=20	29.2 (31.8) n=21
C_{max} (µg/mL)	5.89 (47.3) n=20	8.44 (38.0) n=21
T_{max} (hours)	1.5 (0.47, 3.07) n=20	1.9 (0.45, 4.12) n=21
CL_{ss}/F (L/h)		51.2 (31.8) n=21
Ro		1.4 (20.4) n=19
Urine		
Ae 12h (mg)	299 (107.6) n=20	460 (55.8) n=21
Urine $AUC_{0\text{-}12h}$ (µg*h/mL)	3742 (93.9) n=16	5973 (87.2) n=18
Fe%	19.9 (107.6) n=20	30.7 (55.8) n=21
CLr (L/h)	14.8 (118.2) n=20	15.7 (45.2) n=21

Source: Adapted from Tables 20, 22 in clinical study report 2018N388745_00.
Note: values are presented as geometric mean (%CVb), except for T_{max} which is presented as median (min, max)
Two subjects were excluded from the summary statistics analysis on Day 1 due to emesis.
Abbreviations: Ae, amount of drug excreted in urine or feces; $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0 to 12 h; CL_r, renal clearance (total amount excreted/AUC0-t); CL_{ss}/F, apparent total body clearance after oral administration (at steady state); C_{max}, maximum concentration; Fe, fraction of the dose administered excreted unchanged in urine; n, number of subjects; Ro, accumulation ratio T_{max}, time to maximum concentration; uUTI, uncomplicated urinary tract infection

14.3. Bioanalytical Method Validation and Performance

The bioanalytical methods validation was performed for determination of gepotidacin in blood, plasma, urine, and dialysate using either ultra-high performance liquid chromatography-mass spectroscopy/mass spectroscopy or high-performance liquid chromatography-mass spectroscopy/mass spectroscopy.

The bioanalytical methods used to measure concentrations of gepotidacin in human biological samples were acceptable and met precision and accuracy criteria (±15%, ±20% at the lower limit of quantification) and the incurred sample re-analysis criteria (≥66.7%) as recommended in the ICH M10 Bioanalytical Method Validation and Study Sample Analysis- Guidance for Industry (2022) (FDA 2022b). Of note, incurred sample re-analyses were not conducted for gepotidacin concentrations in urine for studies BTZ 114595, BTZ115198. For additional information see Table 145 and Table 146.

Table 145. Review of Bioanalytical Method Validation and Performance for Plasma and Whole Blood Assay

Method Parameters	Method Details		
Method type	UHPLC- MS/MS	UHPLC-MS/MS	HPLC-MS/MS
Method number	P1184.00, P1184.01	GSK2140944HUPLVALC	GSK2140944HUBHVALA
Validation report#	2013N158095_00	2013N177569_00	2011N119871_00
Studies analyzed	BTZ116778, BTZ116849, BTZ117349, BTZ117351, BTZ117352, EAGLE-2, 206899, 209611, 213678	BTZ115774	BTZ 114595, BTZ115198
Biological matrix	Plasma	Plasma	Whole blood
Method validation summary			
Validation range (ng/mL)	10 to 5000	10 to 10000	10 to 5000
Within-run accuracy (all QC concentrations)	-0.445 to 8.41%	-3.4 to 11.7%	-4.5 to 5.9%
Within-run precision (all QC concentrations)	≤7.96%	≤8.2%	≤7.0%
Inter-run accuracy (all QC concentrations)	0.631 to 6.10%	-1.5 to 7.6%	-0.9 to 4.3%
Inter-run precision (all QC concentrations)	≤5.4%	≤5.2%	≤2.7%
Long-term storage	707 days at -25°C and -80°C	41 days at -80°C	319 days at -20°C
Method performance summary			
Incurred Sample Reanalysis	89.0	>66.7%	≥66.7
Inter-run accuracy	-5.1 to 10.9	-2.6 to 1.0	-2.6 to 2.2
Inter-run precision	≤23.1*	≤7.5	≤8.1

Source: Reviewer's analysis
*Study117349 had 1 of 25 samples of QC2 (~60 ng/mL) that did not meet acceptable criteria (125 ng/mL); if sample removed, then the %CV was 3.8. There is no impact on data. All other studies had %CV <15%.
Abbreviations: CV%, co-efficient of variation expressed as percent; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation; QC, quality control; RE%, relative error expressed as percent; UHPLC-MS/MS, ultra high-performance liquid chromatography-tandem mass spectrometry

Table 146**. Review of Bioanalytical Method Validation and Performance for Urine and Dialysate**

Method Parameters	**Method Details**		
Method type	HPLC- MS/MS	HPLC-MS/MS	UHPLC- MS/MS
Method number	P1312.00, P1312.01	GSK2140944HUURVALA	P1512.00
Validation report#	2014N220714_01	2011N124449_00	2016N304915_00
Studies analyzed	BTZ116849, BTZ117351, BTZ117352, 209611, 213678, 206899, EAGLE-2	BTZ 114595, BTZ115198	BTZ116849
Biological matrix	Urine		Dialysate
Method validation summary			
Validation range (ng/mL)	1,000 to 500,000	100 to 50,000	10 to 5,000
Within-run accuracy (all QC concentrations)	-9.7 to 7.0%	-5.7 to 7.2%	-17.9[a] to 15.8%
Within-run precision (all QC concentrations)	≤8.05%	≤8.4%	≤ 7.8%
Inter-run accuracy (all QC concentrations)	-6.90 to 4.4%	-0.8 to 2.8%	-3.1 to 2.6%
Inter-run precision (all QC concentrations)	≤6.8	≤5.8%	≤15.8[a]%
Long-term storage	1125 days at -25°C and -80°C	70 days at 4°C	167 days at -20°C and -70°C
Method performance summary			
Incurred sample reanalysis	88.9%	Not conducted for either study	78.6%
Inter-run accuracy (all QC concentrations)	-5.7 to 7.3	-5.0 to 7.4%	0.8 to 8.2
Inter-run precision (all QC concentrations)	≤13.7	≤12.9	≤10.7

Source: Reviewer's analysis
[a] LLOQ (10 ng/mL) were -17.9% and 15.8%; other QC concentrations were <15%
Abbreviations: CV%, co-efficient of variation expressed as percent; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation; QC, quality control; RE%, relative error expressed as percent; UHPLC-MS/MS, ultra high-performance liquid chromatography-tandem

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

The population PK analyses were considered reasonable for describing gepotidacin concentrations in plasma and urine. The PK model was used to predict exposure metrics used for the exposure-efficacy (microbiological, clinical and therapeutic) and exposure-safety (cholinergic adverse events) analyses. The PK and PD modelling were utilized to support the current submission as outlined below:

Table 147. Utility of the Population PK Modeling

Utility of the Final Model	Reviewer's Comments
• The PK model of a 2-compartment disposition model with a delayed absorption (3 and 4 transit compartments for fasted and fed status, respectively) and linear elimination from the central compartment. Body weight on all clearances and volumes parameters and eGFR on renal clearance (CLr) were the most significant covariates affecting gepotidacin exposure. The estimated bioavailability was 48.9%. • The PK model-predicted plasma concentrations were used to evaluate the relationship between gepotidacin plasma exposure and the observed efficacy responses (microbiological, clinical and therapeutic), and between gepotidacin plasma exposure and the occurrence of treatment emergent cholinergic adverse events. • No exposure-efficacy response relationship was observed for the microbiological, clinical and therapeutic responses in the phase 3 study, EAGLE-2. • No exposure-treatment emergent cholinergic adverse events relationship was observed for treatment-emergent cholinergic adverse events in the phase 3 study, EAGLE-2 and the Japanese phase 3 study, EAGLE-J.	• The PK model reasonably predicted median and individual observed concentrations of gepotidacin and their variability in healthy volunteers and patients with uUTI. • Body weight, eGFR and hepatic function were the most significant intrinsic factors affecting drug exposure. • The reviewer agrees with the Applicant's assessment indicating that exposure was not a significant predictor of efficacy responses in EAGLE-2, even after adjusting for body weight groups. • The reviewer agrees with the Applicant's assessment suggesting that exposure was not a significant predictor of treatment emergent cholinergic adverse events in the phase 3 study, EAGLE-2 and the Japanese phase 3 study, EAGLE-J, after adjusting for study and body weight groups.

Source: FDA reviewer.
Abbreviations: eGFR, estimated glomerular filtration; PK, pharmacokinetic; uUTI, uncomplicated urinary tract infection

14.5.1. Applicant's PK Analysis

The Applicant developed a population PK model for gepotidacin to characterize the PK properties of gepotidacin administered orally (PO) or IV. The data for PK modeling were collected from 14 clinical studies, with eleven Phase 1 studies in healthy subjects (BTZ116778, BTZ117349, BTZ117351, 209611, 213678, BTZ115198, BTZ115774, BTZ115775, BTZ116849, BTZ116666 and BTZ117352), two phase 2 studies (BTZ116576, 206899) in subjects with uncomplicated urogenital gonorrhea and uUTI, and one phase 3 study (EAGLE-2) in subjects with uUTI, respectively (Table 148). The studies covered dose levels ranging from 200 mg to 3000 mg.

The final PK dataset used for analysis consisted of 11608 quantifiable plasma concentrations from 1177 subjects and 2700 quantifiable urine concentrations from 231 subjects. Concentrations below the limit of quantification were excluded from the analysis dataset as they represented less than 10% of the plasma and urine PK data.

Table 149 summarizes the demographic characteristics of subjects included in the PK analyses, stratified by study.

Table 148. Studies Included in the Population PK Analysis

Study	Study Description/Phase	Dose(s)/Frequency/Formulation
BTZ116778	A Randomized, Single Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Repeat Escalating Oral Doses of GSK2140944 in Healthy Adult Subjects/Phase I	400 (n=6), 800 (n=12), 1500 (n=12), 1500 (fasted) (n=6), and 2300 (n=6) mg BID; 1500 (n=6) and 2000 (n=6) mg TID Day 1: SD Days 3-16: 14 Days BID or TID Immediate-release capsule
BTZ117349	A Single-Center, Three-Part, Open Label Study to Evaluate the Relative Bioavailability of Two Formulations, Food Effect, and Interaction with Itraconazole Following Single Dose of GSK2140944 in Healthy Subjects and Effect of Food on Safety, Tolerability, and Pharmacokinetics Following Multiple Doses of GSK2140944 in Healthy Elderly Subjects/Phase I	Part 1: 1500 mg SD (immediate-release capsule vs. immediate-release tablet; fasted vs. fed) (n=15) Part 2: 1500 mg SD w/wo Itraconazole 200 mg (n=15). Part 2 data excluded from population PK analysis. Part 3: 1500 mg BID (immediate-release tablet; fasted vs. fed) (elderly subjects) (n=15)
BTZ117351	A Phase I; Multi- Center; Open-Label (Parts 1 and 2); Randomized, Double- Blind, Placebo- Controlled (Part 3); Single-Dose; 3-Part Study to Evaluate the Relative Bioavailability of Three Formulations in Healthy Subjects, Food Effect on Tablet Formulation in Healthy Subjects, and Pharmacokinetics of Gepotidacin (GSK2140944) in Japanese Subjects in Fasted and Fed States/Phase I	Part 1a: 1500 mg SD (free base tablet [RC and HSWG formulations] vs. capsule) (n=26). Data from HSWG formulation excluded from population PK analysis as this formulation was not further evaluated in the development program. Part 2: 1500 and 3000 mg SD in Japanese subjects (free base tablet [RC], fasted) (n=10) Part 3: 1500, 2250, and 3000 mg SD in Japanese subjects (free base tablet [RC], fed) (n=10)

(Table 148 continued)

Study	Study Description/Phase	Dose(s)/Frequency/Formulation
BTZ115198	A Two Part Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Single and Repeat IV Doses of GSK2140944 in Healthy Adult Subjects	Part A: 200 mg SD1 hr IV (n=6) 600 mg SD 1 hr IV (n=6) 1200 mg SD 1 hr IV (n=6) 1800 mg SD 1 hr IV (n=5) 1800 mg SD 2 hr IV (n=6) Part B: 400 mg SD/BID 7 days 2 hr IV (n=6) 750 mg SD/BID 7 days 2 hr IV (n=6) 1000 mg SD/BID 7days 2 hr IV (n=6) 1000 mg SD/TID 7 days 2 hr IV (n=6) 1000 mg SD/TID 10 days 2 hr IV (n=6) 1500 mg SD/TID 10 days 3 hr IV (n=6) Urine data from this study excluded from population PK analysis due to potential sample collection error at the clinical site noted in the clinical study report.
BTZ116666	An Open-label Study to Evaluate Plasma and Pulmonary Pharmacokinetics Following Intravenous Administration of GSK2140944 in Healthy Adult Subjects (BTZ116666)	1000 mg SD 2 hr IV (n=22)
BTZ115775	A Phase I, Randomized, Double-Blinded, Placebo- and Moxifloxacin-Controlled, 4-Period Crossover Study to Evaluate the Effect of GSK2140944 on Cardiac Conduction as Assessed by 12-Lead Electrocardiogram in Healthy Volunteers	1000 mg SD 2 hr IV (n=50) 1800 mg SD 2 hr IV (n=53)
BTZ116849	A Phase I, Open-Label, Single-Dose, Multi-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Subjects with Varying Degrees of Renal Impairment and in Matched Control Subjects with Normal Renal Function	750 mg SD 2 hr IV (n=32)
BTZ115774	An Open-Label, Non- Randomized, Two-Period, Cross-Over, Mass Balance Study to Investigate the Recovery, Excretion and Pharmacokinetics of 14C-GSK2140944 Administered as a Single Intravenous and Single Oral Dose to Healthy Adult Male Subjects	1000 mg SD 2hr IV (n=6) 2000 mg SD oral (Immediate release capsules) (n=6)

(Table 148 continued)

Study	Study Description/Phase	Dose(s)/Frequency/Formulation
209611	A Phase I, Double-Blind, Two-Part, Sequential Study to Evaluate the Pharmacokinetics of Gepotidacin Tablets in Healthy Adult and Adolescent Participants	Part 1 (Adults): Oral doses (fed; tablets): 1500 mg SD 2 × 3000 mg 12 h apart 2 × 3000 mg 6 h apart (n=14) Part 2 (Adolescent, 12 to <18 years of age): Oral doses (fed; tablets): 1500 mg SD 2 × 3000 mg 6 h apart (n=14)
213678	A Pharmacokinetic, multi-cohort study in Healthy Adult Subjects to Assess Gepotidacin as Victim and as Perpetrator of Drug-Drug Interactions via CYP450, Renal and Intestinal Transporters, and to Assess Gepotidacin Pharmacokinetics in Japanese Healthy Adults	Cohort 1: 1500 mg SD (tablet) (n=14) **Plasma and urine data in the co-administration arm excluded from population PK analysis.** Cohort 2 (Gepotidacin only arm): 1500 mg SD (tablet) (n=14) **Plasma and urine data in the co-administration arm excluded from population PK analysis** Cohort 3: 3000 mg × 2, 12 h apart (tablet) (n=19) Cohort 4: 1500 mg SD (fed, fasted) up to 3000 mg (fed) × 2, 12 h apart (tablet) (n=14)
BTZ117352	A Phase I, Open-Label, Single-Dose, Two-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function	1500 mg SD (N=25)
BTZ116576	A Phase II, Randomized, Multicenter, Dose- Ranging Study in Adult Subjects Evaluating the Efficacy, Safety, and Tolerability of Single Doses of GSK2140944 in the Treatment of Uncomplicated Urogenital Gonorrhea Caused by *Neisseria gonorrhoeae*	1500 and 3000 mg SD (n=105) Immediate-release capsule (fed)

(Table 148 continued)

Study	Study Description/Phase	Dose(s)/Frequency/Formulation
206899	A Phase II[a] Single- Center, Open-Label Study Evaluating the Pharmacokinetics of Repeat Oral Doses of Gepotidacin (GSK2140944) in Adult Female Participants With Uncomplicated Urinary Tract Infection (Acute Cystitis)	1500 mg BID (n=22) Tablet (fed)
EAGLE-2	A Phase III Randomized, Multicenter Parallel- Group, Double-Blind, Double-Dummy study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)	1500 mg BID (fed)

Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Appendix A1, Table 1, page 262.
[a] The PD data from 206899 were not included in the PK-PD assessment.
Abbreviations: BID, twice daily; HSWG, high shear wet granulation; RC, roller compacted; SD, single dose; TID, three times daily

Table 149. Summary of Demographic Characteristics, Stratified by Study

	206899	BTZ116576	BTZ116778	BTZ117349	BTZ117351
	(N = 22)	(N = 70)	(N = 54)	(N = 30)	(N = 46)
Population					
Healthy Subjects	0 (0.0%)	0 (0.0%)	54 (100.0%)	30 (100.0%)	46 (100.0%)
UTI Subjects	22 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GC Subjects	0 (0.0%)	70 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex					
Male	0 (0.0%)	65 (92.9%)	45 (83.3%)	21 (70.0%)	28 (60.9%)
Female	22 (100.0%)	5 (7.1%)	9 (16.7%)	9 (30.0%)	18 (39.1%)
Race					
American Indian or Alaska Native	0 (0.0%)	1 (1.4%)	2 (3.7%)	1 (3.3%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (3.3%)	20 (43.5%)
Black or African American	4 (18.2%)	27 (38.6%)	22 (40.7%)	8 (26.7%)	10 (21.7%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (1.4%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
White	18 (81.8%)	34 (48.6%)	28 (51.9%)	19 (63.3%)	16 (34.8%)
Not Reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
Missing	0 (0.0%)	7 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age (Years)					
Mean (SD)	37.1 (12)	33.9 (12)	35.8 (11)	51.4 (20)	42.5 (11)
Median (range)	35.5 (19.0 - 60.0)	31.0 (18.0 - 69.0)	32.5 (20.0 - 58.0)	63.0 (19.0 - 78.0)	41.0 (24.0 - 64.0)
Subject Weight (kg)					
Mean (SD)	72.0 (16)	79.5 (16)	78.8 (14)	80.8 (12)	71.3 (15)
Median (range)	65.9 (50.2 - 106)	77.0 (49.3 - 122)	77.0 (55.7 - 110)	80.4 (52.8 - 106)	69.8 (50.1 - 115)
Total Bilirubin ($\mu mol/L$)					
Mean (SD)	7.24 (4.3)	10.2 (6.9)	8.96 (3.6)	9.80 (3.9)	9.39 (3.7)
Median (range)	5.64 (2.91 - 22.2)	8.00 (4.00 - 38.0)	7.70 (3.42 - 20.5)	10.3 (5.13 - 23.9)	8.60 (3.40 - 18.8)
Albumin (g/L)					
Mean (SD)	43.9 (2.8)	45.6 (3.2)	42.9 (2.2)	42.1 (1.6)	43.5 (2.6)
Median (range)	44.0 (37.0 - 48.0)	46.0 (38.0 - 57.0)	43.0 (39.0 - 49.0)	42.5 (39.0 - 45.0)	43.0 (38.0 - 49.0)
eGFR ($mL/min/1.73m^2$)					
Mean (SD)	115 (34)	101 (19)	101 (16)	102 (24)	97.3 (23)
Median (range)	98.5 (66.4 - 180)	99.7 (55.2 - 151)	101 (69.1 - 144)	96.8 (62.5 - 160)	96.6 (56.8 - 187)

(Table 149 continued)

	209611	213678	BTZ115198	BTZ115774	BTZ115775
	(N = 27)	(N = 60)	(N = 65)	(N = 6)	(N = 53)
Population					
Healthy Subjects	27 (100.0%)	60 (100.0%)	65 (100.0%)	6 (100.0%)	53 (100.0%)
UTI Subjects	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GC Subjects	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex					
Male	17 (63.0%)	37 (61.7%)	65 (100.0%)	6 (100.0%)	28 (52.8%)
Female	10 (37.0%)	23 (38.3%)	0 (0.0%)	0 (0.0%)	25 (47.2%)
Race					
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)
Asian	2 (7.4%)	13 (21.7%)	3 (5.8%)	0 (0.0%)	1 (1.9%)
Black or African American	11 (40.7%)	26 (43.3%)	0 (0.0%)	2 (33.3%)	11 (20.8%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	2 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	12 (44.4%)	16 (26.7%)	49 (94.2%)	4 (66.7%)	37 (69.8%)
Not Reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	2 (7.4%)	3 (5.0%)	0 (0.0%)	0 (0.0%)	3 (5.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age (Years)					
Mean (SD)	29.7 (16)	39.0 (8.1)	27.3 (6.6)	38.2 (7.4)	30.9 (9.2)
Median (range)	27.0 (12.0 - 59.0)	40.0 (24.0 - 51.0)	25.0 (18.0 - 55.0)	37.5 (31.0 - 51.0)	28.0 (18.0 - 53.0)
Subject Weight (kg)					
Mean (SD)	72.2 (15)	77.1 (13)	73.6 (9.2)	81.6 (8.0)	72.7 (12)
Median (range)	72.3 (47.0 - 103)	78.3 (47.1 - 106)	73.8 (52.2 - 102)	83.3 (67.6 - 89.0)	71.7 (52.1 - 99.8)
Total Bilirubin ($\mu mol/L$)					
Mean (SD)	10.9 (4.6)	11.7 (5.8)	11.4 (6.3)	12.0 (3.9)	9.37 (4.5)
Median (range)	10.3 (5.13 - 27.4)	10.3 (3.42 - 39.3)	11.0 (4.00 - 43.0)	13.0 (6.50 - 16.1)	8.60 (4.10 - 33.2)
Albumin (g/L)					
Mean (SD)	45.0 (2.9)	42.5 (2.7)	46.9 (2.2)	40.3 (2.3)	45.5 (2.8)
Median (range)	45.0 (40.0 - 51.0)	43.0 (37.0 - 49.0)	47.0 (41.0 - 53.0)	39.5 (38.0 - 44.0)	46.0 (39.0 - 51.0)
eGFR ($mL/min/1.73m^2$)					
Mean (SD)	93.2 (19)	100 (17)	97.8 (15)	110 (17)	98.1 (17)
Median (range)	91.7 (60.4 - 139)	99.3 (69.8 - 137)	97.9 (66.8 - 143)	109 (88.5 - 131)	98.3 (68.0 - 140)

(Table 149 continued)

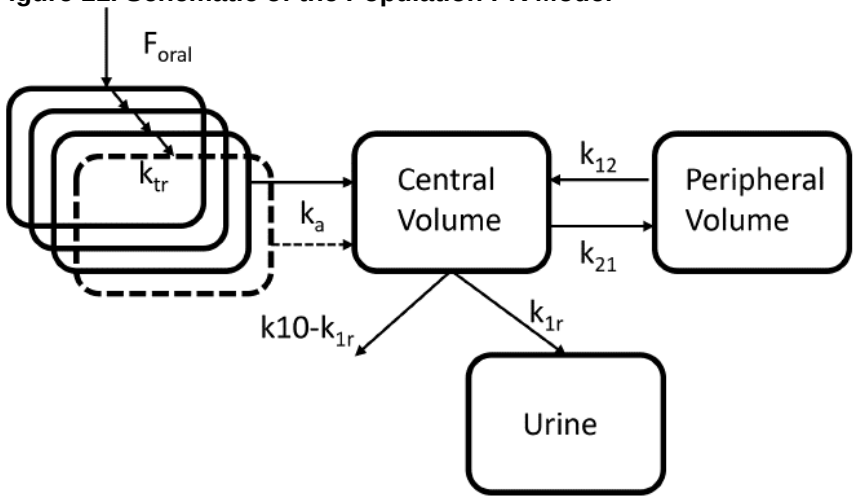
parameter	BTZ116849	BTZ116666	BTZ117352	204989	All
	(N = 32)	(N = 22)	(N = 25)	(N = 735)	(N = 1247)
Population					
Healthy Subjects	32 (100.0%)	22 (100.0%)	25 (100.0%)	0 (0.0%)	420 (33.7%)
UTI Subjects	0 (0.0%)	0 (0.0%)	0 (0.0%)	735 (100.0%)	757 (60.7%)
GC Subjects	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	70 (5.6%)
Sex					
Male	23 (71.9%)	20 (90.9%)	23 (92.0%)	0 (0.0%)	378 (30.3%)
Female	9 (28.1%)	2 (9.1%)	2 (8.0%)	735 (100.0%)	869 (69.7%)
Race					
American Indian or Alaska Native	1 (3.1%)	0 (0.0%)	0 (0.0%)	59 (8.0%)	65 (5.3%)
Asian	0 (0.0%)	0 (0.0%)	1 (4.0%)	18 (2.4%)	60 (4.9%)
Black or African American	12 (37.5%)	16 (72.7%)	3 (12.0%)	39 (5.3%)	191 (15.5%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	7 (0.6%)
White	18 (56.2%)	6 (27.3%)	21 (84.0%)	604 (82.2%)	882 (71.5%)
Not Reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	1 (3.1%)	0 (0.0%)	0 (0.0%)	12 (1.6%)	22 (1.8%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (0.6%)
Age (Years)					
Mean (SD)	61.7 (12)	36.5 (9.8)	60.1 (6.3)	49.7 (18)	45.1 (17)
Median (range)	62.0 (38.0 - 79.0)	38.0 (19.0 - 53.0)	61.0 (51.0 - 72.0)	51.0 (14.0 - 89.0)	44.0 (12.0 - 89.0)
Subject Weight (kg)					
Mean (SD)	85.3 (14)	80.9 (10)	92.2 (15)	72.3 (15)	74.4 (15)
Median (range)	86.5 (58.5 - 116)	81.9 (56.2 - 93.5)	90.1 (67.5 - 133)	70.0 (40.5 - 140)	73.0 (40.5 - 140)
Total Bilirubin ($\mu mol/L$)					
Mean (SD)	8.44 (4.0)	9.40 (3.0)	19.5 (14)	6.68 (3.9)	8.27 (5.3)
Median (range)	6.84 (3.42 - 23.9)	10.3 (5.13 - 17.1)	13.7 (5.13 - 51.3)	5.80 (2.60 - 28.6)	6.84 (2.60 - 51.3)
Albumin (g/L)					
Mean (SD)	41.9 (3.7)	41.5 (2.8)	37.8 (7.3)	45.1 (3.1)	44.6 (3.4)
Median (range)	42.0 (35.0 - 49.0)	41.0 (37.0 - 48.0)	41.0 (21.0 - 49.0)	45.0 (25.0 - 54.0)	45.0 (21.0 - 57.0)
eGFR ($mL/min/1.73m^2$)					
Mean (SD)	44.5 (44)	108 (20)	98.1 (25)	106 (34)	102 (31)
Median (range)	30.2 (4.92 - 159)	111 (67.1 - 140)	96.7 (60.4 - 164)	103 (16.6 - 230)	101 (4.92 - 230)

Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Table 6, page 49.

Final Population PK model

The PK model for gepotidacin consisted of a 2-compartment disposition model with a delayed absorption and linear elimination from the central compartment. Three transit compartments for the fasted state and four for the fed state were included to describe the delayed absorption process. Separate renal clearance and non-renal clearance (CLnr) described the linear elimination of gepotidacin from the central compartment, based on the collected plasma and urine concentrations. Inter-individual variability terms were included on CLr, CLnr, central and peripheral volumes of distribution, inter-compartmental clearance (Q), mean transit time, and the oral bioavailability (F_{oral}). The residual unexplained variability was described by a proportional error model, implemented as an additive residual error on the log-transformed concentrations. The residual unexplained variability consisted of different errors for plasma concentrations from the IV route, plasma concentrations from PO route, plasma concentrations from the phase 3 study, and urine concentrations data. A schematic of the structural PK model is represented in Figure 11. The parameter estimates from the final PK model are listed in Table 150.

Figure 11. Schematic of the Population PK Model



Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Figure 29, page 101
Abbreviations: F_{oral}, oral bioavailability; k_a, absorption rate constant from last transit compartment to the central compartment; k_{tr}, transit rate constant between transit compartments; k_{12} and k_{21}, transfer rate constants describing the inter-compartmental clearance (Q); k_{1r}, elimination rate constant describing CLr; k_{10}, overall elimination rate constant describing the total renal and non-renal clearance (CLr+CLnr); PK, pharmacokinetic

Weight was included as a covariate on clearances (CLr, CLnr and Q), central and peripheral volumes of distribution, using allometric scaling. The estimated glomerular filtration rate (eGFR), calculated using modified Schwartz for adolescents and MDRD equation for adults, was an influential covariate on CLr. The PK model estimated a lower CLnr in black and African American, a higher CLnr and mean transit time in healthy volunteers, and an increase in peripheral volumes of distribution with increasing age. Weight, eGFR and age were included as covariates of respective parameters according to a power model normalized to 70 kg, 44 years and 97.3 mL/min/1.73m^2, respectively.

The goodness of fit (GOF) plots from the final PK model are shown in Figure 12 and the prediction-corrected visual predictive check plots are shown in Figure 13.

Reviewer's Comments

Assessment of the Population PK Model:

Overall, the Applicant's PK model is acceptable for descriptive labeling and adequately describes the individual observed concentrations of gepotidacin and their variability in healthy volunteers and patients.

- *The PK parameters from the PK model were estimated with an acceptable precision (relative standard error [RSE] <25%), except for the logit of F_{oral} which was estimated with an RSE of 95%. However, the calculated F_{oral} (anti-logit of F_{oral}) was precisely estimated.*
- *Although, most of the studies collected rich informative PK data, the estimated interindividual random error (eta-) shrinkages were high (>30%) not allowing for reliable graphical assessment of covariate effects.*
- *The residual error (epsilon-) shrinkage was low (5.6%), indicating the informativeness of the GOF plots to diagnose structural and residual error model misspecifications. The GOF plots show that the PK model fitted the plasma and urine observed data well with no critical trends or bias in the predicted versus the observed concentrations of gepotidacin and in the conditional weighted residuals versus predictions or time from all studies, particularly for plasma concentrations and after exclusion of few (n=5) over-predicted urine concentrations (likely due to uncertainties in volumes of urine collected, as reported by the Applicant).*
- *The prediction-corrected visual predictive check plots, stratified by the samples' matrix (plasma and urine) and by route of administration (IV and PO), indicate that the Applicant's PK model reasonably captures and describes the observed median gepotidacin concentrations and their variability from all studies with minimal bias.*

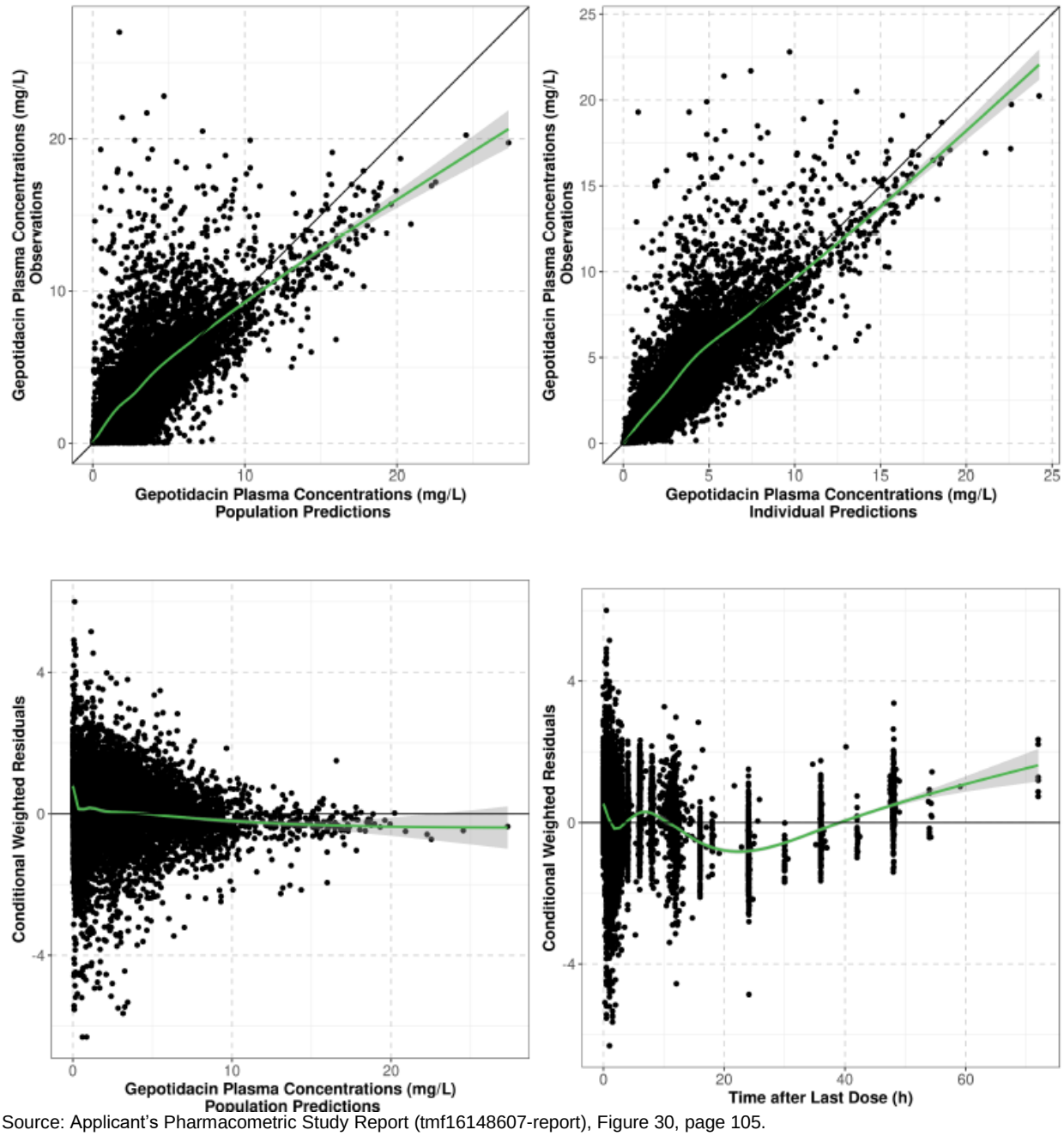
Table 150. Parameter Estimates of the Final Gepotidacin PK Model

Parameter	Label	Unit	Estimate	RSE (%)	CI95	CV (%)	Shrinkage (%)	SIR Median	SIR 95% CI
θ_1	CL_r	L/h	12.5	2.52	(11.9 - 13.1)			12.5	(11.9 - 13.0)
θ_{14}	CL_{nr}	L/h	16.9	5.28	(15.2 - 18.7)			16.9	(15.3 - 18.6)
θ_2	V_c	L	44.4	3.79	(41.2 - 47.9)			44.4	(41.8 - 47.0)
θ_6	Q	L/h	13.1	1.65	(12.7 - 13.5)			13.1	(12.6 - 13.6)
θ_7	V_p	L	121	2.04	(116 - 125)			120.	(116. - 125.)
θ_3	K_a	h^-1	0.459	2.35	(0.438 - 0.480)			0.458	(0.440 - 0.475)
θ_{11}	MTT fasted	h	0.187	7.68	(0.161 - 0.218)			0.183	(0.156 - 0.224)
θ_{12}	MTT fed	h	0.709	7.05	(0.617 - 0.814)			0.700	(0.609 - 0.814)
θ_{10}	$F_{plasma,oral}$	proportion	0.489	4.35	(0.467 - 0.510)			0.489	(0.469 - 0.509)
θ_5	$Error_{plasma,t.v.}$	SD	0.38	1.23	(0.371 - 0.390)		5.1	0.380	(0.371 - 0.390)
θ_4	$Error_{urine}$	SD	0.6	0.773	(0.591 - 0.609)		3.84	0.600	(0.587 - 0.613)
θ_{13}	$Error_{oral}$	SD	0.548	0.376	(0.544 - 0.552)		5.16	0.548	(0.543 - 0.554)
θ_{16}	$Error_{phase3}$	SD	0.948	2.29	(0.906 - 0.991)		15.8	0.948	(0.897 - 1.00)
θ_{15}	CL_r-eGFR	Exponent	1.06	2.6	(1.01 - 1.11)			1.06	(0.992 - 1.13)
θ_{17}	CL_{nr}-Black	Proportional change	-0.119	20.4	(-0.166 - -0.0711)			-0.118	(-0.161 - -0.0746)
θ_{18}	CL_{nr}-Healthy	Proportional change	0.483	15.2	(0.338 - 0.627)			0.477	(0.365 - 0.624)
θ_{19}	MTT-Healthy	Proportional change	1.15	21.1	(0.674 - 1.62)			1.19	(0.778 - 1.65)
θ_{20}	V_p-Age	Exponent	0.269	12.4	(0.203 - 0.335)			0.269	(0.203 - 0.322)
$\omega_{1.1}$	IIV CL_r	Variance (lognormal)	0.0766	10.1	(0.0614 - 0.0918)	28.2	56.6	0.0771	(0.0597 - 0.0968)
$\omega_{6.6}$	IIV CL_{nr}	Variance (lognormal)	0.0136	22.3	(0.00766 - 0.0196)	11.7	69.8	0.0141	(0.00861 - 0.0208)
$\omega_{2.2}$	IIV V_c	Variance (lognormal)	0.155	12.2	(0.118 - 0.191)	40.9	55.7	0.156	(0.117 - 0.199)
$\omega_{4.4}$	IIV V_p	Variance (lognormal)	0.0384	9.4	(0.0313 - 0.0454)	19.8	54.6	0.0386	(0.0311 - 0.0473)
$\omega_{3.3}$	IIV MTT	Variance (lognormal)	1.13	8.5	(0.944 - 1.32)	145	40.1	1.14	(0.971 - 1.35)
$\omega_{8.8}$	IIV F_{oral}	Variance (logit)	0.247	13.6	(0.181 - 0.313)	N/A	55.3	0.249	(0.190 - 0.327)

Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Table 14, page 103.
Allometric exponents of 0.75 and 1 were included on all clearance and volume parameters.
Abbreviations: CI, confidence interval; CL_r, renal clearance; CL_{nr}, non-renal clearance; %CV, coefficient of variation of inter-individual variability; eGFR, estimated glomular filtration rate; F_{oral}, bioavailability; IIV, interindividual variability; K_a, absorption rate; MTT, mean transit time; Q, intercompartment clearance; RSE, relative standard error; SD, standard deviation; SIR, sampling importance resampling; V_c, central volume of distribution; V_p, peripheral volume of distribution; ω^2_x, variance of the IIV of parameter X

Figure 12. Goodness-of-fit Plots From the Final PK Model for Plasma and Urine Data

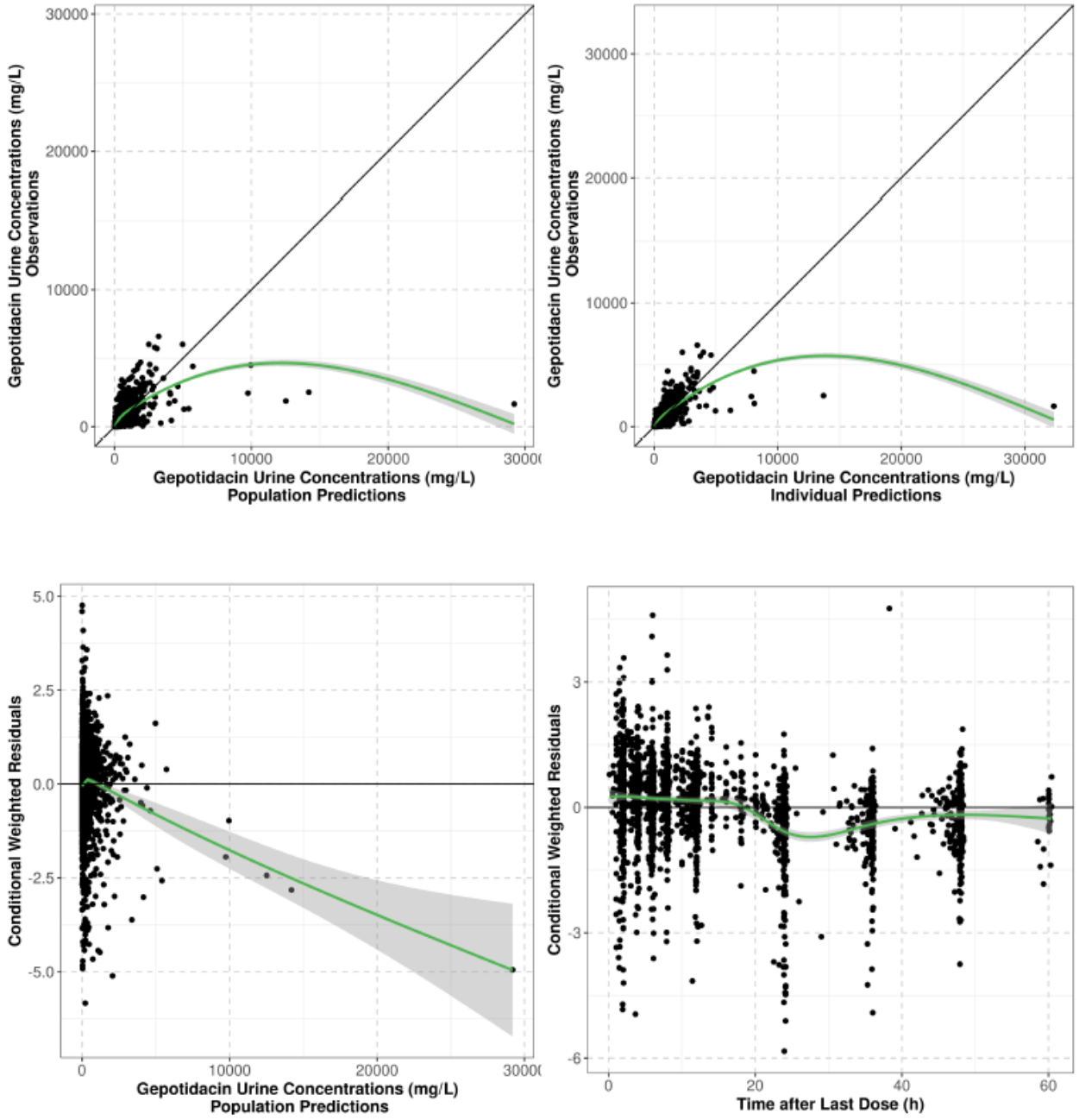
A. Plasma data:



Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Figure 30, page 105.
The green lines and shaded areas represent loess smooth curves and the 95%CI. The black lines represent the line of unity y = x or y = 0.

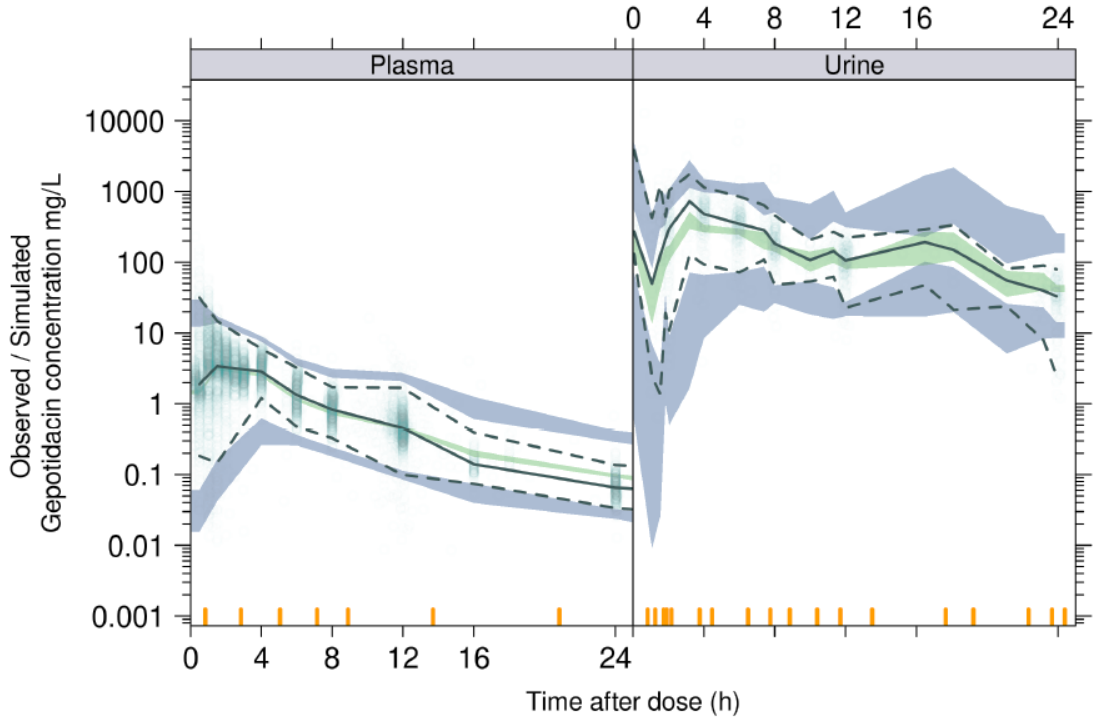
(Figure 12 continued)

B. Urine data:



Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Figure 32, page 107.
The green lines and shaded areas represent loess smooth curves and the 95%CI. The black lines represent the line of unity y = x or y = 0.

Figure 13. Prediction-Corrected Visual Predictive Check From Final PK Model

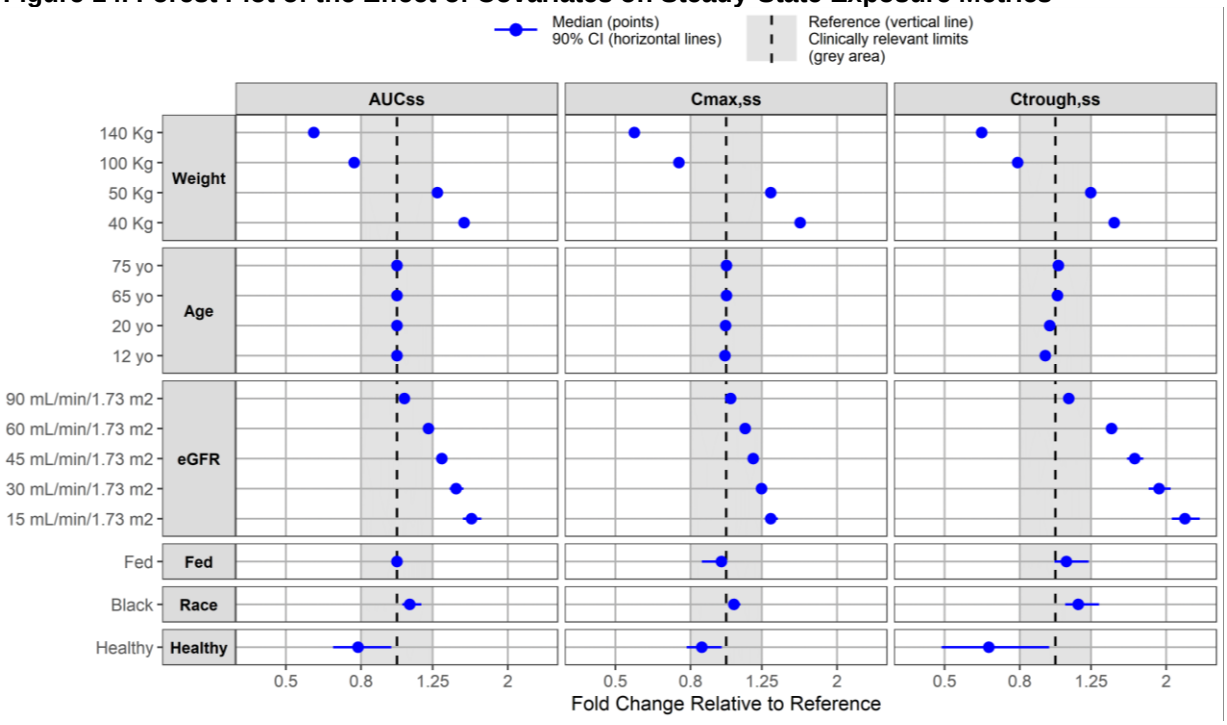


Black line: Observed median, **Dashed lines:** Observed 5^{th} and 95^{th} percentiles, **Green area:** 95% CI of simulated median, **Blue areas:** 95% CI of simulated 5^{th} and 95^{th} percentiles.

Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Figure 50, page 125.

Among the covariates evaluated by the Applicant in the PK model, body weight and eGFR are the most influential intrinsic factors significantly affecting the exposure of gepotidacin (Figure 14). Although, the PK dataset included data from the hepatic impairment study (BTZ117352), the degree of hepatic impairment was not tested as a covariate on CLnr. The review team updated the Applicant's PK model to estimate the effect of various degrees of hepatic function (normal, Child-Pugh B and Child-Pugh C) on CLnr from Study BTZ117352. Participants of Study BTZ117352 with normal hepatic function, Child-Pugh B and Child-Pugh C were estimated to have, respectively, 1.29, 1.04 and 0.829-fold the typical CLnr (in a 70 kg, not black or African American subjects with uUTI). The estimates of the remaining PK parameters did not change and were similar to those in the original PK model. According to the updated PK model, BTZ117352 participants with moderate and severe hepatic impairment have 24% and 56% higher AUC_{ss} compared to BTZ117352 participants with normal hepatic function. These estimates were comparable to those estimated from the non-compartmental analysis of Study BTZ117352, with an estimated 20% and 70% higher AUC_{ss} in moderate and severe hepatic impairment, respectively.

Figure 14. Forest Plot of the Effect of Covariates on Steady-State Exposure Metrics



Source: FDA reviewer.
The reference subject is a 45-year-old, 70 kg, not black or African American subject with normal renal function (eGFR), receiving gepotidacin 1500 mg BID. Dots and error bars represent the median of the predicted point estimate compared to the reference subject and its associated 90% CI for each covariate evaluated in a univariate manner; these values are calculated based on 1000 sampled PK parameter vectors from the variance-covariance matrix of the final PK model. The reference area indicates the 80%-125% margins relative to the reference subject.
Abbreviations: BID, twice daily; CI, confidence interval; eGFR, estimated glomerular filtration; PK, pharmacokinetic

14.5.2. Applicant's Exposure-Response Analyses

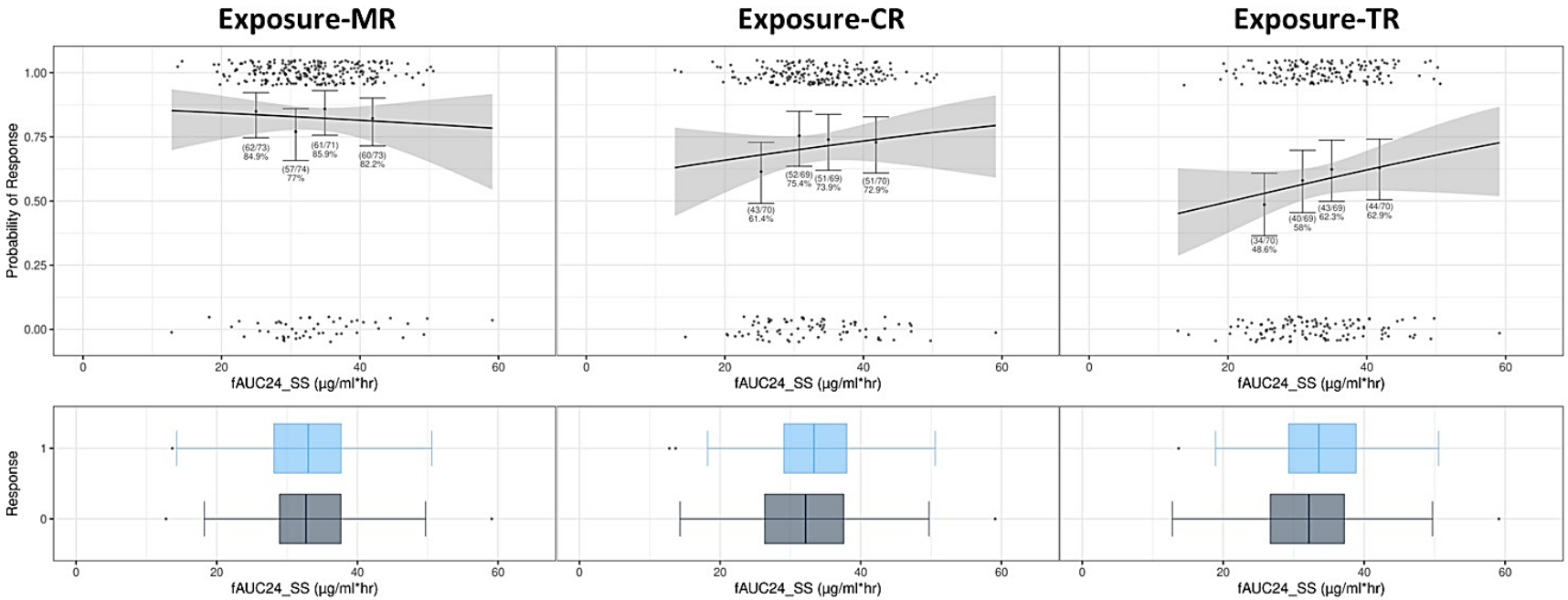
The Applicant used the model-predicted PK and exposure metrics to perform plasma exposure-response analyses for efficacy (microbiological, clinical, and therapeutic response) and safety (cholinergic effect), from collected data in the phase 3 Study EAGLE-2.

14.5.3. Exposure-Efficacy Response Analyses

Exploratory analyses of plasma exposure-response relationships were performed for subjects infected with *E. coli* and non-*E. coli* Enterobacterales (including *K. pneumoniae, P. mirabilis*), respectively. Not enough observations were available for S. saprophyticus (n = 6).

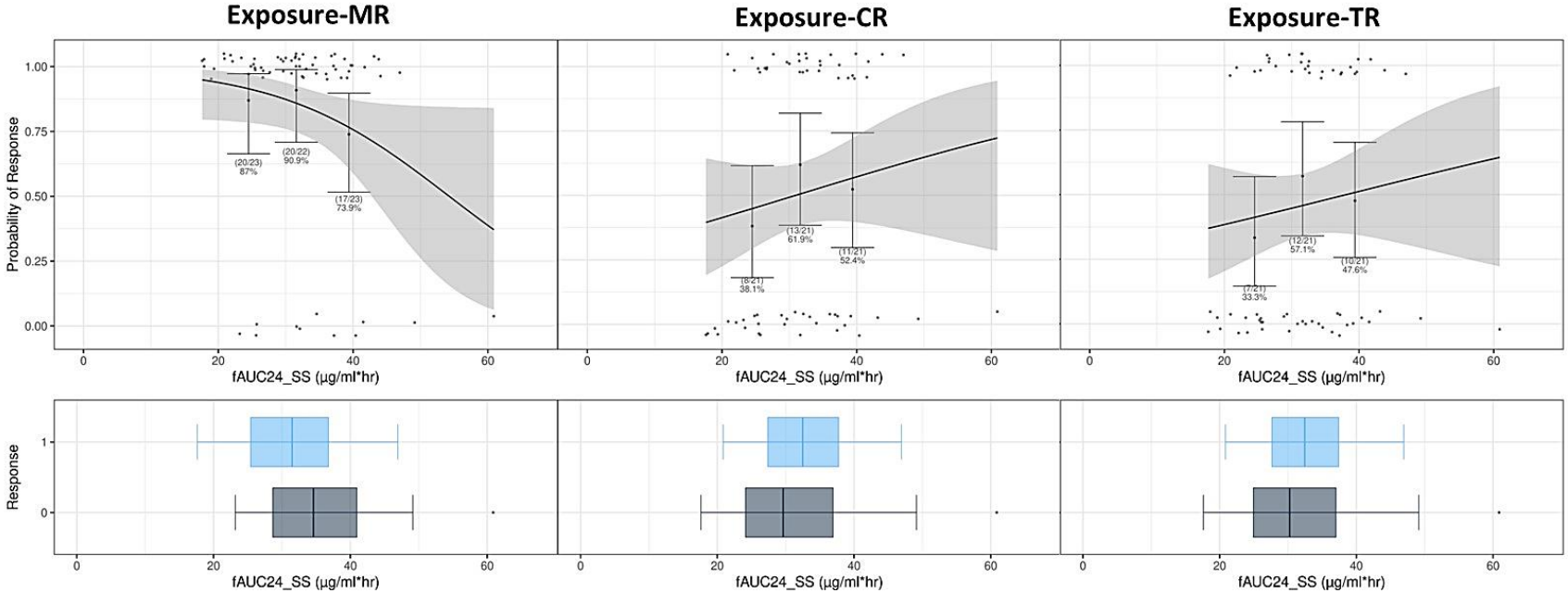
No significant ($p < 0.05$) relationships were observed for the microbiological response (MR), clinical response (CR), and therapeutic response (TR) as function of either plasma daily free AUC_{ss} ($fAUC_{ss}$) or $fAUC_{ss}$/MIC for *E. coli* (Figure 15 and Figure 17) and non-*E. coli* Enterobacterales (Figure 16 and Figure 18).

Figure 15. Exposure-Response Relationships of MR, CR, and TR vs. Daily $fAUC_{ss}$ for Subjects Infected With *E. coli*



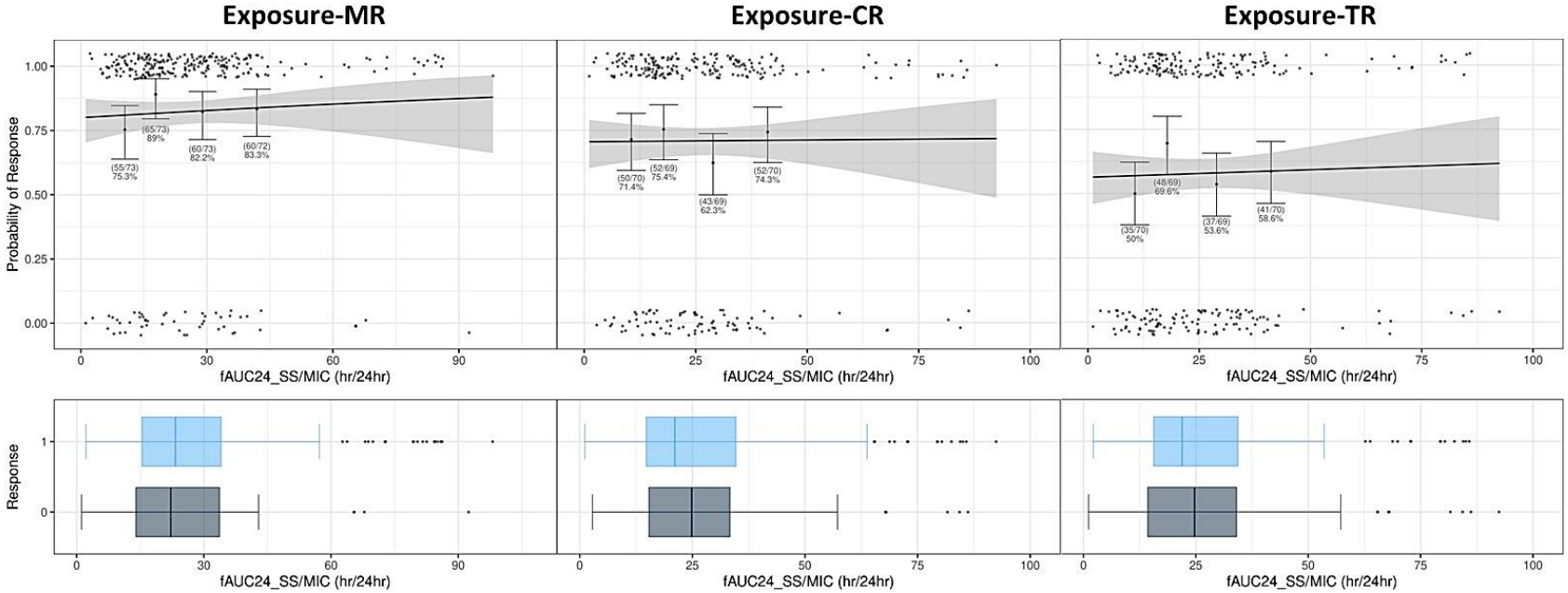
Source: Adapted from Applicant's Pharmacometric Study Report (tmf16148607-report), Figures 130, 131, 132, page 222, 224, 226.
Upper panel: the solid line is the fit from logistic regression, and the shaded area is the 95% CI of the fit. The solid circles represent the response rates of participants in the respective exposure quantiles, and the error bars are the binomial 95% CI calculated based on the response rate and the number of participants in the exposure quantiles. Lower panel: box plots of the overall exposures in participants with success response (coded as 1) and failure response (coded as 0).
Abbreviations: CR, clinical response; fAUC24_SS, total daily steady-state AUC of free plasma gepotidacin concentrations; MR, microbiological response; TR, therapeutic response defined as MR+CR; vs, versus

Figure 16. Exposure-Response Relationships of MR, CR and TR vs. Daily $fAUC_{ss}$ for Subjects Infected With Non-*E. coli* Enterobacterales



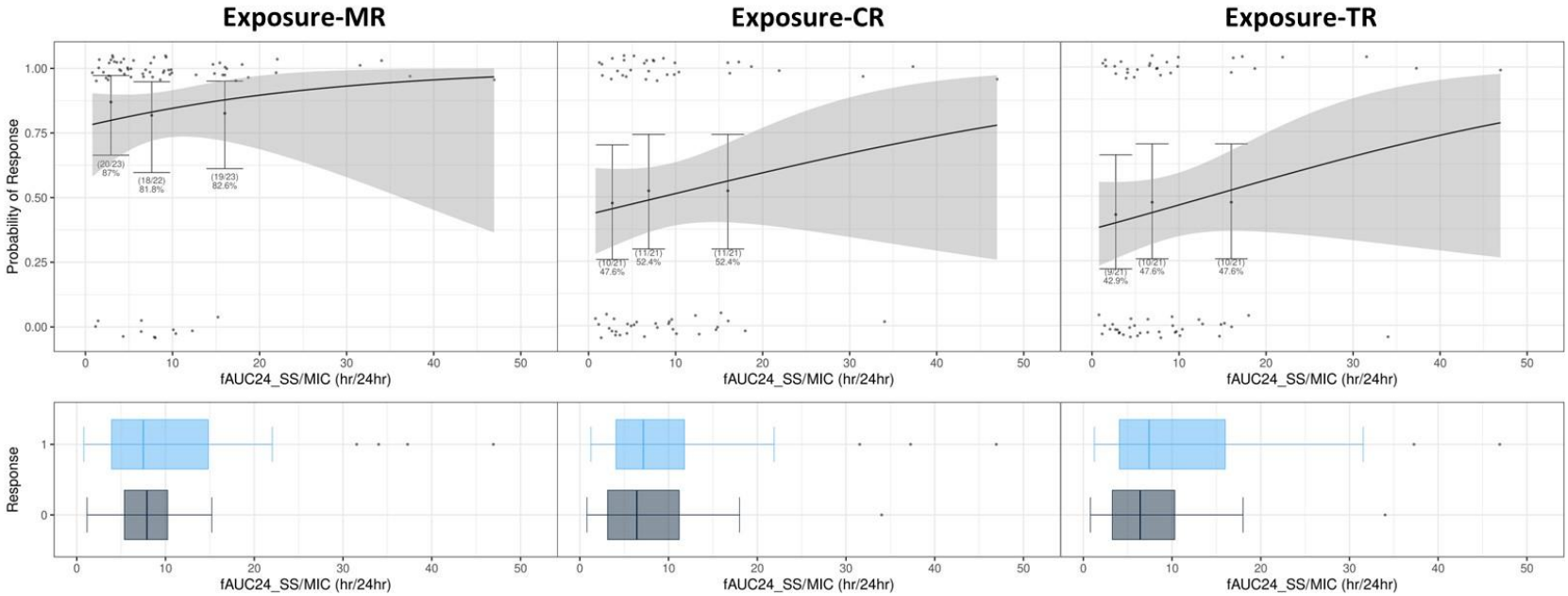
Source: Adapted from Applicant's Pharmacometric Study Report (tmf16148607-report), Figures 136, 137, 138, page 234, 236, 238.
Note: Upper panel: the solid line is the fit from logistic regression, and the shaded area is the 95% CI of the fit. The solid circles represent the response rates of participants in the respective exposure quantiles, and the error bars are the binomial 95% CI calculated based on the response rate and the number of participants in the exposure quantiles. Lower panel: box plots of the overall exposures in participants with success response (coded as 1) and failure response (coded as 0).
Abbreviations: CR, clinical response; fAUC24_SS, total daily steady-state AUC of free plasma gepotidacin concentrations; MR, microbiological response; TR, therapeutic response defined as MR+CR; vs, versus

Figure 17. Exposure-Response Relationships of MR, CR and TR vs. Daily $fAUC_{ss}$/MIC for Subjects Infected With *E. coli*



Source: Adapted from Applicant's Pharmacometric Study Report (tmf16148607-report), Figures 133, 134, 135, page 228, 230, 232.
Abbreviations: CR, clinical response; fAUC24_SS, total daily steady-state AUC of free plasma gepotidacin concentrations; MIC, minimum inhibitory concentration; MR, microbiological response; TR, therapeutic response defined as MR+CR; vs, versus

Figure 18. Exposure-Response Relationships of MR, CR and TR vs. Daily $fAUC_{ss}$/MIC for Subjects Infected With non-*E. coli* Enterobacterales



Source: Adapted from Applicant's Pharmacometric Study Report (tmf16148607-report), Figures 139, 140, 141, page 240, 242, 244.
Abbreviations: CR, clinical response; fAUC24_SS, total daily steady-state AUC of free plasma gepotidacin concentrations; MIC, minimum inhibitory concentration; MR, microbiological response; TR, therapeutic response defined as MR+CR; vs, versus

Reviewer's Comments

Assessment of the Exposure-Efficacy Responses:

- *The Reviewer agrees with the Applicant's assessment suggesting the absence of an apparent or significant trend for the exposure-efficacy responses relationship.*
- *As body weight was a significant covariate on gepotidacin PK, with up to 40% lower exposure in subjects with a body weight of 140 kg, the reviewer evaluated the exposure-responses (MR, CR and TR) relationships, after adjusting for weight category.*
- *The body weight in the exposure-efficacy dataset ranged between 45 to 129 kg, with fewer subjects with body weight higher or equal to 100 kg (n = 10). Exposure was not found to be a predictor of MR, CR and TR for E. coli and non-E. coli Enterobacterales, even after adjusting for body weight groups (including at the highest weight group of 100 kg to 129 kg). Body weight and body weights groups were also not found as predictors of the MR, CR and TR.*

14.5.4. Exposure-Cholinergic Adverse Events Analyses

The Applicant evaluated the relationship between gepotidacin plasma exposure metrics ($C_{max,ss}$, daily AUC_{ss}, $C_{min,ss}$) and the occurrence of cholinergic treatment-emergent adverse events (due to the reversible inhibition of acetylcholinesterase enzyme by gepotidacin).

The exposure-cholinergic treatment-emergent adverse events (TEAEs) analyses included data from the phase 3 uUTI studies EAGLE-2 and EAGLE-J and were evaluated either separately by study or jointly from both studies combined. Subjects in the Japanese study (EAGLE-J) reported a higher rate of cholinergic TEAEs of 64.1% compared to those enrolled in EAGLE-2 with a rate of 23.1%. The plasma exposure metrics for participants in EAGLE-J (Japanese participants) were generated using a population PK model updated with EAGLE-J concentration data, as EAGLE-J was not included in the original PK model. Of note, participants in EAGLE-J had 29% and 20% higher gepotidacin $C_{max,ss}$ and AUC_{ss}, respectively, compared to participants in EAGLE-2 (only 2 participants with Japanese heritage). The differences in $C_{max,ss}$ and daily AUC_{ss} was attributable to the different weight distributions between studies with a lower body weight in Japanese population (median [range] weight = 52.8 [40 - 96.5 kg] for EAGLE-J compared to 70.0 kg [40.5 - 140 kg] for EAGLE-2).

The analyses were conducted for all cholinergic TEAEs (i.e., combined gastro-intestinal [GI] and non-GI events) and for GI cholinergic TEAEs. The number of participants with non-GI cholinergic TEAEs was small in the exposure-response dataset (n = 5 in EAGLE-2 and 7 in EAGLE-J) compared to the GI events, not allowing for a meaningful assessment of exposure-response for non-GI cholinergic TEAEs. For the GI cholinergic TEAEs, diarrhea was the most prevalent event. Cholinergic AEs were flagged as potential cholinergic TEAEs (Flag 1, Flag2 and Flag3, see Section 7.7.1), if they met the prespecified criteria for the preferred term as defined by the Applicant or the FDA and if the onset was ≤60 hours after a dose of gepotidacin (i.e., about 5 half-lives).

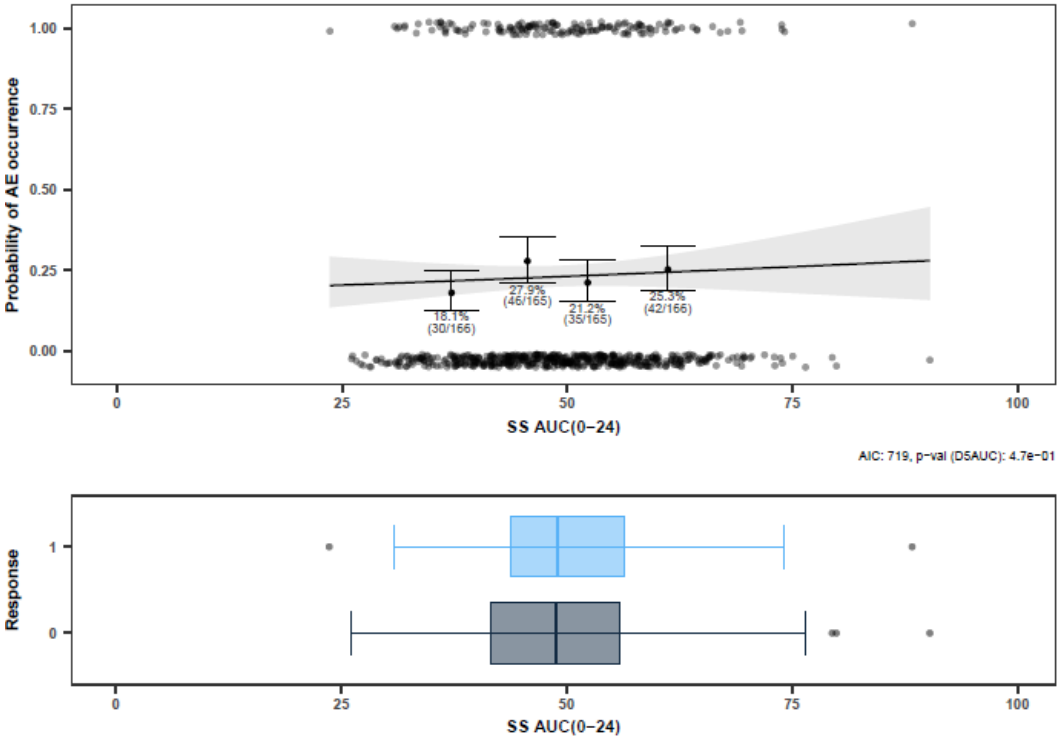
Gepotidacin systemic exposure metrics (daily AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) were not found to be significant predictors of cholinergic TEAEs, in EAGLE-2 Study or EAGLE-J study data

separately (Figure 19 A and B). However, when evaluated using pooled EAGLE-2 and EAGLE-J study data, gepotidacin systemic exposure metrics were significant predictors of cholinergic TEAEs (Figure 19 C). This trend from the pooled studies was confounded by the higher occurrence of cholinergic TEAEs in EAGLE-J compared to EAGLE-2, in conjunction with the higher exposures in EAGLE-J (due to the lower body weight distribution, with increasing number of EAGLE-J participants in the higher pooled exposure quartiles) compared to EAGLE-2. After adjusting for either Japanese vs. non-Japanese (almost completely correlated with study), study or weight (also correlated with Japanese versus non-Japanese and study), the exposure metrics were no longer significant predictors of cholinergic TEAEs. Instead, Japanese versus non-Japanese subjects, study or weight covariates were significant. Among these three covariates, weight was the least significant with the highest p-value, whereas Japanese versus non-Japanese and study had very similar p-values.

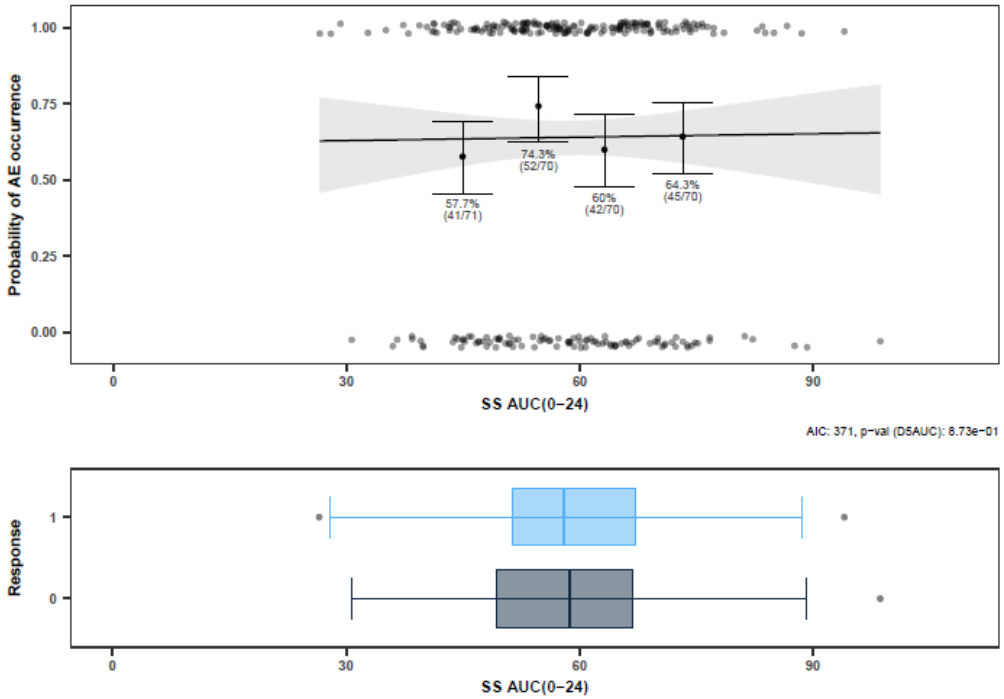
As GI cholinergic TEAEs constituted most cholinergic events, only the results that include all pooled cholinergic TEAEs are summarized below. Additionally, only the results using daily AUC_{ss} for an exposure metric are summarized below, as results based on all exposure metrics (daily AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) and definitions of cholinergic TEAEs (Flag 1, 2 and 3, see Section 7.7.1) were similar.

Figure 19. Exposure-Response Relationship of all Cholinergic AEs vs. Daily AUCss, Stratified by Study and for Pooled EAGLE-2 and EAGLE-J Studies

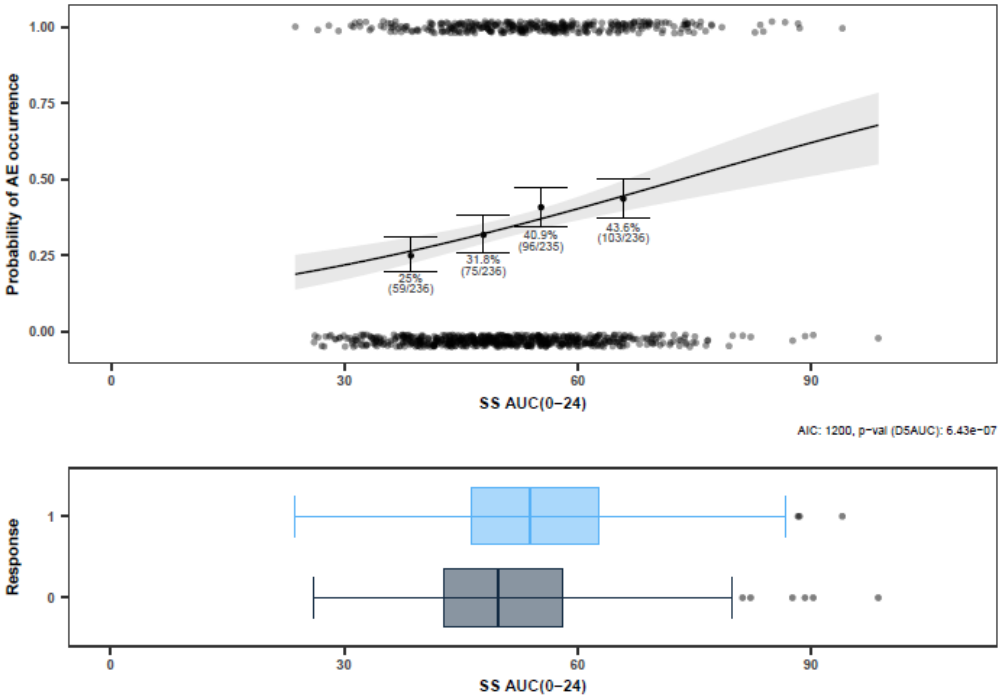
A. Study EAGLE-2:



B. Study EAGLE-J:



C. Pooled studies EAGLE-2 and EAGLE-J:



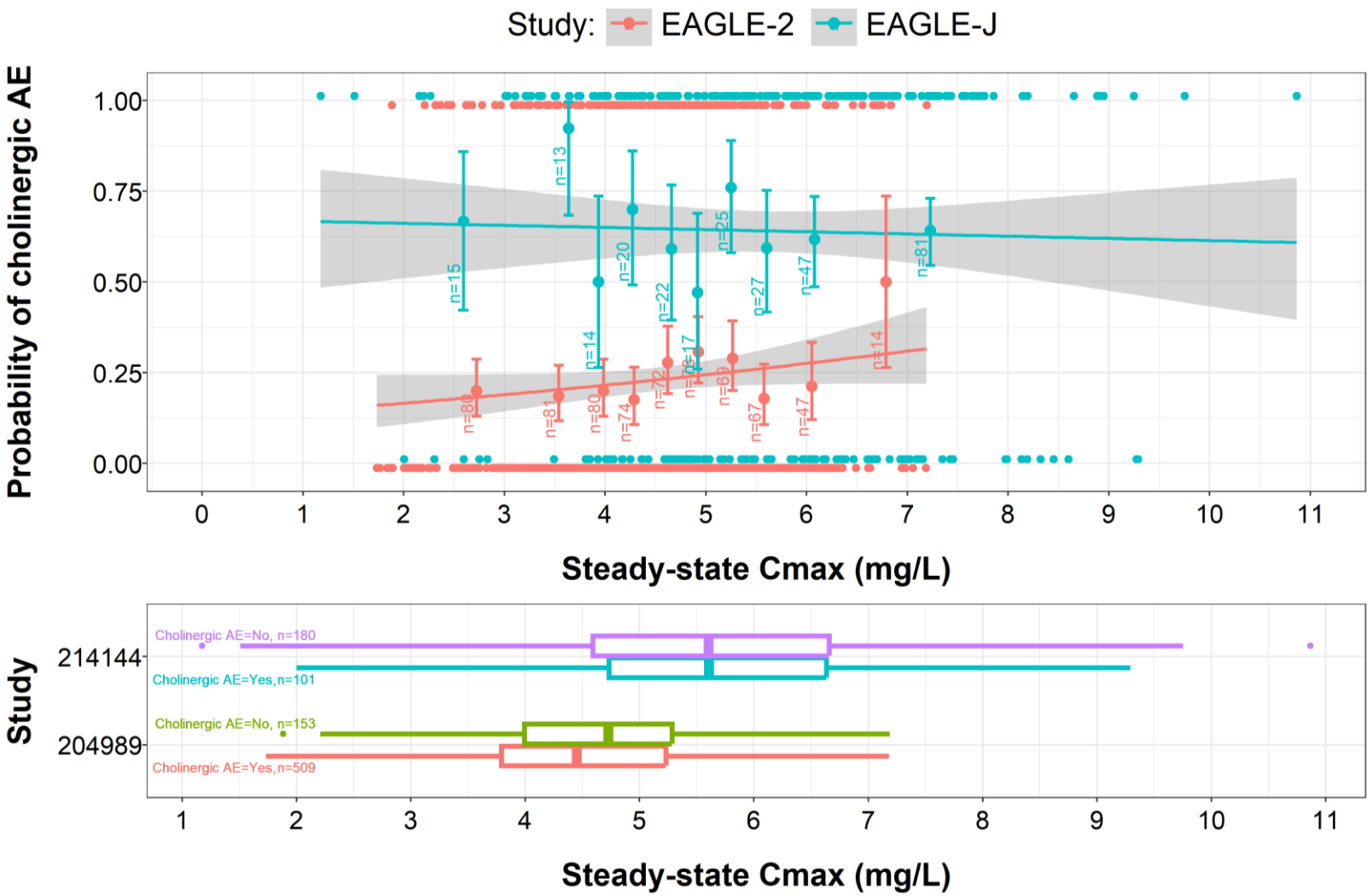
Source: Applicant's Response to Information Request of November 26, 2024, Figure 4 and 5, pages 10.
Note: SS AUC(0-24) represent the Day 5 steady-state AUC (daily AUCss) from the twice daily dosing regimen. Response "0" indicates no event occurred; response "1" indicates event occurred according to Applicant's preferred terms.
Abbreviations: Daily AUC_{ss}, AUC_{Tau} divided by the number of days in the dosing interval

Reviewer's Comments

Assessment of the Exposure-Cholinergic AEs analyses:

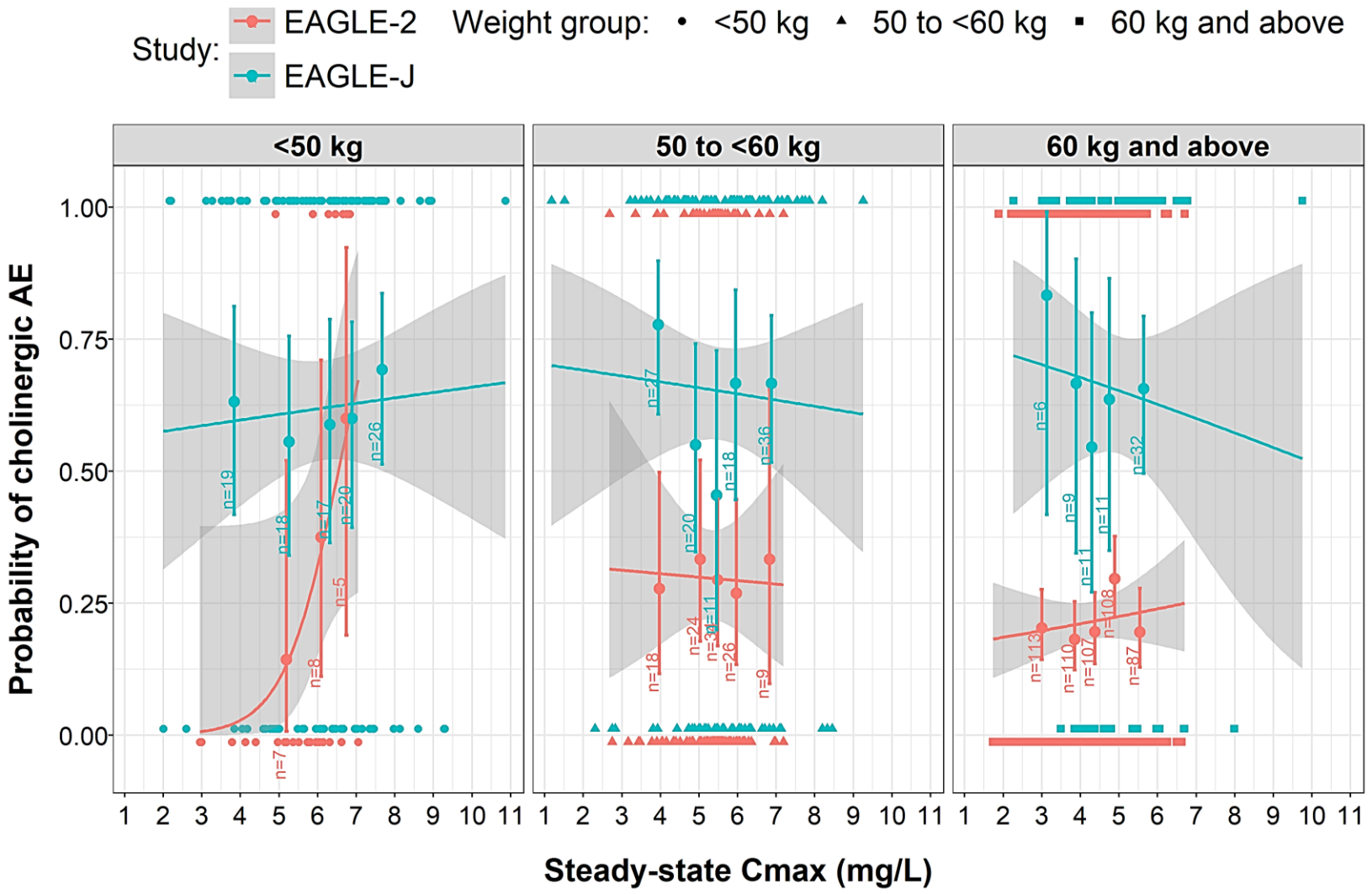
- *The plasma exposure metrics for participants in EAGLE-J were generated using the original developed population PK model updated with PK data from Study EAGLE-J. The re-estimated PK model parameters with pooled EAGLE-2 and EAGLE-J concentrations reasonably described the PK data from both studies. The re-estimated population PK parameters from the pooled studies PK data were comparable to those estimated from the EAGLE-2 data only. In addition, the individual PK parameters of EAGLE-J participants estimated for the updated PK model were similar to those predicted from the original PK model (using maxeval = 0 approach in non-linear mixed-effects modeling).*
- *The reviewer agrees with the Applicant's assessment suggesting that the observed significant relationship between gepotidacin exposure metrics (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) and all cholinergic TEAEs, from the pooled studies, is due to a study effect driven by the higher prevalence of cholinergic TEAEs in EAGLE-J study, regardless of the exposure. However, in EAGLE-2 study, there was an apparent trend of higher prevalence of cholinergic TEAEs at the highest quantile of $C_{max,ss}$ (Figure 20 and Figure 21), with fewer EAGLE-2 participants (n = 5 for weight <50 kg, n = 6 for weight 50 to <60 kg, n = 3 for weight ≥60 kg, for a total n = 14) at the highest quantile of $C_{max,ss}$ (> 6.5 mg/L). The effect of $C_{max,ss}$ in the different weight groups and studies was not found to be statistically significant from the logistic regression analysis adjusting for study and weight groups, with a non-statistically significant regression coefficient (p-value of 0.06) for the predictor $C_{max,ss}$ in Study EAGLE-2 and weight group <50 kg (Figure 21). Study (EAGLE-J vs EAGLE-2) remained the only statistically significant predictor of cholinergic TEAEs.*
- *The difference in the incidence of cholinergic TEAEs between EAGLE-J and EAGLE-2 is likely related to a study effect (with no identified source) and not to a difference in gepotidacin exposure. The apparent but not statistically significant trend between the highest $C_{max,ss}$ and the prevalence of cholinergic TEAEs is not conclusive and should be interpreted with caution due to very few subjects with high $C_{max,ss}$ values (>6.5 mg/L) and the single dose level studied (1500 mg twice daily).*

Figure 20. Exposure-Response Relationship of all Cholinergic AEs vs. $C_{max,ss}$, by Study



Source: FDA reviewer.
Dots (error bars) represent the observed proportion of subject experiencing a cholinergic AE (90% CI based on the exact method).
Abbreviations: AE, adverse event; CI, confidence interval; $C_{max,ss}$, Maximum plasma concentration at steady state; vs., versus

Figure 21. Exposure-Response Relationship of all Cholinergic AEs vs. $C_{max,ss}$, by Study and Weight Groups



Source: FDA reviewer
Note: dots (error bars) represent the observed proportion of subject experiencing a cholinergic AE (90% CI based on the exact method)
Abbreviations: AE, adverse event; CI, confidence interval; $C_{max,ss}$, Maximum plasma concentration at steady state

14.5.5. Physiologically-Based Pharmacokinetics

The objective of this review is to evaluate the adequacy of the Applicant's PBPK analyses to 1) predict impact of weak or moderate CYP3A inhibitors or inducers on the PK of gepotidacin; 2) to predict gepotidacin as a precipitant on the PK of MATE substrates.

The Division of Pharmacometrics has reviewed the PBPK report (report # 2022N524769 and 2020N458711), modeling files, and Response to the FDA's Information Request (IR) received on November 27, 2024, December 2nd, 2024, January 2nd, 2025, January 15, 2025, January 20, 2025, and January 30, 2025. The Reviewers concluded that the final PBPK model can used for the following applications:

- The DDI simulation results indicated the AUC and C_{max} for gepotidacin increase approximately 1.4 and 1.2-fold, respectively, with co-administration with a moderate CYP3A4 inhibitor (such as fluconazole)
- The DDI simulation results indicated the AUC and C_{max} for gepotidacin would decrease approximately ~50% and ~30%, respectively, with co-administration of a moderate CYP3A4 inducer (such as efavirenz)
- The weak CYP3A inhibitor and weak CYP3A inducer would have minor effect on gepotidacin's PK exposure parameters
- The parameter sensitivity analysis results suggest the gepotidacin's DDI effect on MATE substrates, such as metformin, cannot be ruled out.

The Applicant conducted a clinical DDI study to assess gepotidacin's effect following two 3000 mg doses as a CYP3A inhibitor on midazolam's PK. The PBPK simulation results for the effect of gepotidacin 1500 mg BID for 5 days on midazolam's PK or other CYP3A4 substrates are not reviewed by the FDA. Gepotidacin is recommended to be administered with food.

Background

Gepotidacin selectively inhibits bacterial DNA gyrase and topoisomerase IV, and it is active in vitro against most target pathogens carrying resistance determinants to established antibacterials, including fluoroquinolones. Gepotidacin is proposed for the treatment of uncomplicated urinary tract infection for which the target dosing regimen is 1500 mg given as repeat oral dose BID for 5 days.

In human plasma, in vitro protein binding was 11% to 41%. The in vitro blood-to-plasma ratio of gepotidacin was approximately unity (range: 0.82 to 1.2) in nonclinical species and human, indicating roughly equal distribution between plasma and blood cells. Plasma protein binding and blood cell partitioning is not concentration dependent.

In vitro data suggested that CYP3A4 is the only oxidative enzyme responsible for gepotidacin metabolism (2014N210367_00) and gepotidacin is a substrate of P-gp and BCRP. Following IV administration of 1000 mg gepotidacin (Study ID BTZ115774), 54.6% and 26.8% of the dose was excreted in urine and feces, respectively, with 43.93% and 16.9% of the dose being unchanged drug (Study BTZ115774). These results indicate that renal clearance (fe 54%) is a major clearance component for gepotidacin, followed by metabolism (25%) and biliary clearance

(20.8%). Following oral administration of 2000 mg gepotidacin, 28.2% and 47.4% of the dose was excreted in urine and feces, respectively, with 20.2% and 40.5% of the dose being unchanged drug, respectively. These results indicate that renal clearance (fe,renal, 46%) is a major clearance component for gepotidacin, followed by metabolism (33%) for which CYP3A4 is responsible for gepotidacin metabolism (~33% of total human clearance).

Both the $AUC_{0\text{-}inf}$ and C_{max} of gepotidacin increased by approximately 40% to 50% when coadministered with itraconazole, a strong inhibitor of CYP3A4 (Study BTZ117349). Coadministration of gepotidacin with a strong index CYP3A4 inducer (rifampicin) resulted in a decrease of 52% in gepotidacin plasma $AUC_{0\text{-}inf}$ (Study 213678). Coadministration of gepotidacin with a nonspecific MATE and OCT inhibitor (cimetidine) resulted in no clinically relevant changes in gepotidacin plasma exposures for Cmax or for plasma and urine AUCs (Study 213678).

Gepotidacin is an in vitro inhibitor of CYP3A4, P-gp and BCRP, and gepotidacin inhibits MATE1, MATE2K, BCRP, OCT3 and Pgp with IC50 values of 16.61, 6.375, 9711, 356.3 and 2530 μM, respectively (GSK Study No. 2020N436056_00).

A clinical DDI study with midazolam (MDZ) showed that co-administration with two 3000 mg gepotidacin dose resulted in a 1.92-fold and 1.24-fold increases in geometric mean AUC and Cmax of MDZ, respectively (213678-Cohort 3). Coadministration of digoxin with gepotidacin as a P-gp inhibitor resulted in a 1.1-fold increase in digoxin $AUC_{0\text{-}inf}$ with a 1.5-fold increase in C_{max}.

Methods

The Applicant submitted two PBPK reports: report # 2022N524769 and 2020N458711. The PBPK model reported in report 2022N524769 was built in Simcyp Version 21 based on the original PBPK model reported in the report 2020N458711 using Simcyp Version 19. Most PBPK applications enclosed in the NDA were included in the report 2022N524769. The report 2020N458711 provides the DDI simulation of gepotidacin with fluconazole or fluvoxamine as CYP3A inhibitor. Gepotidacin's PBPK compound file was revised in the report 2022N524769 based on the emerging clinical PK data after the report 2020N458711 was published. Therefore, the report 2022N524769 is the final PBPK model and 2020N458711 was not reviewed and assessed in this document.

The reviewer repeated the abovementioned DDI simulations using the updated PBPK model reported in report # 2022N524769 with refined age criteria for virtual population (see discussion in Model Application section).

Model Development

The PBPK analyses were performed using the PBPK software Simcyp® V21 (Simcyp Ltd., Sheffield, UK).

The gepotidacin PBPK model was developed based on physicochemical properties, preclinical, and clinical PK data. Gepotidacin's absorption was described by the advanced dissolution, absorption and metabolism (ADAM) model. The MechPeff model was used to predict the regional Peff,man. The (Q)SAR model using polar surface area (90.4Å) and hydrogen bond donors (=1) as inputs predicted Jejunum I Peff,man value (=1.519 × 10-4 cm/s). The MechPeff model was then used to apply regional permeability values to the remaining intestinal and

colonic segments. The Peff,man value for the colon was manually set to 0.0001 to minimize drug absorption in the colon. The simulated fa of gepotidacin is approximately 0.62, comparable to an estimated fa of approximately 0.50 from the human mass balance study (Study BTZ115774). The diffusion layer model was used. The measured pH-solubility in aqueous media and intrinsic solubility of the free base drug substance were incorporated in the model as user defined pH-solubility profile. The dissolution profile of the phase 3 clinical batch CCVKG used in the Clinical Study 209611 was inputted in the model as a disintegration profile.

Distribution model was a full PBPK model established via Method 2 in Simcyp. The predicted V_{ss} was 3.36 L/kg, comparable to the PopPK estimated V_{ss} of 160 L (PopPK Report TMF-16148607).

The geometric mean CL_{iv} value of 38.8 L/h derived from Clinical Study BTZ115774 was used in the retrograde model (extrapolation from in vivo data) to estimate a CL_{uint}. The CLr was estimated to be 17.4 L/h (Study BTZ114595). The biliary clearance was estimated to be 20.8% of CL_{iv}. These fmCYP values were confirmed by two DDI study results with rifampin (Study 213678) or itraconazole (Study BTZ117349-cohort 2).

Reviewer's Comments:

Gepotidacin is a P-gp substrate. In the PopPK analysis report (BTZ114595), gepotidacin's dose proportionality was assessed using a power model where the slope parameter, a measure of dose proportionality, was estimated to be 1.19 (0.989 – 1.39) for AUC versus dose, or 1.11 (0.825 – 1.40) for C_{max} versus dose. Such results suggest the over-dose proportional PK for gepotidacin, to which P-gp might contribute. The P-gp is not incorporated in gepotidacin's model either in the gut or in the liver; thus, such omission might result in the over-prediction gepotidacin's PK at low dose. As the objective of the PBPK report in the scope of the NDA submission was to assess the DDI effect following a 1500 mg gepotidacin dose as a CYP3A substrate, the weakness in gepotidacin's PBPK model for simulating the PK after a single dose <1500 mg would not affect the DDI prediction results significantly. In the DDI study with itraconazole (Study BTZ117349-cohort 2), according to the study report, gepotidacin was dosed under a fed state and was dosed 1 h after the itraconazole dose. In the meantime, it is not clear to the reviewer when the meal was given to the study participant, before the itraconazole dosing or 30 minutes before the gepotidacin dose. In the response to IR received on January 30, 2025, the Applicant clarified that itraconazole was to be administered with a standard breakfast, and gepotidacin was to be administered one hour after itraconazole dosing. Nevertheless, the actual timing of the meal relative to itraconazole and gepotidacin dosing was not captured in the clinical database. It was possible that gepotidacin's absorption could be different following the 2nd dose compared to its absorption following the 1st dose in Study BTZ117349-cohort 2 due to the differing mealtime. The estimation of gepotidacin's fmCYP3A4 was further validated by modeling the DDI effect by rifampin (Study 213678), which helped reduce the uncertainty of the fmCYP3A value derived from modeling the gepotidacin/itraconazole DDI results. *The uncertainty in predicted gepotidacin's PK following 1500 mg BID dosing as a MATE inhibitor could be minimized via parameter sensitivity analysis. Another concern is the high-fat meal effect on gepotidacin's PK with or without CYP3A modulator(s). The Applicant has not assessed the effect of a high-fat meal on gepotidacin's PK. Gepotidacin's AUC and C_{max} may either increase, decrease, or remained unchanged in the presence of a high fat meal and a moderate CYP3A inhibitor. A potential for a higher DDI effect can't be excluded.*

Model Verification

PK Performance

- A single 1500 mg gepotidacin dose in healthy subjects (Study).
- Multiple gepotidacin dosing (800, 1500, 2300 mg q12h) in healthy subjects (Study BTZ116778)
- Two 3000-mg doses of gepotidacin given 12 hours apart in Japanese population under a fed state (Study BTZ116778)

DDI potential of Gepotidacin as a CYP3A Substrate

- Verification the contribution of CYP-mediated metabolic pathways using the clinical DDI data with a strong CYP3A inhibitor itraconazole (Study BTZ117349-cohort 2) in healthy subjects: 200 mg of itraconazole was administered orally once a day for 6 days at 9 AM and a single dose of 1500 mg of gepotidacin on Day 4 at 10 AM in a fed state
- Verification the contribution of CYP-mediated metabolic pathways using the clinical DDI data with a strong CYP3A inducer rifampin (Study 213678 cohort 2) in healthy subjects: 600 mg of rifampin was administered orally once a day for 7 days, followed by a single dose of 1500 mg gepotidacin on Day 8 at 9 AM. With the continued rifampin once daily (QD) at 9 PM on Day 8 and Day 9 in a fed condition

Model Application

The Applicant conducted the DDI simulation in healthy subjects ages 20 to 50 years, with 50% of the subjects being female. However, the intended patient population consists of female patients, with no upper age limit specified. According to the PopPK report, body weight and age were identified as significant covariates of gepotidacin PK. Therefore, the reviewer conducted the DDI simulations using Simcyp V21 or Simcyp V23. The selected population for these simulations included healthy subjects ages 18 to 65 years, with an equal distribution of males and females (50%). Additionally, the reviewer conducted simulations specifically for female subjects ages 18 to 65 years for gepotidacin as a CYP3A substrate. The DDI results were found to be similar between the 50% female population and the 100% female population ages 18 to 65 years. As a result, the DDI findings for the 18 to 65-year-old healthy subject group with 50% females are presented in the summary. Table 151 summarizes the PBPK model applications for gepotidacin as a substrate or as a precipitant.

Table 151. Summary of the Gepotidacin's PBPK Model Applications

Dosing Regimen for the Substrate	Dosing regimen for the Precipitant	Age Range	Female %	Simcyp Version
A single 1500 mg Gepotidacin dose on Day 10	Fluconazole (A single 400 mg Day 1, 200 mg QD Day 2 – Day 11)	18 - 65	50	21
A single 1500 mg Gepotidacin dose on Day 8	Fluvoxamine (100 mg TID for 12 days	18 - 65	50	21
A single 1500 mg Gepotidacin dose on Day 8	Efavirenz 600 mg QD for 11 days	18 - 65	50	21
A single 1500 mg Gepotidacin dose on Day 8	Rifampin 10 mg QD for 11 days	18 - 65	50	21
Gepotidacin 1500 mg BID for 5 days	A single metformin dose co-administered with the 7th Gepotidacin dose	18 - 65	50	23

Source: FDA Reviewer
Abbreviations: BID, twice daily; PBPK, physiologically based pharmacokinetic; QD, once daily; TID, three times daily

- Prediction of the effect of a moderate CYP3A inhibitor on gepotidacin's PK: Simulation: Gepotidacin 1500 mg single dose (on day 10), administered with fluconazole (a single 400 mg Day 1, 200 mg QD day 2 – day 11) in healthy volunteers, fasted state.
- Prediction of the effect of a weak CYP3A inhibitor on gepotidacin's PK: Gepotidacin 1500 mg single dose (on day 8), administered with fluvoxamine (100 mg TID day 1 –12) in healthy volunteers, fasted state
- Prediction of the CYP3A induction effect of a moderate CYP3A inducer on gepotidacin's PK: Gepotidacin 1500 mg single dose (on day 8), administered with Efavirenz (600 mg QD for 10 days) in healthy volunteers, fasted state
- Prediction of the CYP3A induction effect of a weak CYP3A inducer on gepotidacin's PK: Gepotidacin 1500 mg single dose (on day 8), administered with rifampin (10 mg QD day 1 – 13) in healthy volunteers, fasted state
- Prediction of the effect of gepotidacin on a MATE substrate: parameter sensitivity analysis using a 100-fold lower Ki value for MATE and metformin as the substrate using Simcyp V23.

Results

Q1. What is the Gepotidacin's PBPK Model Performance for Simulating Gepotidacin PK Profiles

A limitation was identified for the PBPK model of gepotidacin according to its performance. The model predicted and the observed gepotidacin plasma concentration – time profiles following administration of single 800 mg, 1500 mg, 2300-mg dose are depicted in Figure 22 and the predicted and observed oral PK parameters are summarized in Table 152. Following multiple dosing (BID of 800 mg, 1500 mg, 2300 mg) in healthy subjects, the model predicted and the observed gepotidacin plasma concentration – time profiles are depicted in Figure 23, and the predicted and observed oral PK parameters are summarized in Table 152.

Table 152. Summary of Observed and Predicted Exposure PK Parameters of Gepotidacin Following QD or BID Dosing Under a Fasted Condition.

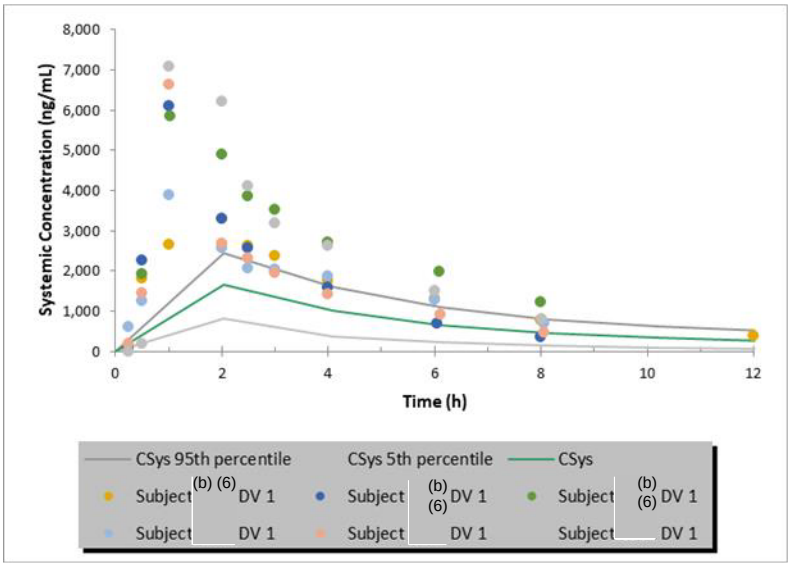
		Obs[a]		Pred[b]		Pred/Obs. Ratio	
Dose (mg)	**Parameter**	**Day 1**	**Day 16**	**Day 1**	**Day 16**	**Day 1**	**Day 16**
800[c]	$AUC_{0\text{-}tau}$ (ng.h/mL)	6600 (40.5)	8400 (40.1)	10363 (39.0)	10425 (39.0)	1.57	1.24
	C_{max} (ng/mL)	1860 (53.2)	2280 (85.4)	1741 (24.0)	1996 (27.0)	0.94	0.87
1500[d]	$AUC_{0\text{-}tau}$ (ng.h/mL)	13000 (24.9)	19800 (31.5)	19411 (39.0)	19527 (39.0)	1.49	0.99
	C_{max} (ng/mL)	5070 (20.3)	6500 (35.9)	3259 (24.0)	3737 (27.0)	0.64	0.57
2300[e]	$AUC_{0\text{-}tau}$ (ng.h/mL)	23900 (21.5)	36000 (11.7)	29745 (39.0)	29907 (39.0)	1.24	0.83
	C_{max} (ng/mL)	6730 (30.2)	7850 (7.4)	4990 (24.0)	5716 (26.0)	0.74	0.73

Source: the applicant's report 2022N524769_00
[a]Observed data reported from Study BTZ116778 with geometric mean values and CV%, and T_{max} range shown in parentheses.
[b]Simulations with geometric mean values with CV% shown in parentheses using direct input of customized study design (Table 2).
[c] Reported 800 mg data from n=12 subjects on Day 1, and Day 16.
[c] Reported 1500 mg data from n=12 subjects on Day 1, and Day 16
[e] Reported 2300 mg data from n=6 subjects on Day 1 and Day 16
Abbreviations: $AUC_{0\text{-}tau}$, area under the concentration-time curve during the dosing interval; CV%, co-efficient of variation expressed as percent; GM, Geometric Mean; Obs, observed; PK, pharmacokinetic; Pred, predicted; $T_{max,}$ time to maximum concentration

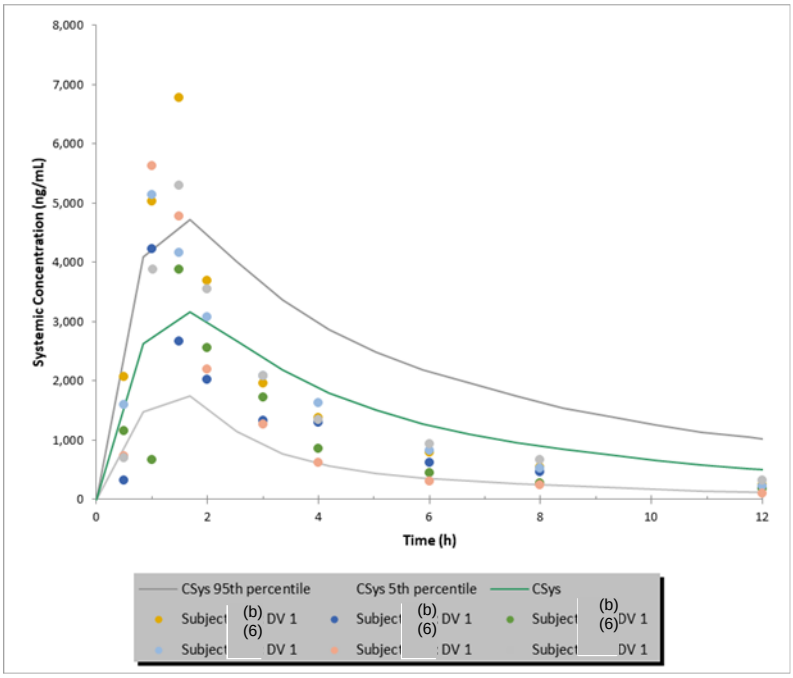
Following a single 800, 1500 mg or 2300-mg dose, the observed AUC was ~ 25 – 50% lower than the predicted AUC on Day 1 (Table 152). Most observed concentrations were higher than the predicted 95th percentile of the predicted gepotidacin concentration in plasma after an 800-mg dose in Figure 22.

Figure 22. Predicted and Observed Plasma PK Profiles of Gepotidacin After a Single 800 mg, 1500 mg, 2300-mg Dose in Healthy Subjects.

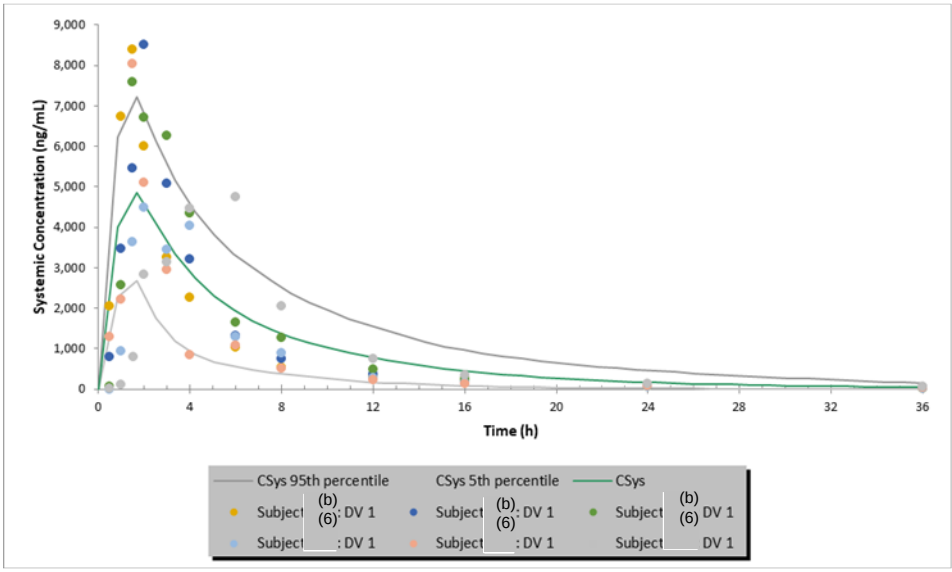
800 mg



1500 mg



2300 mg

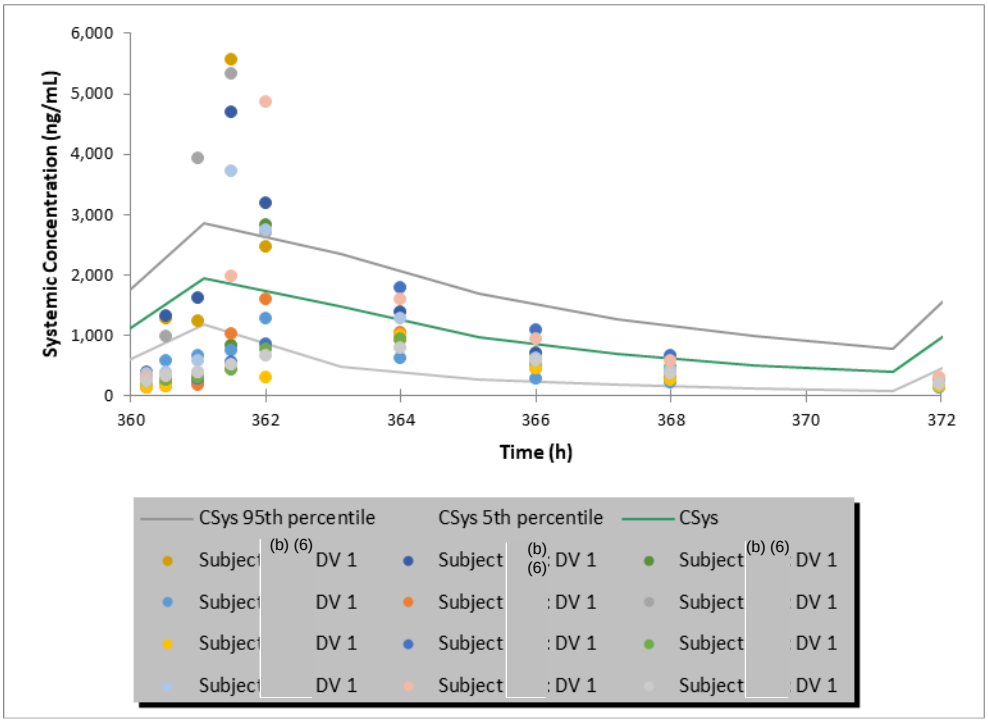


Source: The reviewer modified Figure 3 in report 2022n524769
Solid symbols represent the observed data from each subject from study BTZ116778. Solid lines represent simulated mean and shaded areas represent area between the 5th and 95th percentile of the virtual population.
Abbreviation: CSys, systemic concentration; Pk, pharmacokinetic

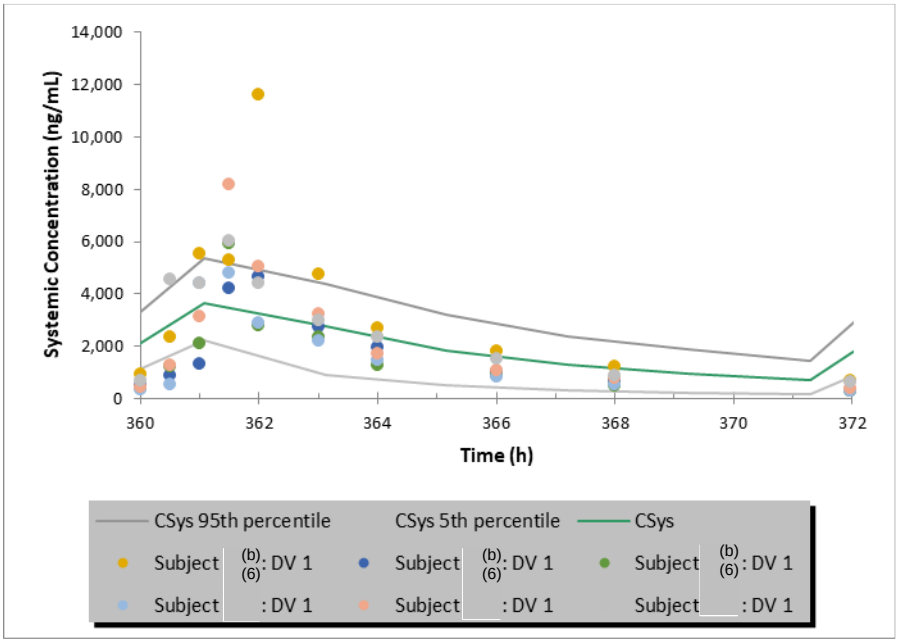
Following 1500 mg BID, the predicted C_{max} was ~ 50% lower than the observed C_{max}, and the predicted T_{max} (1.3 to 1.4 hours) was consistently shorter than the observed median T_{max} (2 hours) and the minimum observed T_{max} (1.5 hours) on Day 1 or Day 16 in 12 subjects (Table 152). Figure 23 depicts the observed and predicted gepotidacin concentrations in plasma versus time profiles on Day 16.

Figure 23. Observed and Predicted Gepotidacin's Plasma Concentration-Time Profile on Day 16 Following BID of 800 mg, 1500 mg, 2300 mg

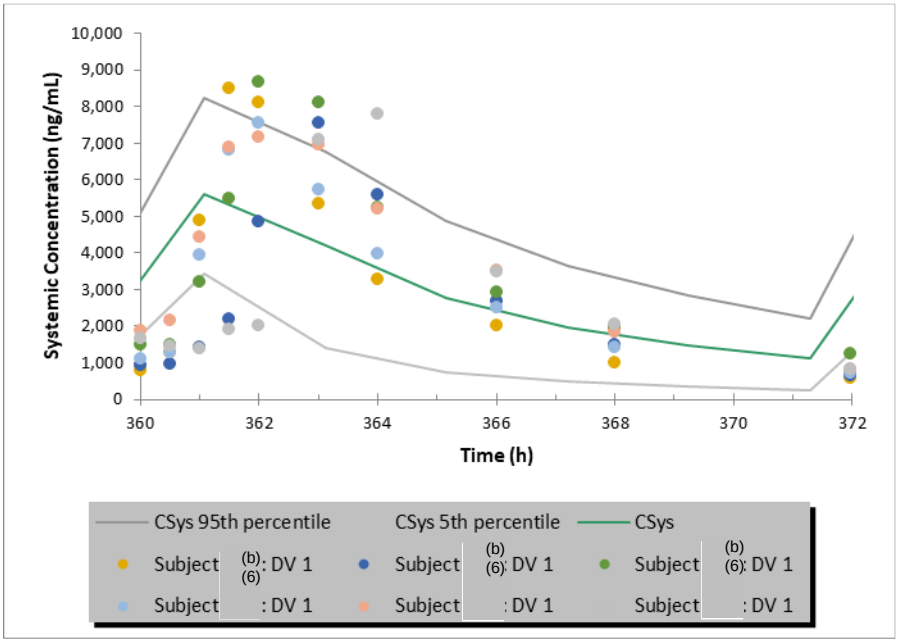
800 mg BID



1500 mg BID



2300 mg BID



Source: Modified from the applicant's report 2022N524769_00.
Abbreviation: BID, twice daily; CSys, systemic concentration

The Applicant further simulated the PK following a single 1500 mg gepotidacin dose under a fed or fasted state, and simulated the PK after 2 gepotidacin doses of 3000 mg under fed state in Japanese subjects using the Japanese population library. The validity of the Japanese population library and the food effect prediction are not reviewed by the agency. The Applicant recommends administration of gepotidacin in the presence of meal. Nevertheless, PBPK simulations for gepotidacin as a CYP3A substrate in the presence of moderate CYP3A modulators were conducted under a fasted state. Likewise, the parameter sensitivity analysis via PBPK modeling for gepotidacin as a MATE inhibition was conducted under a fasted state.

Q2. Can PBPK Analyses Predict the Effect of a Strong CYP3A Inhibitor or Inducer on Gepotidacin's PK?

Yes, the PBPK model adequately simulated the DDI magnitude following a single 1500 mg Gepotidacin dose under a fasted state, as shown in Table 152, though the gepotidacin PK simulation was suboptimal. In Table 9 of the PBPK report (2022n524769), the predicted gepotidacin AUC ratio of 1.66 (1.63 to 1.70) was reported in the presence of itraconazole. Nevertheless, in the response to the IR received on December 2, 2024, the Applicant indicated that the source of the simulation results in Table 9 following a dosing regimen for itraconazole and gepotidacin in Study BTZ117834 is the excel file named 1500-mg-sd-gepo-vs-200-mg-itz-ddi-prediction-study-btz11734.xlsx, where the predicted DDI results for geometric mean AUC ratio (5^{th} to 95^{th} confidence interval of the geometric mean) was 1.77 (1.73-1.80) and the dosing regimen used in the simulation differed from the one implemented in the Study BTZ117834. Hence, the reviewer conducted the simulation according to the dosing regimen that consists of a 200 mg itraconazole capsule QD for 3 days under a fed state, followed by a single 1500 mg gepotidacin dose on Day 4, with continued 200 mg itraconazole QD in the ensuing time period in Study BTZ117834. The predicted AUC ratio was 1.8, 20% higher than the observed AUC ratio of 1.5 in Study BTZ117834, and the predicted C_{max} ratio was 1.3, similar to the observed C_{max} ratio of 1.4 (Table 153).

DDI simulation results with a strong CYP3A inducer (rifampin) on gepotidacin's PK was ~ 50% decrease on C_{max} and ~65% decrease on AUC, compared to the observed ~25% decrease on Cmax and ~50% decrease on AUC. The predicted DDI effect by rifampin was ~ 0.7 fold of the observed DDI effects.

In the case of a strong CYP3A inhibitor or inducer-mediated DDI, the magnitude is primarily determined by the perpetrator's PBPK model. Though the performance of gepotidacin's PBPK model appears suboptimal, the derived fmCYP3A4 value (~0.4) via modeling the DDI effect with itraconazole or rifampin is valid. The reviewer concludes that gepotidacin's PBPK model could be further utilized to predict the DDI effect for gepotidacin as a substrate with moderate or weak CYP3A modulators.

Table 153. Summary of Observed and Predicted Gepotidacin's PK Exposure Parameter Ratio With or Without Itraconazole or Rifampin

	DDI With Itraconazole			DDI With Rifampin		
	Gepotidacin + Itraconazole vs. Gepotidacin			Gepotidacin + Rifampin vs. Gepotidacin		
Parameter	**[a]Obs.**	**[b]Pred.**	**Pred./Obs. Ratio**	**[a]Obs.**	**[b]Pred.**	**Pred./Obs. Ratio**
C_{max} (ng/mL)	1.42 (1.25, 1.62)	1.3 (1.3-1.4)	0.93	0.730 (0.635-0.840)	0.48 (0.46-0.50)	0.66
$AUC_{(0-t)}$ (ng*h/mL)	1.50 (1.41, 1.59)	1.8 (1.8-1.9)	1.2	0.476 (0.433-0.525)	0.34 (0.32-0.36)	0.71

Source: Study BTZ117349-Part 2 or Study 213678-Cohort 2, given as geometric mean
[a] Observed data
[b] Calculated Ratio of DDI given as geometric mean and 90% confident interval of reported ratios. Note: DDI simulation was conducted by the reviewer.
Abbreviations: AUC_{0-t}, from time 0 to last quantifiable timepoint; C_{max}, maximum plasma concentration; DDI, drug drug interaction; Obs, observed; PK, pharmacokinetic; Pred, predicted

Q3. Can PBPK Analyses Predict the Effect of a Weak or Moderate CYP3A Modulator on the Gepotidacin's PK Following a Single Gepotidacin Dose?

Yes, the PBPK model is adequate to predict the effect of a weak or moderate CYP3A modulator on gepotidacin after a single 1500-mg dose. The simulation results are summarized in Table 154. The Applicant reported the DDI effect for gepotidacin as a substrate and fluconazole or fluvoxamine as precipitant using Simcyp V19. The dosing regimen for fluvoxamine as a weak CYP3A4 perpetrator implemented in the simulation was 100 mg intravenous injection, which differed from the fluvoxamine drug label (the US FDA, 2008). Additionally, gepotidacin's compound file was revised in report 2022N524769 based on the emergent clinical PK data. Hence, the reviewer conducted the DDI simulation using gepotidacin's compound file reported in report 2022N524769 in Simcyp V21. The simulation results suggest that gepotidacin's AUC or C_{max} would increase by 40% or 20% by fluconazole, and 20% or 10% by fluvoxamine (Table 153). In the presence of a moderate CYP3A inducer (efavirenz), Gepotidacin's AUC_{last} and C_{max} was predicted to decrease by 49% and 34%, respectively. In the presence of a weak CYP3A inducer (10 mg rifampin), gepotidacin's AUC_{last} and C_{max} was predicted to decrease by 13% and 9%, respectively.

Table 154. Summary of the Predicted Effects of a Moderate or Weak CYP3A Modulator on Gepotidacin's Oral PK Exposure Parameters

Perpetrator (Dosing Regimen)	**AUC ratio [a]**	**C_{max} ratio [a]**
Fluconazole (A single 400 mg Day 1, 200 mg QD day 2 – day 11, Gepotidacin dosed on Day 8)	1.4 (1.4 – 1.4)	1.2(1.1 -1.2)
Fluvoxamine (100 mg TID for 12 days, Gepotidacin dosed on Day 8)	1.2 (1.1 -1.2)	1.1 (1.1 -1.1)
Efavirenz (600 mg QD for 11 days, Gepotidacin dosed on Day 8)	0.51 (0.48 – 0.53)	0.66 (0.64 – 0.68)
Rifampin (10 mg QD, Gepotidacin dosed on Day 8)	0.87 (0.85 – 0.88)	0.91 (0.90 – 0.93)

Source: The reviewer's analysis results based on the applicant's PBPK model in the report 2022N524769_00.
PBPK simulation results performed by the reviewer
[a] Values as geometric mean (GM) (90% CI)
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic; QD, once daily; TID, three times daily

Q4 Can PBPK Analyses Predict the Effect of Gepotidacin on MATE Substrates Following 1500 mg BID of Gepotidacin for 5 Days?

Yes, the PBPK analyses can be used to predict the effect of gepotidacin on MATE substrates following 1500 mg BID for 5 days. Employing the PBPK model in Simcyp V21, the Applicant predicted the AUC_R of 1.4 and C_{maxR} of 1.3 for metformin after entered a 20-fold lower Ki value for MATE compared to the measured value. These results are enclosed in the response to IR received on January 20, 2025. The reviewer conducted the parameter sensitivity analysis for the Ki value of MATE using Simcyp V23 where the permeability-limited kidney model (Mech KiM) is incorporated. When the entered Ki value was 100-fold lower than the measured value via the in vitro study, the predicted AUC_R was ~2. Hence, a virtual population simulation (10 females ages 18 to 65-year-old × 10 trials) was conducted using Simcyp V23 for metformin. The output AUC_R and C_{maxR} was 1.6 and 1.3, respectively. These simulated results suggest the likelihood of DDI effect on MATE substrates cannot be ruled out, as it exceeds the recommended screening cut-off value when in-vitro parameters were applied for the DDI effect estimation (e.g. AUC ratio of 1.25).

14.6. Pharmacogenetics

N/A.

15. Study/Trial Design

Please refer to Section 6 for the study designs of the two phase 3 uUTI studies (EAGLE-2 and EAGLE-3).

15.1. Study Design, Study 206899

Study 206899 was a phase 2, single-center, open-label study conducted in the United States that evaluated the safety, tolerability, and PK of 1500 mg of gepotidacin administered twice daily for 5 days in adult women 18 to 65 years of age with uUTIs. The total study duration was 28 days, of which the 22 study subjects were confined to a study clinic for 5 days, with two follow-up outpatient visits.

While confined to the clinic, all study subjects provided blood and urine samples for PK assessments. Urine samples for bacteriology cultures were collected at baseline, test-of-cure (TOC) (Day 10) and follow-up (Day 28) visits. Each study subject was observed by study staff while they took each dose of gepotidacin with food and adhered to prespecified activity restrictions. Study staff assessed and recorded clinical signs and symptoms of acute cystitis and adverse events (AEs). All AEs and SAEs were followed through subsequent study visits until the event resolved, stabilized, was otherwise explained or the subject was lost to follow-up. Study subjects could be discontinued if they met prespecified criteria for abnormal liver chemistries or QT interval corrected for heart rate (QTc) prolongation.

The primary study objective assessed plasma PK parameters, with secondary objectives to assess urinary PK and the safety or tolerability of repeat oral doses of gepotidacin. Efficacy for the

treatment of uUTI was assessed as an exploratory objective via a therapeutic response endpoint, defined as combined microbiological and clinical response at the TOC visit.

15.1.1. Eligibility Criteria, Study 206899

Participants were considered eligible for enrollment if they met all of the following inclusion criteria:

1. ≥18 to ≤65 years of age
2. Female sex
3. Two or more of the following clinical signs and symptoms of acute cystitis with onset ≤72 hours of the screening assessment: dysuria, frequency, urgency, or lower abdominal pain
4. Pyuria defined as ≥10 white blood cell (WBC)/mm^3 or the presence of leukocyte esterase and/or nitrates present in a urine sample.

Participants were not considered eligible for enrollment if they met any of the following summarized key exclusion criteria:

1. Residence in a nursing home or dependent care-type facility
2. BMI ≥40.0 kg/m^2 or a BMI ≥35.0 kg/m^2 with obesity-related health conditions
3. Presence of immunocompromise, altered immune defenses or receipt of immunosuppressive therapy, including corticosteroid therapy
4. Uncontrolled diabetes
5. Presence of a medical condition that requires medication that could be affected by acetylcholinesterase inhibition, such as: poorly controlled asthma or chronic obstructive pulmonary disease, acute uncontrolled severe pain, active peptic ulcer disease, Parkinson disease, myasthenia gravis or seizure disorders requiring medications
6. Any surgical or medical condition that may interfere with drug absorption, distribution, metabolism, or excretion of the study drug, including history of gastric bypass or a cholecystectomy
7. Hemoglobin value <12 g/dL or a known uncorrected iron deficiency.
8. Presence of acute cystitis known or suspected to be due to fungal, parasitic, viral pathogens, *Pseudomonas aeruginosa* or non-*E. coli* Enterobacteriaceae
9. Symptoms known or suspected to be caused by another disease process such as asymptomatic bacteriuria or chronic interstitial cystitis
10. Presence of anatomical, physiological or functional urogenital anomalies or neurogenic bladder
11. Presence of indwelling catheter, nephrostomy, ureter stent, or other foreign material in the urinary tract
12. Symptoms of a complicated urinary tract infection (UTI), pyelonephritis, or urosepsis

13. Anuria, oliguria, or significant impairment of renal function defined as creatinine clearance (CrCl) <30 mL/min or clinically significant elevated serum creatinine
14. Presence of vaginal discharge

Congenital long interval from the start of the Q wave to the end of the T wave (QT) syndrome or prolongation of the QTc

15. Uncompensated heart failure, defined as New York Heart Association Class ≥III
16. Severe left ventricular hypertrophy
17. Family history of QT prolongation or sudden death
18. Vasovagal syncope or episodes of symptomatic bradycardia or bradyarrhythmia within the last 12 months
19. Use of QT-prolonging drugs or drugs known to increase the risk of torsades de points
20. Use of a strong cytochrome P450 enzyme 3A4 inhibitor or a strong P-glycoprotein inhibitor
21. QTc >450 msec or a QTc >480 msec for participants with bundle-branch block
22. Alanine aminotransferase (ALT) value >2 × upper limit of normal (ULN)
23. Bilirubin value >1.5 × ULN
24. Liver disease, or known hepatic or biliary abnormalities, including symptomatic viral hepatitis or moderate-to-severe liver insufficiency (Child Pugh class B or C)

Participants were also excluded if they had previously received systemic antimicrobial/antifungal treatment, had been previously enrolled in the study or received gepotidacin, had a known allergy to study drug or any component, had previously received an investigational drug, had a life-threatening medical condition or otherwise would not complete the study.

15.1.2. Statistical Analysis Plan, Study 206899

Formal hypothesis testing was not conducted as part of Study 206899. The target sample size of 20 participants was selected on the basis of feasibility and PK assessments. The following analysis populations were defined:

- PK Population: Subjects who receive at least 1 dose of gepotidacin and have evaluable plasma, urine, or tissue concentration data for gepotidacin.
- PK Parameter Population: All subjects in the PK Population who received gepotidacin 1500 mg BID through the completion of all PK collections for whom valid and evaluable plasma or urine PK parameters are derived for gepotidacin.
- Intent-to-treat (ITT) Population: All subjects assigned to study treatment.
- Microbiological ITT (micro-ITT) Population: All subjects assigned to study treatment who receive at least 1 dose of gepotidacin have a qualifying baseline uropathogen from a quantitative bacteriological culture of a pretreatment clean catch midstream urine specimen.
- Safety Population: All subjects who take at least 1 dose of gepotidacin.

For the purposes of the exploratory efficacy assessment, therapeutic failures were defined as any study subject who did not meet the criteria for clinical success and microbiological success. Microbiologic success was defined as a quantitative urine culture taken at the TOC Visit shows reduction of the qualifying bacterial uropathogen recovered at Baseline to $<10^3$ CFU/mL or presence of a new qualifying bacterial uropathogen, not identified at Baseline, at the TOC Visit in a participant who is a clinical success. Qualifying uropathogens included Gram-negative bacilli, *S. aureus, S. saprophyticus*, pure cultures of Beta-hemolytic streptococci, *Enterococcus* sp., *Gardnerella vaginalis,* and *Aerococcus urinae.* Clinical success at the TOC visit was defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs or symptoms) and no use of other antimicrobial therapy.

16. Efficacy

Primary Efficacy Endpoint Subgroup Analyses, Study EAGLE-2

Subgroup analyses are summarized in Table 155. Treatment effect with gepotidacin were generally consistent in subgroup analyses except certain categories with small sample sizes.

Table 155. Proportion of Subjects With Composite Response at TOC, Micro-ITT NTF-S, Complete Data, Study EAGLE-2

Demographic Parameters	Gepotidacin (N=336)	Nitrofurantoin (N=298)	Difference[a] in % (95% CI)
Overall (Female)	174/336 (51.8%)	140/298 (47.0%)	5.8% (-1.3%, 13.0%)
Age group per CRF			
≤50	75/145 (51.7%)	65/130 (50.0%)	1.7% (-10.1%, 13.5%)
>50	99/191 (51.8%)	75/168 (44.6%)	7.2% (-3.2%, 17.4%)
Race			
White	144/283 (50.9%)	115/247 (46.6%)	4.3% (-4.2%, 12.8%)
American Indian or Alaska Native	15/26 (57.7%)	14/31 (45.2%)	12.5% (-13.5%, 36.9%)
Black or African American	7/10 (70.0%)	6/10 (60.0%)	10.0% (-31.4%, 48.3%)
Asian	5/10 (50.0%)	3/8 (37.5%)	12.5% (-32.7%, 52.5%)
Native Hawaiian or Other Pacific Islander	1/1 (100%)	0	
Multiple	2/6 (33.3%)	2/2 (100%)	-66.7% (-91.1%, 16.9%)
Ethnicity			
Hispanic or Latino	45/107 (42.1%)	39/94 (41.5%)	0.6% (-13.1%, 14.1%)
Not Hispanic or Latino	129/229 (56.3%)	101/204 (49.5%)	6.8% (-2.6%, 16.1%)
Region			
Americas	81/166 (48.8%)	71/153 (46.4%)	2.4% (-8.6%, 13.3%)
Europe	89/162 (54.9%)	67/140 (47.9%)	7.1% (-4.2%, 18.2%)
Asia-Pacific	4/8 (50.0%)	2/5 (40.0%)	10.0% (-42.5%, 56.4%)
Acute cystitis recurrence per CRF			
Nonrecurrent infection	105/194 (54.1%)	96/187 (51.3%)	2.8% (-7.2%, 12.7%)
Recurrent infection	69/142 (48.6%)	44/111 (39.6%)	9.0% (-3.4%, 21.0%)
Baseline symptom score category			
2 to 5	49/83 (59.0%)	45/87 (51.7%)	7.3% (-7.6%, 21.9%)
6 to 8	70/131 (53.4%)	55/122 (45.1%)	8.4% (-4.0%, 20.4%)
9 to 12	54/120 (45.0%)	40/89 (44.9%)	0.1% (-13.5%, 13.5%)
Missing	1/2 (50.0%)	0	

Demographic Parameters	Gepotidacin (N=336)	Nitrofurantoin (N=298)	Difference[a] in % (95% CI)
Number of qualified uropathogens at baseline			
Only one qualifying uropathogen	156/296 (52.7%)	126/268 (47.0%)	5.7% (-2.6%, 13.9%)
One qualifying uropathogen + any # of Non-qualified uropathogens	11/31 (35.5%)	13/26 (50.0%)	-14.5% (-38.7%, 11.2%)
Two qualifying uropathogen	7/9 (77.8%)	1/4 (25.0%)	52.8% (-6.3%, 84.3%)
Baseline qualifying uropathogen			
Gram-negative isolates			
Escherichia coli	156/305 (51.1%)	123/268 (45.9%)	5.3% (-3.0%, 13.4%)
Klebsiella pneumoniae	3/7 (42.9%)	4/8 (50.0%)	-7.1% (-51.8%, 40.8%)
Other *Klebsiella* spp.[b]	2/3 (66.7%)	1/4 (25.0%)	41.7% (-33.4%, 84.7%)
Enterobacter cloacae complex	0	2/2 (100%)	
Citrobacter freundii complex	5/7 (71.4%)	1/3 (33.3%)	38.1% (-26.8%, 79.5%)
Citrobacter koseri	0	2/2 (100%)	
Gram-positive isolates			
Staphylococcus saprophyticus	4/6 (66.7%)	6/7 (85.7%)	-19.0% (-62.1%, 29.5%)
Enterococcus faecalis	6/10 (60.0%)	1/5 (20.0%)	40.0% (-15.0%, 73.7%)
Enterococcus faecium	1/1 (100%)	0	

Source: Statistical Reviewer Analysis; adsl.xpt; adeff.xpt;
[a] Unadjusted MN method.
[b] Other *Klebsiella* spp. included *Klebsiella aerogenes*, *Klebsiella oxytoca/Klebsiella Raoultella ornithinolytica, and Klebsiella variicola.*
Abbreviations: BMI, body mass index; CI, confidence interval; CRF, case report forms; log, logarithm; micro-ITT, microbiological intent-to-treat; N, total number of subjects; n, number of subjects in sample; NTF-S nitrofurantoin susceptible; TOC, test-of-cure

Primary Efficacy Endpoint Subgroup Analyses, Study EAGLE-3

Subgroup analyses are summarized in Table 156. Treatment effect with gepotidacin were generally consistent in subgroup analyses except certain categories with small sample sizes.

Table 156. Proportion of Subjects With Composite Response at TOC, Micro-ITT NTF-S, Complete Data, Study EAGLE-3

Demographic Parameters	Gepotidacin (N=292)	Nitrofurantoin (N=275)	Difference[a] in % (95% CI)
Overall (Female)	172/292 (58.9%)	121/275 (44.0%)	14.9% (6.7%, 22.9%)
Age group per CRF			
≤50	83/148 (56.1%)	56/125 (44.8%)	11.3% (-0.1%, 22.9%)
>50	89/144 (61.8%)	65/150 (43.3%)	18.5% (7.1%, 29.4%)
Race			
White	152/247 (61.5%)	104/233 (44.6%)	16.9% (8.0%, 25.6%)
Black or African American	12/28 (42.9%)	10/19 (52.6%)	-9.8% (-37.1%, 18.9%)
Asian	7/15 (46.7%)	7/21 (33.3%)	13.3% (-18.6%, 43.6%)
American Indian or Alaska Native	0/1 (0%)	0	
Multiple	0	0/2 (0%)	
Missing	1/1 (100.0%)	0	
Ethnicity			
Hispanic or Latino	43/86 (50.0%)	22/62 (35.5%)	14.5% (-1.8%, 29.8%)
Not Hispanic or Latino	129/206 (62.6%)	99/213 (46.5%)	16.1% (6.6%, 25.4%)
Region			
Americas	105/192 (54.7%)	72/188 (38.3%)	16.4% (6.4%, 26.1%)
Europe	62/89 (69.7%)	44/70 (62.9%)	6.8% (-7.9%, 21.6%)
Asia-Pacific	5/11 (45.5%)	5/17 (29.4%)	16.0% (-19.7%, 49.8%)
Acute cystitis recurrence per CRF			
Nonrecurrent Infection	111/172 (64.5%)	78/162 (48.1%)	16.4% (5.8%, 26.7%)
Recurrent Infection	61/120 (50.8%)	43/113 (38.1%)	12.8% (0%, 25.2%)

Demographic Parameters	Gepotidacin (N=292)	Nitrofurantoin (N=275)	Difference[a] in % (95% CI)
Baseline symptom score category			
2 to 5	45/69 (65.2%)	30/57 (52.6%)	12.6% (-4.7%, 29.3%)
6 to 8	77/133 (57.9%)	51/134 (38.1%)	19.8% (7.9%, 31.2%)
9 to 12	50/90 (55.6%)	40/84 (47.6%)	7.9% (-6.9%, 22.5%)
Number of qualified uropathogens at baseline			
Only 1 qualifying uropathogen	150/262 (57.3%)	109/253 (43.1%)	14.2% (5.5%, 22.6%)
One qualifying uropathogen + any # of non-qualified uropathogens	19/25 (76.0%)	8/16 (50.0%)	26.0% (-4.0%, 53.1%)
Two qualifying uropathogen	3/5 (60.0%)	4/6 (66.7%)	-6.7% (-57.5%, 46.6%)
Baseline qualifying uropathogen			
Gram-negative isolates			
Escherichia coli	156/261 (59.8%)	111/252 (44.0%)	15.7% (7.1%, 24.1%)
Klebsiella pneumoniae	3/7 (42.9%)	2/8 (25.0%)	17.9% (-30.0%, 59.6%)
Other Klebsiella spp.[b]	3/4 (75.0%)	1/3 (33.3%)	41.7% (-33.4%, 84.7%)
Citrobacter spp.[c]	5/9 (55.6%)	3/5 (60.0%)	-4.4% (-50.6%, 46.0%)
Enterobacter cloacae complex	0/1 (0%)	0/2 (0%)	0% (-74.2%, 85.2%)
Gram-positive isolates			
Staphylococcus saprophyticus	5/9 (55.6%)	5/7 (71.4%)	-15.9% (-56.2%, 32.1%)
Enterococcus faecalis	2/4 (50.0%)	1/2 (50.0%)	0% (-66.5%, 66.5%)

Source: Statistical Reviewer Analysis; adsl.xpt; adeff.xpt;
[a] Unadjusted MN method.
[b] Other *Klebsiella* spp. included *Klebsiella aerogenes* and *Klebsiella oxytoca/Klebsiella raoultella ornithinolytica.*
[c] *Citrobacter* spp included *Citrobacter freundii* complex, *Citrobacter koseri, and Citrobacter amalonaticus group.*
Abbreviations: BMI, body mass index; CI, confidence interval; CRF, case report forms; log, logarithm; micro-ITT, microbiological intent-to-treat; N, total number of subjects; n, number of subjects in sample; NTF-S nitrofurantoin susceptible; TOC, test-of-cure

17. Clinical Safety

17.1. Phase 1 and Phase 2 Studies

A total of 859 (746 gepotidacin, 113 placebo) subjects were enrolled into 13 phase 1 and 3 phase 2 clinical studies to assess the safety, tolerability, and pharmacokinetic properties of gepotidacin (Table 157). Most study subjects were healthy adults and adolescents between the ages of 12 and 79, however, two studies enrolled adult subjects with renal or hepatic impairment. Oral dosages ranged from 100 mg to 6000 mg (2000 mg TID) and IV dosages ranged from 200 mg to 4500 mg (1500 mg TID). Most adverse events observed during the phase 1 and 2 clinical studies were gastrointestinal disorders (e.g., nausea, abdominal pain) and were categorized as mild or moderate severity.

Three SAEs and 2 deaths were reported in 4 subjects from the phase 1 and phase 2 studies. The narratives are as follows:

- A 50-year-old previously healthy woman who received a single oral dose of gepotidacin reported an SAE of chest discomfort. The SAE was described as Grade 1 “mild lateral chest pressure” and the subject was hospitalized for cardiac evaluation. Electrocardiogram (ECG) and echocardiograms revealed pronounced T inversion and ST depression attributed to a right bundle branch block, and right sided cardiomegaly. Troponins were negative; the event resolved within 24 hours and was not attributed to gepotidacin by the Sponsor or investigator.
- A 32-year-old man with a history of substance abuse who received six days of gepotidacin at 750 mg IV every 12 hours for cellulitis reported an SAE of right ankle cellulitis with abscess. The right ankle cellulitis was determined by study staff to be unrelated to the initial episode of “right body” cellulitis. The subject was admitted for imaging and IV antimicrobial therapy with clindamycin and ceftaroline. Gepotidacin was discontinued and the episodes of cellulitis and abscess were resolving at time of discontinuation.
- A 51-year-old man with a history of hypoglycemia who received one dose of 1000 mg IV gepotidacin for treatment of acute bacterial skin and skin structure infection (ABSSSI) experienced an SAE of septic shock. He received only a single dose of gepotidacin and progressed to multiorgan failure and death within 48 hours of enrollment. No other AEs were reported, and the investigator and Sponsor did not consider this SAE or death as related to gepotidacin.
- A 64-year-old male with a past medical history significant for obesity, hypertension, and elevated blood glucose received a single oral dose of 1500 mg gepotidacin. Approximately 60 hours after receiving gepotidacin, the subject experienced bloating, epigastric burning, and belching. He went to bed and was found unresponsive the next morning. The family declined an autopsy, and no further information was available for review. The Sponsor and investigator determined the death to be unrelated to gepotidacin.

Table 157. Summary of Completed Phase 1 and Phase 2 Studies of Gepotidacin

Study ID	Safety Population	Gepotidacin Dosing Regimen(s)	Safety Results
209611	Healthy Subjects N=34 (Gepotidacin 28; Placebo 5)	1500 mg PO single dose, 2 × 3000 mg PO 12 hours apart, 2 × 3000 mg PO 6 hours apart	Most common type of AEs were gastrointestinal disorders. All AEs were mild or moderate severity. SAEs: None Deaths: None
BTZ114595	Healthy Subjects N=48 (Gepotidacin 36; Placebo 12)	Single PO dose: 100 mg, 800 mg, 1500 mg, 2300 mg, 3000 mg	Most common type of AEs were gastrointestinal disorders. Most AEs were mild or moderate severity. SAE: Chest Discomfort Deaths: None
BTZ116778	Healthy Subjects N=72 (Gepotidacin 54; Placebo 18)	Single PO dose: 400 mg, 800 mg, 1500 mg, 2000 mg, 2300 mg Repeat PO doses for 14 days: 400 mg BID, 800 mg BID, 1500 mg BID, 2300 mg BID, 1500 mg TID, 2000 mg TID	Proteinuria and gastrointestinal disorders were the most common AEs. Most AEs were mild or moderate severity. SAEs: None Deaths: None
BTZ117349	Healthy Subjects N=46	Single PO 1500 mg dose of capsule or tablet, with or without 200 mg itraconazole, Repeat PO doses for 5 days of 1500 mg BID	Proteinuria and gastrointestinal disorders were the most common AEs. Most AEs were mild or moderate severity. SAEs: None Deaths: None
207729	Healthy Subjects N=24	Single 1500 mg dose of powder for oral suspension or PO tablet	Most common type of AEs were gastrointestinal disorders. Most AEs were mild or moderate severity. SAEs: None Deaths: None
BTZ117351	Healthy Subjects N=48 (Gepotidacin 46; Placebo 2)	Single 1500 mg PO capsule or tablet, Two escalating PO doses: 1500-mg tablet, 3000-mg tablet, Three escalating PO doses: 1500 mg, 2250 mg, 3000-mg tablet	Most common type of AEs were gastrointestinal disorders. All AEs were mild or moderate severity. SAEs: None Deaths: None
213678	Healthy Subjects N=63 (Gepotidacin 60, Placebo 3)	One or two doses of 1500 mg or 3000 mg PO, co-administered with cimetidine, rifampicin, digoxin, or midazolam	Most common type of AEs were gastrointestinal disorders. Most AEs were mild or moderate severity. SAEs: None Deaths: None

Study ID	Safety Population	Gepotidacin Dosing Regimen(s)	Safety Results
BTZ117352	Hepatically impaired and healthy subjects N=25	Single dose of 1500 mg PO tablet	Most common type of AEs were gastrointestinal disorders. Most AEs were mild or moderate severity. SAE/Death: 1 episode of nocturnal death
BTZ116666	Healthy Subjects N=22	Single dose of 1000 mg 2-hr IV	No trends in AEs observed. All AEs were mild severity. SAEs: None Deaths: None
BTZ115775	Healthy Subjects N=105 (Gepotidacin 53, Placebo 52)	Single dose of 1000 mg 2-hr IV or 1800 mg 2-hr IV co-administered with PO moxifloxacin	Most common type of AEs were gastrointestinal disorders. All AEs were mild or moderate severity. SAEs: None Deaths: None
BTZ116849	Renally impaired and healthy subjects N=32	Single dose of 750 mg IV	Most common type of AEs were gastrointestinal disorders. All AEs were mild or moderate severity. SAEs: None Deaths: None
BTZ115198	Healthy Subjects N=86 (Gepotidacin 65; Placebo 21)	Single 1-hr IV dose of 200 mg, 600 mg, 1200 mg or 1800 mg Single 2-hr IV dose of 1800 mg/Single PO dose of 1800 mg Single 2-hr IV dose of 400 mg, 750 mg, 1000 mg or 3-hr IV dose of 1500 mg Repeat 2-hr IV doses for 7 days: 400 mg BID, 750 mg BID, 1000 mg BID or 1000 mg TID Repeat doses of 2-hr IV for 10 days: 1000 mg TID Repeat doses of 3-hr IV for 10 days: 1500 mg TID	Dizziness and abdominal pain were the most common AEs Most AEs were mild or moderate severity. SAEs: None Deaths: None
BTZ115774	Healthy Subjects N=6	Single 2-hr dose of 1000 mg IV Single dose of 2000 mg PO capsule	Most common type of AEs were gastrointestinal disorders. All AEs were mild severity. SAEs: None Deaths: None

Study ID	Safety Population	Gepotidacin Dosing Regimen(s)	Safety Results
BTZ116576	Adult subjects with suspected or confirmed uncomplicated urogenital gonorrhea N=105	Single dose of 1500 mg PO Single dose of 3000 mg PO	Most common type of AEs were gastrointestinal disorders. Most AEs were mild or moderate severity. SAEs: None Deaths: None
BTZ116704	Adult subjects with suspected or confirmed Gram-positive acute bacterial skin and skin structure infections N=122	Repeat 2-hr IV dose of 750 mg q12h for 2 days followed by 8 days of repeat 2-hr IV doses of 750 mg q12h, 1000 mg q12h or 1000 mg q8hr or repeat PO doses of 1500 mg BID, 2000 mg BID or 2000 mg TID	Most common type of AEs were gastrointestinal disorders. Most AEs were mild or moderate severity. SAEs: 2 events including cellulitis and sepsis. Deaths: 1 episode of fatal sepsis.
206899	Adult female subjects with uUTI N=22	1500 mg PO BID for 5 days	Most common type of AEs were gastrointestinal disorders. Most AEs were mild or moderate severity. SAEs: One episode of depression. See Section 7.6.2.3 Deaths: None.

Source: Adapted from Table 40 in Module 2.7.4 Summary of Clinical Safety and Table 1 in Module 2.7 Synopsis of Individual Studies
Abbreviations: AE, adverse events; BID, twice daily; PO, by mouth; IV, intravenous; N, number of exposed subjects; SAE, serious adverse event; TID three times daily

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Gepotidacin is a bactericidal, first in class triazaacenaphthylene antibacterial that inhibits DNA replication through inhibition of DNA gyrase and topoisomerase IV. It has activity against gram-negative and gram-positive pathogens including those associated with the uUTI indication.

19.1. Activity in Vitro

19.1.1. Antibacterial Activity

The tables below summarize the in vitro activity for the organisms associated with the Applicant's proposed labeling and that were evaluated for relevance to the indication. This analysis included the in vitro antibacterial activity of gepotidacin against isolates from the United States or globally, including the MIC90 and the number of isolates tested. These factors were taken into consideration when determining whether gepotidacin has activity against particular pathogens.

Table 158. In Vitro Activity of Gepotidacin Against Indicated Pathogens Listed in the Applicant's Proposed First List

Pathogen	N	MIC_{90} (mcg/mL)
Staphylococcus saprophyticus	250	0.12
Enterococcus faecalis	500	4
Escherichia coli	1001	4
Klebsiella pneumoniae	2001	16
Citrobacter freundii complex	250	8
Proteus mirabilis	250	16

Source: Reviewer's table adapted from information in this submission.
Abbreviations: MIC, minimum inhibitory concentration; N, number of replicates

The Applicant also provided in vitro antibacterial activity data from studies on the following organisms in the Applicant's proposed second list as shown in the table below:

Table 159. In Vitro Activity of Gepotidacin Against Indicated Pathogens in the Applicant's Proposed Second List

Pathogen	N	MIC_{90} (mcg/mL)
Citrobacter koseri	250	8
Enterobacter cloacae complex	500	32
Klebsiella aerogenes	250	8
Klebsiella oxytoca/Raoltella ornithinolytica	250	4
Morganella morganii	40	8
Provedencia rettgeri	250	16

Source: Reviewer's table adapted from information in this submission.
Abbreviation: MIC, minimum inhibitory concentration; N, number of replicates

Reviewer's Comments

The Applicant's in vitro data on the antibacterial activity of gepotidacin were evaluated for adequacy. The recommended number of isolates for in vitro testing of antibacterial drugs is described in the clinical microbiology guidance document, "Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation; Guidance for Industry" (FDA 2018). Typically, 300 isolates are recommended for Enterobacterales, *and 100 isolates are recommended for most other organisms or organism groups. For the first list, clinical experience is also taken into consideration. All second list organisms had greater than 100 isolates except for M. morganii, which had 40 isolates. M. morganii was still considered for the second list because of the MIC90 of 8 mcg/mL. Removal of E. cloacae complex from the second list is recommended as the MIC90 is 32 mcg/mL. For the discussion of surveillance data, the most recent data, and data from the United States are emphasized in this review. Although the Applicant provided data on beta-lactamase status and phenotypic drug resistance, information that is specifically related to gepotidacin activity is also emphasized.*

The antibacterial activity of gepotidacin against *E. coli* is shown below:

Table 160. Summary of Gepotidacin Activity Against Subsets of *E. coli* Isolates With Phenotypic Drug Resistance to Oral Agents From the Gepotidacin Uropathogen Global Surveillance Study 2022 (Global Data)*

E. coli drug-resistant phenotype	Number of isolates	Gepotidacin MIC (µg/mL)		
		MIC range	MIC50	MIC90
ESBL	235	0.5 to 32	2	4
MDR	89	0.5 to 16	2	8
FQ-R	363	0.06 to 32	2	4
AMC-R	79	0.5 to 16	2	4
AMP-R	783	0.06 to 32	2	4
FOF-R	12	0.5 to 8	2	8
MEC-R	68	0.12 to 16	2	4
NTF-R	19	0.5 to 8	2	4
SXT-R	460	0.06 to 32	2	4

Source: m5.3.5.4, GSK Study Report 2023N545082
*Summary gepotidacin MICs against all *E. coli* were provided in Table 11

Abbreviation: MIC, minimum inhibitory concentration

Table 161. Gepotidacin MIC Distributions Against *E. coli* From the Gepotidacin Uropathogen Global Surveillance Study During 2022 (Global and United States Data)

Region (number of isolates)	Number of isolates and cumulative percent inhibition at each gepotidacin MIC (µg/mL) of:										
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Global (1726)	3	5	11	98	532	878	162	22	11	4		
	0.2	0.5	1.1	6.8	37.6	88.5	**97.9**	99.1	99.8	100.0		
United States (1001)	2	1	5	46	298	527	110	5	5	2		
	0.2	0.3	0.8	5.4	35.2	87.8	**98.8**	99.3	99.8	100		

Source: m5.3.5.4, GSK Study Report 2023N545082
Bolding corresponds to MIC90

Abbreviation: MIC, minimum inhibitory concentration

Table 162. Summary of Gepotidacin Activity Against *E. coli* Isolates That met the MIC Screening Criteria for ESBL, MLST, O:H Types, fimH and FQ Resistance From the Gepotidacin Uropathogen Global Surveillance Study During 2022 (Global Data)

E. coli genotypic subgroup	Number of isolates	Gepotidacin MIC (µg/mL)		
		MIC range	MIC50	MIC90
Met MIC screening criteria for ESBL, MLST, O:H types and *fimH*				
ESBL MIC- screen negative	1491	0.06 to 32	2	2
ESBL MIC screen positive	235	0.5 to 32	2	4
AmpC[a]	36	0.5 to 16	2	4
cAmpC[a]	15	1 to 4	2	4
pAmpC[a]	21	0.5 to 16	2	4
CTX-M[b]	192	0.5 to 32	2	8
ST1193	22	0.5 to 2	1	2
ST131	89	0.5 to 8	2	4
O16:H5[c]	19	0.5 to 2	1	1
O25b:H4[d]	70	0.5 to 8	2	4
fimH30	67	0.5 to 8	2	4
Other STs[e]	124	0.5 to 32	2	8
Met MIC criteria for screening for FQ resistance[f]				
FQ MIC screen-negative	1322	0.06 to 16	2	2
FQ MIC screen-positive[g]	404	0.06 to 32	2	4
S83L, WT, S80I, WT	14	0.25 to 4	1	4
S83L, WT, WT, WT	16	0.5 to 16	2	8
S83L/D87N, WT, S80I, L416F	108	0.06 to 4	1	2
S83L/D87N, WT, S80I, WT	68	0.25 to 32	2	4
S83L/D87N, WT, S80I/E84V, WT	148	0.25 to 8	2	4
WT, WT, WT, WT[n]	24	2 to 32	8	32
FQ MIC screen-positive/FQ plasmid gene-negative[h]	312	0.06 to 8	1	2
S83L, WT, S80I, WT	10	0.25 to 1	1	1
S83L, WT, WT, WT	10	0.5 to 4	2	4
S83L/D87N, WT, S80I, L416F	107	0.06 to 2	1	2
S83L/D87N, WT, S80I, WT	53	0.25 to 8	2	2
S83L/D87N, WT, S80I/E84V, WT	109	0.25 to 4	2	4
FQ plasmid genes/WT QRDR[i]	24	2 to 32	8	32
All FQ plasmid genes[j]	92	0.5 to 32	2	16
aac(6')-Ib-cr[k]	42	0.5 to 4	2	4
qnrB[l]	17	1 to 8	4	8
qnrS[m]	29	1 to 32	8	32
qnrS1[m]	27	1 to 32	8	32

Source: m5.3.5.4, GSK Study Report 2023N545083 and m5.3.5.4, GSK Study Report 2024N550635

Genotypic subgroups are shown for groups of ≥10 isolates only.

a. Isolates were confirmed to overexpress the chromosomal AmpC or carry plasmid-mediated AmpC (16 CMY and 5 DHA) only. Isolates carrying both plasmid-medicated AmpC and CTX-M were excluded
b. Two isolates carrying both plasmid-mediated AmpC and CTX-M were excluded
c. All isolates were fimH41, except for 2 strains belonging to fimH89
d. Includes O25b:H4 and close variants
e. Includes isolates belonging to 58 STs other than ST131 and ST1193
f. QRDR mutations listed as GyrA, GyrB, ParC, ParE.
g. This group and the subsets below (unless otherwise noted) contain isolates with and without PMQR genes
h. Includes isolates where PMQR genes were not detected
i. Includes isolates where QRDR mutations were not detected
j. This group and subsets contain isolates with and without QRDR mutations
k. This group excludes 4 isolates that also carried *qnrB* and 1 that carried both *qnrB* and *qnrS1*
l. This group includes 4 isolates that also carried *aac(6')-Ib-cr*, 1 isolate with both *aac(6')-Ib-cr* and *qnrS1*, and 1 isolate with *qnrS1*
m. This group excludes 1 isolate with *qnrB* and *aac(6')-Ib-cr*, and 1 isolate with *qnrB*
n. All strains carred *qnrB* or *qnrS*

Abbreviations: ESBL, extended spectrum beta-lactamases; MIC, minimum inhibitory concentration; MLST, multi-locus sequence typing

Reviewer's Comments

In the Applicant's genotypic subgroup analysis of E. coli isolates that met the screening criteria from global surveillance in 2022, the majority of the isolates had MIC90 values of 1-8 mcg/mL. The isolates with MIC90 values of 16 mcg/mL and above were those with fluoroquinolone plasmid genes including qnrS and qnrB.

Table 163. Summary of Gepotidacin Activity Against Subsets of *K. pneumoniae* Isolates With Phenotypic Drug Resistance to Oral Agents From the Gepotidacin Uropathogen Global Surveillance Study During 2019-2022 (Global Data)*

K. pneumoniae drug-resistant phenotype	Number of isolates	Gepotidacin MIC (µg/mL)		
		MIC range	MIC50	MIC90
ESBL	789	0.5 to >64	8	32
MDR	559	0.5 to 64	8	32
FQ-R	665	0.5 to >64	8	32
AMC-R	356	0.5 to 64	8	32
NTF-R	1473	0.5 to >64	4	32
SXT-R	876	0.5 to >64	8	32

Source: m5.3.5.4, GSK Study Report 2024N548388
*Summary gepotidacin MICs against all *K. pneumoniae* were provided in Table 33

Abbreviation: MIC, minimum inhibitory concentration

Table 164. Gepotidacin MIC Distributions Against *K. pneumoniae* From Gepotidacin Uropathogen Global Surveillance Study During 2019 to 2022 (Global and United States Data)

Region (number of isolates)	Number of isolates and cumulative percent inhibition at each gepotidacin MIC (µg/mL) of:											
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Global (3385)		0	1	3	9	73	285	1737	736	325	163	47	6
		0	≤0.01	0.1	0.4	2.5	11.0	62.3	84.0	**93.6**	98.4	99.8	100.0
United States (2001)		0	1	3	3	27	187	1112	430	136	80	21	1
		0	≤0.01	0.2	0.3	1.7	11.0	66.6	88.1	**94.9**	98.9	99.9	100.0

Source: m5.3.5.4, GSK Study Report 2024N548388
Bolding corresponds to MIC90

Abbreviation: MIC, minimum inhibitory concentration

Table 165. Summary of Gepotidacin Activity Against *K. pneumoniae* Isolates That met the MIC Screening Criteria for ESBL and FQ Resistance From the *K. pneumoniae* Gepotidacin Uropathogen Global Surveillance Study During 2019-2022 (Global Data)

K. pneumoniae genotypic subgroup[a]	Number of isolates	Gepotidacin MIC (µg/mL)		
		MIC range	MIC50	MIC90
Met MIC screening criteria for ESBL				
ESBL MIC screen-negative	2595	≤0.12 to >64	4	8
ESBL MIC screen-positive	790	0.5 to >64	8	32
CTX	516	0.5 to >64	8	32
CTX-M, SHV	24	2 to 64	16	64
DHA	25	4 to 64	16	32
KPC	86	1 to 64	8	16
NDM	33	1 to >64	8	64
OXA-48	32	1 to 64	8	16
SHV	16	1 to 32	8	32
Negative	34	1 to 32	8	32
Met MIC criteria for screening for FQ resistance[b]				
FQ MIC screen-negative	2514	≤0.5 to 64	4	8
FQ MIC screen-positive[c]	871	≤0.5 to >64	8	32
S83F/D87A, WT, S80I, WT	67	1 to 32	4	16
S83F/D87N, WT, E84K, WT	22	4 to 32	4	16
S83F, WT, WT, WT	12	8 to 32	8	32
S83I, WT, S80I, WT	290	≤0.5 to 64	8	32
S83Y/D87G, WT, S80I, WT	16	1 to 32	8	16
S83Y, WT, WT, WT	14	4 to 64	8	32
WT, WT, WT, WT	393	≤0.5 to >64	16	32
FQ MIC screen-positive/PMQR gene-negative[d]	282	≤0.5 to 64	8	32
S83F/D87A, WT, S80I, WT	43	1 to 32	4	16
S83F/D87N, WT, E84K, WT	15	4 to 16	4	8
S83I, WT, S80I, WT	95	≤0.5 to 32	4	16
WT, WT, WT, WT[e]	77	4 to 64	32	32
PMQR genes/WT QRDR	316	≤0.5 to >64	16	64
PMQR genes[f]				
aac(6')-Ib-cr	51	1 to 16	4	16
qnrB	234	≤0.5 to 64	8	32
qnrB, aac(6')-Ib-cr	130	2 to 64	8	32
qnrB, qnrS	12	4 to 64	16	64
qnrS	135	≤0.5 to >64	16	64
Negative	282	≤0.5 to 64	8	32

Source: m5.3.5.4, GSK Study Report 2024N551074

a. Genotypic subgroups are shown for groups of >10 isolates only.
b. QRDR mutations listed as GyrA, GyrB, ParC, ParE.
c. This group and the subsets below (unless otherwise noted) contain isolates with and without PMQR genes
d. The group and the subsets below (unless otherwise noted), includes isolates where PMQR genes were not detected
e. 93.5% (all but 5 isolates) overexpressed *oqxAB* and/or *acrAB*
f. This group and subsets contain isolates with and without QRDR mutations

Abbreviation: MIC, minimum inhibitory concentration

Reviewer's Comments

In the Applicant's genotypic subgroup analysis of K. pneumoniae isolates that met the screening criteria from global surveillance in 2022, the isolates had MIC90 values of 8-32 mcg/mL. The

majority of isolates with MIC90 values of 64 mcg/mL and above were those with Plasmid-mediated Quinolone Resistance (PMQR) genes including qnrS and qnrB. Beta-lactamase genes are not likely to influence gepotidacin activity as beta-lactamases are enzymes produced by bacteria that make them resistant to the beta-lactam class of antibacterials.

The antibacterial activity of gepotidacin against *Proteus* species is shown below:

Table 166. Summary of Gepotidacin In Vitro Activity Against *Proteus* spp. From In Vitro Profile Studies

Organism	Year of isolate collection or study date	Number of isolates	Gepotidacin MIC90 or MIC range (µg/mL)[a]	GSK study report [m5.3.5.4]
P. mirabilis	2007	30	16[b]	UH2010/00068
P. mirabilis	2008 to 2009	5	8 to 16[b]	UH2009/00049/00
Proteus spp. (*P. mirabilis* [54], *P. hauseri* [1], *P. penneri* [1])	2012 to 2018	56	32[c]	2018N385667
P. mirabilis CIP-NS	2019 to 2020	250 84	16 32	2021N483801

a. Results reported as a MIC range when the n was <10.
b. Different salt version used for testing. Further explanation of the 1 dilution shift in MICs for this salt version are discussed in Section 3.1.4.2
c. MICs were determined by AD according to CLSI approved methodology and guidelines [CLSI,M07; CLSI, M100]

Abbreviation: MIC, minimum inhibitory concentration

Table 167. Gepotidacin MIC Distributions Against *P. mirabilis* and Ciprofloxacin Non-Susceptible (CIP-NS) Global *P. mirabilis* Isolates Collected From 2019 to 2020

Organism/drug-resistant phenotype (n)	Number of isolates and cumulative percent inhibition at each gepotidacin MIC (µg/mL) of:												
	0.06	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**>128**
P. mirabilis (250)			1	2	4	12	38	102	69	13	6	3	
			0.4	1.2	2.8	7.6	22.8	63.6	**91.2**	96.4	98.8	100	
CIP-NS (84)			1	2	4	12	27	12	10	8	5	3	
			1.2	3.6	8.3	22.6	54.8	69	81	**90.5**	96.4	100	

Source: m5.3.5.4, GSK Study Report 2021N483801
Bolding corresponds to MIC90

Abbreviation: MIC, minimum inhibitory concentration

The antibacterial activity of gepotidacin against *S. saprophyticus* is shown below:

Table 168. Gepotidacin MIC Distributions Against *S. saprophyticus* Isolates From the Gepotidacin Uropathogen Global Surveillance Study (2022; Global and United States Data)

Region (number of isolates)	Number of isolates and cumulative percent inhibition at each gepotidacin MIC(µg/mL) of:									
	≤0.015	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
Global (191)		2	134	53	2					
		1.0	71.2	**99.0**	100.0					
United States (92)		2	61	29						
		2.2	68.5	**100.0**						

Source: m5.3.5.4, GSK Study Report 2023N545082
Bolding corresponds to MIC90 (when N≥10)

Abbreviation: MIC, minimum inhibitory concentration

Table 169. Gepotidacin MIC Distributions Against *S. saprophyticus* Isolate Subsets With Resistance to Oral Agents From Gepotidacin Uropathogen Global Surveillance Study (2022; Global Data)

S. saprophyticus drug-resistant phenotype (number of isolates)	No. and cumulative % of isolates inhibited at gepotidacin MIC (µg/mL) of:											
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Penicillin-R (180)	2	125	51	2								
	1.1	70.6	**98.9**	100.0								
SXT-R (7)		2	5									
		28.6	**100.0**									

Source: m5.3.5.4, GSK Study Report 2023N545082
Resistant per CLSI [CLSI, M100]
Bolding corresponds to MIC90 (when N≥10)

Abbreviation: MIC, minimum inhibitory concentration

S. saprophyticus with MIC results ≥2 mcg/mL for ciprofloxacin (CIP) and/or levofloxacin (LVX) were screened by the Applicant for fluoroquinolone resistance. Three *S. saprophyticus* met the MIC criteria and these isolates had gepotidacin MICs of 0.06-0.12 mcg/mL. One *S. saprophyticus* isolate had wild-type quinolone-resistance determining region (QRDR) sequences, and the other two isolates had GyrA S84L/ParC S80L variations. None of the *S. saprophyticus* isolates in the 2022 surveillance study met the criteria for screening for fluoroquinolone resistance mechanisms.

Reviewer's Comments

QRDR are the quinolone resistance determining regions. These are regions of amino acid residues within bacterial DNA gyrase and topoisomerase IV that are hotspots for mutations leading to resistance to quinolone antibacterials.

Information on the antibacterial activity of gepotidacin against *E. faecalis and Citrobacter* spp. are summarized in the tables below:

Table 170. Gepotidacin MIC Distributions Against *E. faecalis* and CIP-NS Global *E. faecalis* Isolates Collected From 2015-2020

Organism/drug-resistant phenotype (n)	Number of isolates and cumulative percent inhibition at each gepotidacin MIC (µg/mL) of:												
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
E. faecalis (500)			2	24	85	311	74	2	1		1		
			0.4	5.2	22.2	84.4	**99.2**	99.6	99.8		100		
CIP-NS (149)			1	18	63	46	18	2	1				
			0.7	12.8	55	85.9	**98**	99.3	100				

Source: m5.3.5.4, GSK Study Report 2021N483801
Bolding corresponds to MIC90

Abbreviation: MIC, minimum inhibitory concentration

Table 171. Summary of Gepotidacin In Vitro Activity Against *E. faecalis* From In Vitro Profile Studies

Organism	Year of isolate collection or study date	Number of isolates	Gepotidacin MIC90 (µg/mL)	GSK study report [m5.3.5.4]
E. faecalis	2008 to 2009	25	4[a]	UH2009/00049
E. faecalis	2015 to 2020	500	4	2021N483801
CIP-NS		149	4	

a. Different salt version used for testing. Further explanation of the 1 dilution shift in MICs for this salt version are discussed in Section 3.1.4.2

Abbreviation: MIC, minimum inhibitory concentration

Table 172. Gepotidacin MIC Distributions Against *Citrobacter* spp. and CIP-NS Global *Citrobacter* spp. Isolates Collected From 2019-2020

Organism/drug-resistant phenotype (n)	Number of isolates and cumulative percent inhibition at each gepotidacin MIC (µg/mL) of:											
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Citrobacter spp. (250)				3	55	117	47	17	8	2		1	
				1.2	23.2	70	88.8	**95.6**	98.8	99.6		100	
CIP-NS (24)					2	4	8	6	2	1	0	1	0
					8.3	25	58.3	83.3	**91.7**	95.8	0	100	0

Source: m5.3.5.4, GSK Study Report 2021N483801
Bolding corresponds to MIC90
Abbreviation: MIC, minimum inhibitory concentration

Information on the antibacterial activity of gepotidacin against second list uUTI pathogens:

Table 173. Gepotidacin MIC Distributions Against Other uUTI Species Collected From 2018-2020

Organism/drug-resistant phenotype (n)	Number of isolates and cumulative percent inhibition at each gepotidacin MIC (µg/mL) of:												
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
K. aerogenes (250)	1	1		1	8	95	116	15	7	5	1		
	0.4	0.8		1.2	4.4	42.4	88.8	**94.8**	97.6	99.6	100		
CIP-NS (22)					2	1	3	7	3	5	1		
					9.1	13.6	27.3	59.1	72.7	**95.5**	100		
K. oxytoca (250)				1	12	108	108	14	5	1	1		
				0.4	5.2	48.4	**91.6**	97.2	99.2	99.6	100		
CIP-NS (32)					10	6	4	7	3	1	1		
					31.2	50	62.5	84.4	**93.8**	96.9	100		
P. rettgeri (250)				2	5	17	99	78	32	5	4	5	3
				0.8	2.8	9.6	49.2	80.4	**93.2**	95.2	96.8	98.8	100
CIP-NS (48)				2	5	1	8	10	10	3	4	3	2
				4.2	14.6	16.7	33.3	54.2	75	81.2	89.6	**95.8**	100

Source: m5.3.5.4, GSK Study Report 2021N483801
Bolding corresponds to MIC90
Abbreviations: MIC, minimum inhibitory concentration; uUTI, uncomplicated urinary tract infection

Information was also provided on other bacterial species that are not related to the uUTI indication; this information was not included in this review.

19.1.2. Activity of Metabolites

The M4 metabolite has been described as the only major metabolite for gepotidacin but the in vitro antibacterial activity is not known. The Applicant stated that multiple attempts to synthesize this metabolite for in vitro MIC testing were not successful.

19.1.3. Time Kill

Gepotidacin bactericidal activity was evaluated by time kill for 27 bacterial clinical isolates from 9 uUTI bacterial species and was found to be generally concentration dependent. The Applicant reported that at 4X and 10X gepotidacin MIC, >80% of isolates were killed by >3-log10 CFUs. Any lack of killing was not attributed to extended-spectrum beta-lactamase (ESBL) or fluoroquinolone-resistance (FQ-R) phenotypes. The Applicant's data is shown in the table below.

Table 174. Log10 Drop in Cell Viability (CFUs) at 24-Hour Time Point for Isolates Exposed to Gepotidacin

Isolate no.	Organism	Phenotype	Gepotidacin concentration (relative to MIC)					
			1/4x	1/2x	1x	2x	4x	10x
ATCC25922	*E. coli*[a]	WT	-1.2	-1.0	4.3	4.9	5.9	5.9
3773	*E. coli*[a]	ESBL	-2.7	-2.0	-2.3	4.6	3.4	3.4
3904	*E. coli*[a]	ESBL, FQ-R	-0.4	-0.3	2.2	3.4	3.2	3.3
1091286	*C. freundii* sc	WT	-2.2	-1.2	-1.6	-0.8	4.4	5.7
1130512	*C. freundii* sc	ESBL	-1.6	-1.1	2.1	2.8	2	1.4
1116313	*C. freundii* sc	FQ-R	-1.7	-1.3	-0.4	5.9	3.6	3.7
1092886	*E. cloacae* sc	WT	-2	-1.8	-1.5	1.9	2.9	3.1
1092279	*E. cloacae* sc	ESBL	-1.7	-2.2	-1.2	-0.9	5.7	5.7
1127328	*E. cloacae* sc	FQ-R	-1	-0.1	2.1	4.1	4.4	4.4
1089847	*K. aerogenes*	WT	-1.2	0.2	0.2	4.4	5.7	5.7
1089299	*K. aerogenes*	ESBL	-1	1.2	1.5	2.9	1.8	1.1
1092937	*K. aerogenes*	FQ-R	-0.1	0.6	4.6	4.3	4.1	4.6
1098581	*K. pneumoniae*	WT	-2.1	-1.4	-2.4	-0.6	3.9	5.9
1130299	*K. pneumoniae*	ESBL	-1.7	-0.9	-0.2	0.2	3.1	3.5
1124085	*K. pneumoniae*	FQ-R	-1.6	-0.4	0.7	3.0	4.6	5.9
1091952	*P. mirabilis*	WT	-1	-0.2	0.1	0.8	5.7	5.7
1106732	*P. mirabilis*	ESBL	-1.1	-1.7	-0.8	0.3	5.2	5.2
1093555	*P. mirabilis*	FQ-R	-1.7	-2.6	-2.3	0.7	3.8	5.1
1089529	*P. rettgeri*	WT	-1.1	0.8	1.6	3.5	4.7	4.4
1090192	*P. rettgeri*	ESBL	-0.6	2.6	6.1	6.1	6.1	6.1
1118004	*P. rettgeri*	FQ-R	-0.9	-0.5	1.8	3.5	3.6	5.7
1103850	*E. faecalis*	WT	-3.1	-2.5	-1.2	3.9	3.3	2.7
1111210	*E. faecalis*	WT	-1.9	-1.2	1.6	3.6	4.2	3.7
1097863	*E. faecalis*	FQ-R	-2.1	-1.2	0.9	2.8	2.6	2.7
1106006	*S. saprophyticus*	WT	-2.6	-2.6	1.7	5.5	5.5	5.5
1113726	*S. saprophyticus*	WT	-2.4	-1.5	1.8	5.6	5.6	5.6
1129086	*S. saprophyticus*	WT	-3	-2.6	-1.8	0.9	5.7	5.7

Source: m5.3.5.4, GSK Study Report 2021N485374; m5.3.5.4, GSK Study Report 2015N231277
a. Studies were performed in duplicate. Only data from replicate 2 is shown. Similar results were seen for the first replicate
sc – species complex
Bold values represent a ≥3-log10 drop in CFUs compared to starting inoculum.
Abbreviations: CFU, colony forming units; MIC, minimum inhibitory concentration

In an additional study of *E. coli* isolates, other Enterobacterales species (*C. freundii, E. cloacae, K. aerogenes, K. oxytoxa, K. pneumoniae, P. mirabilis and P. rettgeri*), *E. faecalis* and *S. saprophyticus*, gepotidacin had a minimum bactericidal concentration (MBC)/MIC ratio ≤4 for 94% of the strains tested.

Table 175. Summary of MBC/MIC Ratios for Gepotidacin Against 50 Isolates

Organism (n)	Gepotidacin MBC/MIC ratio (µg/mL)				
	1	2	4	8	>32
C. koseri (5)	4	1			
E. cloacae (5)	2	2			1
E. coli (5)	2	2		1	
K. aerogenes (5)	4		1		
K. oxytoca (5)	3	1			1
K. pneumoniae (5)	1	4			
P. mirabilis (5)	5				
P. rettgeri (5)	5				
E. faecalis (5)	3	2			
S. saprophyticus (5)	3	2			
Total (50)	32	14	1	1	2
Percent of total	64%	28%	2%	2%	4%

Source: m5.3.5.4, GSK Study Report 2021N483801
Abbreviations: MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration

Reviewer's Comments

The in vitro studies on antibacterial activity of gepotidacin above including those of minimum bactericidal concentration/MIC ratio, show that gepotidacin has bactericidal activity against pathogens proposed by the Applicant in the first and second lists of the labeling except for E. cloacae.

19.1.4. Intracellular Antibacterial Activity

Intracellular activity was evaluated by the Applicant. Gepotidacin was reported to have in vitro activity against intracellular *S. aureus*, *M. tuberculosis*, and *L. pneumophila*, however, as these isolates are not in the proposed lists for this indication, the data is not shown in this review.

19.1.5. Post-Antibiotic Effect

In vitro post-antibiotic effect and the post-antibiotic subinhibitory MIC effect of gepotidacin were evaluated for the uropathogens using time-kill assay methods. In these studies, gepotidacin post-antibiotic effects displayed a concentration dependent effect. The Applicant stated that, "In vitro studies demonstrated a gepotidacin post-antibiotic effect ranging from 1.8 to 2.2 hours for *E. coli*, 1 to >6.6 hours for *K. pneumoniae*, 1.4 to 3 hours for *P. mirabilis*, 1 to 2.6 hours for *C. freundii*, 2.7 to 4.3 hours for *S. saprophyticus*, and 1.2 to 2.7 hours for *E. faecalis* at 5 times the MIC."

Reviewer's Comment

The Applicant's statement above appears to be accurate based on the data from the studies on post-antibiotic effect provided by the Applicant.

Effect on Gut Microflora

The Applicant did exploratory analyses of microbiome diversity on samples from subjects enrolled in the clinical studies and had an in vitro gut colon model, which was used to show microbiota composition and diversity recovered to pre-antibacterial levels after withdrawal of gepotidacin. The clinical significance of the data is unknown.

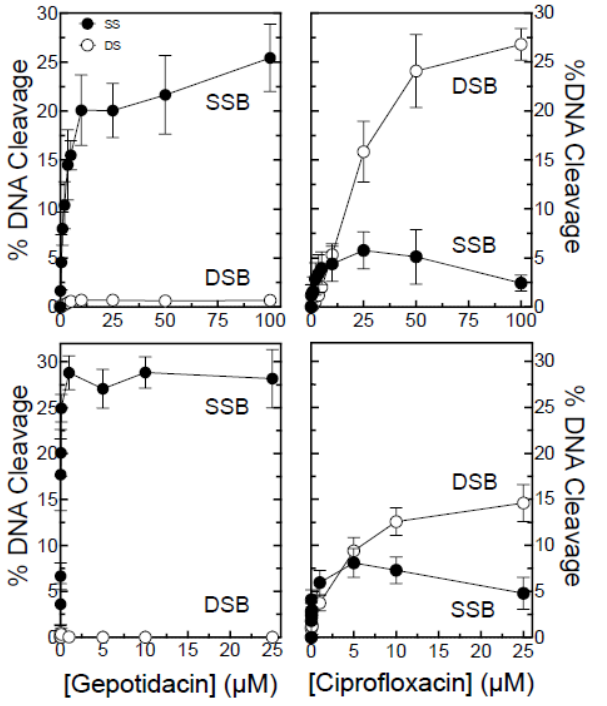
19.2. Mechanism of Action

The Applicant states that gepotidacin is a first in class triazaacenaphylene antibacterial. The chemical structure and the mechanism of action are reported to be novel in comparison to fluoroquinolone antibacterial drugs. For example, gepotidacin is reported to form stable single stranded DNA cleaved complexes with the enzyme that blocks normal function of bacterial topoisomerase. By contrast, fluoroquinolones stabilize double stranded cleaved complexes. Gepotidacin is said to inhibit the pre cleavage step of the topoisomerase catalytic cycle, while fluoroquinolones target the post cleavage step. Additionally, the binding mode for gepotidacin is said to be distinct from fluoroquinolones and to provide a potential explanation for activity against fluoroquinolone resistant mutants.

Two X-ray crystal structures of gepotidacin bound to *S. aureus* gyrase core fusion truncate with nicked or intact (uncleaved) DNA were determined. This information is described in the literature (Gibson et al. 2019). The crystal structures provided information about the mechanism of action of gepotidacin and how it differs from quinolones. The Applicant reported that two molecules of moxifloxacin are bound within the DNA gyrase complex, in contrast to gepotidacin where one molecule is bound. Superimposing the molecules showed 2 distinct binding sites. GyrA S84 and E88 (based on *S. aureus* numbering) are two residues in gyrase which are reported as frequently mutated in fluoroquinolone-resistant clinical isolates. Gepotidacin is thought to have a different binding pocket than fluoroquinolone antibacterials.

In biochemical studies, gepotidacin inhibited DNA supercoiling and decatenation of wild-type *E. coli* DNA gyrase and topoisomerase with IC_{50} values of 0.32 and 0.34µM, respectively. The effect of gepotidacin against mutant proteins with common fluoroquinolone resistance mutations, GyrA S83L and ParC S80L were studied and the IC_{50} values were 0.16µM and 0.05µM, respectively.

Figure 24. Effects of Gepotidacin on Bacterial DNA Cleavage Mediated by Wild-Type *E. coli* Gyrase and Topoisomerase IV Enzymes



Source: m5.3.5.4, GSK Study Report 2022N522298.
The effects of gepotidacin on single stranded (SS) and double stranded (DS) DNA cleavage mediated by WT *E. coli* gyrase are shown in the top left panel. Gepotidacin enhances only SS breaks (SSB) and is very potent. Corresponding results with CIP are shown on the top right panel. The FQ enhances primarily DS breaks (DSB). The effects of gepotidacin on DNA cleavage mediated by WT *E. coli* topoisomerase IV are shown in the bottom left panel. Again, gepotidacin enhances only SS DNA breaks and DS breaks are suppressed. Corresponding results with CIP are shown on the bottom right panel. As is typical of FQs, primarily DS scission is enhanced.

Reviewer's Comments

The figure above illustrates how gepotidacin enhances mostly single stranded breaks, while fluoroquinolones enhance primarily double stranded breaks, suggesting a unique mode of action. It was noted that there was a 2.5-fold reduction in cleavage activity for gepotidacin against GyrA S83L compared to wild-type enzyme. Cleavage activity was maintained against the ParC S80L enzyme. Overall, the Applicant's biochemical and crystallography data suggested that some amino acids are important for gepotidacin activity.

Gepotidacin was also tested for its ability to enhance DNA cleavage with proteins carrying GyrA P35L or ParC D79G mutations, which are thought to be important for gepotidacin binding to target enzymes. Gepotidacin had reduced cleavage induction activity of 8- and 5 -fold against enzymes with GyrA P35L or ParC D79G mutations, respectively. The Applicant reported a possible reduction in susceptibility to gepotidacin during treatment for subject 401298 in Study EAGLE-2 where genotypic data indicated a ParC D79G mutation in the E. coli isolates from on therapy (OT) and TOC visits. The data is shown in the table below.

Table 176. Effect of Gepotidacin and CIP on DNA Cleavage Activities Mediated by *E. coli* DNA Gyrase and Topoisomerase IV Enzymes

Enzyme		Gepotidacin			CIP		
		% conversion to CC	SD	Max CC µM	% conversion to CC	SD	Max CC µM
E. coli DNA gyrase supercoiling	WT	20.1	3.6	10	24.1	3.7	50
	GyrA S83L	8.3	3.2	2	0.8	0.2	100
	GyrA P35L	2.6	0.4	2	6.5	1.3	25
E. coli topoisomerase IV decatenation	WT	28.8	1.8	1	12.6	1.5	10
	ParC S80L	21.7	2.4	1	2.8	1.6	25
	ParC D79G	6.2	1.8	0.025	2.3	2.1	25

Source: m5.3.5.4, GSK Study Report 2022N522298.

CC, cleaved complex. SD, standard deviation. The max CC was quantified as percent (%) maximal conversion of input DNA to single stranded (gepotidacin) or double stranded (CIP) cleaved complexes. The concentration of compound (µM) needed to reach the max CC is also provided. For example, gepotidacin induces a maximal cleaved complex level of 20.1% at 10 µM with WT *E. coli* gyrase, while the maximum value for CIP is 24.1% at 50 µM. Values are from at least 3 independent experiments.

Abbreviations: CC, cleaved complex; CIP, ciprofloxacin; DNA, deoxyribonucleic acid; SD, standard deviation; WT, wild type

Additionally, gepotidacin was tested against *S. aureus* DNA gyrase enzyme and inhibited gyrase-catalyzed DNA supercoiling. Unlike fluoroquinolones, gepotidacin induced high levels of single strand breaks. The Applicant reported that in competition assays, *S. aureus* gyrase binding by gepotidacin and fluoroquinolone were mutually exclusive. Gepotidacin had weak activity against human topoisomerase IIα relaxation activity with an IC50 value of 327µM.

Studies of Resistance Using Isogenic Mutants

Single and double target mutations in GyrA and ParC were genetically engineered by the Applicant. Residues were selected if they were thought to be involved in gepotidacin binding and DNA bending. For *E. coli*, no significant change in gepotidacin MIC occurred for single mutants with GyrA P35L or ParC D79N in comparison to wild-type parents' MIC values. A 64- to 256-fold increase in gepotidacin MIC was observed with the GyrA/B and ParC double mutants as shown in the table below. The Applicant reported a lack of target-specific cross resistance for gepotidacin for isolates with common fluoroquinolone resistance mutations, while an increase in CIP MIC was noted for the isogenic mutants. However, they were considered susceptible according to Clinical & Laboratory Standards Institute (CLSI) criteria.

Table 177. Gepotidacin Activities Against Isogenic *E. coli* Strains Carrying Key Gepotidacin Target Mutations

Strain	Mutation			Gepotidacin		CIP	
	GyrA	GyrB	ParC	MIC (µg/mL)	Fold change to WT	MIC (µg/mL)	Fold change to WT
TOP10	WT	WT	WT	0.125	NA	0.001 to 0.002	NA
TOP10-1	P35L	WT	WT	0.125	0	0.008 to 0.016	8 to 16↑
TOP10-2	WT	WT	D79N	0.125	0	0.002	0 to 2↑
TOP10-3	P35L	WT	D79N	16	128↑	0.008 to 0.016	8 to 16↑
TOP10-4	V44I	WT	D79N	16	128↑	0.008	4 to 8↑
TOP10-5	A175V	WT	D79N	8	64↑	0.016	8 to 16↑
TOP10-6	WT	D426N	D79N	16	128↑	0.032	16 to 32↑
TOP10-7	WT	P445L	D79N	32	256↑	0.032	16 to 32↑

Source: m5.3.5.4, GSK Study Report 2020N451222

Abbreviations: CIP, ciproflaxin; MIC, minimum inhibitory concentration; NA, not applicable; WT, wild type

Isogenic strains of *E. coli* K-12 and *K. pneumoniae* with GyrA D82N and ParC D79N mutations, key residues for gepotidacin binding were constructed and evaluated for gepotidacin MICs (refer to Table 178 below). The individual GyrA D82N or ParC D79N mutations had limited effect on

gepotidacin susceptibility relative to the WT parent. In contrast, the double mutant with both GyrA D82N and ParC D79N showed a >1024-fold MIC increase in gepotidacin MIC.

Table 178. Gepotidacin Activities Against Isogenic *E. coli* and *K. pneumoniae* Strains Carrying Key Gepotidacin Target Mutations

Bacterial species and strain	Mutation		MIC (µg/mL)	
	GyrA	ParC	Gepotidacin	CIP
E. coli K-12 MG1655	WT	WT	0.25	0.016
	D82N	WT	0.5	0.125
	WT	D79N	0.5	0.016
	D82N	D79N	>256	0.25
K. pneumoniae subsp. *pneumoniae* ATCC 10031	WT	WT	0.063	0.004
	D82N	WT	0.5	0.063
	WT	D79N	0.125	0.008
	D82N	D79N	256	0.063

Source: Szilli, 2019

Abbreviations: CIP, ciproflaxin; MIC, minimum inhibitory concentration; WT, wild type

Reviewer's Comment

In other studies by the Applicant in N. gonorrhoeae, mutations that led to increase in gepotidacin resistance were observed. The Applicant also reported that in N. gonorrhoeae gepotidacin had an increase in MICs for isolates with both GyrA A92T and ParC D86N. This organism will not be discussed in detail because it is not an indicated organism for uUTI, but it provided some context for the analysis of mutations in the uUTI pathogens discussed here.

In contrast to the inhibition by gepotidacin of 2 enzymes in E. coli, K. pneumoniae and N. gonorrhoeae, in S. aureus, a single mutation in GyrA led to a higher gepotidacin MICs. The Applicant suggests that this is the primary target for gepotidacin in this organism. For E. faecalis, similar findings were reported in frequency of resistance studies. For isogenic strains of S. pneumoniae, a single mutation in ParC led to higher gepotidacin MIC, indicating that topoisomerase IV is the primary target in this species. For S. saprophyticus, no gepotidacin mutants were observed at 4X or 10X MIC in the frequency of mutation study.

Reviewer's Comment

These results indicate that DNA gyrase and topoisomerase IV are molecular targets of gepotidacin in E. coli. The amino acids thought to be important for gepotidacin activity (as shown through studies with isogenic mutants in E. coli and K. pneumoniae) are in target proteins as follows (using E. coli numbering): GyrA P35, V44, D82, A175; GyrB D426, P445 and ParC D79.

19.2.1. Resistance

Mechanism of Resistance

The Applicant provided information on the possible resistance mechanisms for gepotidacin, including active site mutations, PMQR, efflux/drug penetration and determination of resistance mechanisms for isolates with higher gepotidacin MICs. Information on the activity of gepotidacin against isolates with pre-existing resistance to other antibacterial drugs, examination of isolate cross-resistance was provided by the Applicant. Development of resistance from in vitro studies and in clinical studies was also assessed. Amino acid numbering was done for the specific species described. The Applicant stated that, "No clear mechanisms of resistance to gepotidacin have been identified in these studies."

Active Site Mutations

Active site mutations were investigated by the Applicant using bacterial genetics and X-ray crystallography.

Reviewer's Comments

The Applicant has stated that based on studies with E. coli GyrA D82N alone and with ParC D79N that "individual mutations in one enzyme had no effect on gepotidacin MICs." However, an effect with a single amino acid change has been shown to have an increase in gepotidacin MICs. Although single amino acid mutations tested by the Applicant do not appear to generate a large increase in gepotidacin resistance as was seen with more than one mutation, it is important to note that all mutations have not been tested and that these bacterial isolates can have other resistance factors that are known or unknown that may contribute to resistance. In a publication by Szili et al., "Rapid Evolution of reduced Susceptibility against a balanced dual-targeting antibiotic through stepping-stone mutations" (Antimicrobial Agents and Chemotherapy Sept., 2019 volume 63, issue 9) (Szili et al. 2019), the authors suggest that prolonged exposure to ciprofloxacin selected for reduced susceptibility to gepotidacin. They also suggest that even "balanced multi-targeting antibiotics are prone to resistance evolution".

Using X-ray crystallography, amino acid residues that are important for gepotidacin binding were identified. Direct interaction of the basic nitrogen of gepotidacin with S. aureus GyrA D83 (based on S. aureus numbering) and by homology ParC D79 was observed. In a phase 2 ABSSSI study, GSK-BTZ116704, a S. aureus isolate with higher MIC to gepotidacin had a single GyrA D83N mutation, which the Applicant reported was a preference for mutations in gyrase. Although the mutations were analogous to mutations in Enterobacterales, there was a requirement for two mutations to confer significant resistance in Enterobacterales such as *E. coli, K. pneumoniae, K. oxytoca, K. aerogenes, Citrobacter* spp. and *E. cloacae*. In *P. rettgeri* and *P. mirabilis* the analogous residues are GyrA D88 and ParC D83.

PMQR Genes

A range of MIC90s from 4-32 mcg/mL was observed against *E. coli* isolates harboring PMQR genes from the 2019-2022 gepotidacin uropathogen global surveillance studies. However, the Applicant reported that no single genotype/phenotype or combination could be definitively linked to higher gepotidacin MICs. Most *E. coli* isolates with gepotidacin MICs of 16 to 32 mcg/mL corresponded to a *qnr*-positive genotype. Other factors were suggested as

contributing to gepotidacin activity. The aac(6')-Ib-cr gene, a PMQR gene, was not associated with higher gepotidacin MICs. QRDR profiles and AcrA were also not associated with gepotidacin MIC value. The *acrA* gene encodes AcrA, a protein component of a multidrug efflux pump in *E. coli*.

Efflux and Drug Penetration

Studies were conducted by the Applicant to evaluate the effects of efflux and/or penetration (porins) on the in vitro activity of gepotidacin. Gepotidacin was tested against 100 isolates including 73 Enterobacterales, 21 *P. aeruginosa*, and 6 *A. baumannii-calcoaceticus* species complex which had a loss/disruption or decreased expression of outer membrane proteins associated with antimicrobial resistance and/or overexpression of efflux. Gepotidacin MICs against these isolates ranged from 0.03 to >32 mcg/mL. The data is shown in the table below.

Table 179. Antibacterial Activity of Gepotidacin Against Enterobacterales Isolates Displaying Loss/Disruption or Decreased Expression of Outer Membrane Proteins (OMPs) Associated With Drug Resistance and/or Overexpression of Efflux

Organism/organism group (number of isolates)	Gepotidacin MIC range (µg/mL)	Gepotidacin MIC90 (µg/mL)
Enterobacterales[b] (73)	0.03 to >32	16
Enterobacterales overexpressing efflux (9)	0.5 to 32	[a]
Enterobacterales displaying reduced expression or disruption of OMPs (53)	0.03 to >32	16
Enterobacterales overexpressing efflux and displaying reduced expression or disruption of OMPs (11)	4 to 16	16
E. coli (n=38)	0.03 to 32	16
Efflux (AcrAB-TolC overexpression) (8)	0.5 to 32	[a]
OMP reduced expression or disruption (27)	0.03 to 8	2
Both efflux and OMP (3)	4 to 16	[a]
E. cloacae species complex (11)	2 to >32	16
Efflux (AcrAB-TolC overexpression) (1)	8	[a]
OMP reduced expression or disruption (8)	2->32	[a]
Both efflux and OMP (2)	8 to 16	[a]
K. pneumoniae. (22)	2 to 32	16
OMP reduced expression or disruption (16)	2 to 32	32
Both efflux and OMP (6)	8 to 16	[a]
K. oxytoca. (2)	1 to 32	[a]
OMP reduced expression or disruption (2)	1 to 32	[a]
P. aeruginosa (n=21)	4 to >32	32
Efflux (12)	4 to >32	>32
OMP (OprD loss) (2)	4 to 8	[a]
A. baumannii-calcoaceticus species complex (6)	16 to >32	[a]

Source: m5.3.5.4, GSK Study Report 2017N354508
OMP = outer membrane porin
a. MIC90 not calculated for <10 isolates
b. At the time of the study (and in the report), the nomenclature for this organism was *Enterobacteriaceae*

Abbreviations: MIC, minimum inhibitory concentration; OMP, outer membrane porin

The higher gepotidacin MIC90 against *E. coli*, was reportedly associated with efflux or an unknown mechanism, as the gepotidacin MIC90 against *E. coli* isolates with reduced expression or disruption of outer membrane porin was 2 mcg/mL.

To further investigate the effect of efflux on the in vitro activity of gepotidacin, MIC studies were completed with isogenic FQ-S and FQ-R *E. coli* strains containing knockouts in *tolC* and their corresponding parents. Gepotidacin, CIP, and chloramphenicol MICs decreased 8-, 2- to 4-, and 8-fold, respectively. Against the FQ-R tolC knockout, gepotidacin, CIP, and

chloramphenicol MICs decreased 128- to 256-, 16-, and 32-fold, respectively. Results showed that gepotidacin is effluxed in *E. coli* by the TolC efflux system. TolC is an outer membrane protein important for a multi-drug efflux system in gram-negative bacteria. Refer to the tables below for information.

Table 180. MICs Against Isogenic *E. coli TolC* Deletion Mutants

E. coli strain	MIC (µg/mL)					
	Gepotidacin	Fold change	CIP	Fold change	Chloramphenicol	Fold change
7623	0.125	NA	0.004 to 0.008	NA	8	NA
7623 ΔTolC	0.016	8↓	0.002	2-4↓	1	8↓
W4753R*	0.5 to 1	NA	256	NA	32	NA
W4753R* ΔTolC	0.004	128 to 256↓	16	16↓	1	32↓

Source: m5.3.5.4, GSK Study Report 2020N451222
*GyrA S83L, D87N; ParC S80I; ParE S458A
NA =not applicable

Abbreviations: CIP, ciproflaxin; MIC, minimum inhibitory concentration; NA, not applicable

Table 181. MICs Against Isogenic *K. pneumoniae TolC* Deletion Mutants

K. pneumoniae strain	MIC (µg/mL)					
	GEP	Fold ↓	CIP	Fold ↓	Azithromycin	Fold ↓
JH1	4 to 8	NA	0.032	NA	8	NA
JH1 ΔTolC	0.125 to 0.25	16 to 64	0.004 to 0.008	4 to 8	1	8
1161486	8 to 16	NA	0.063	NA	8	NA
1161486 ΔTolC	0.125 to 0.25	32 to 128	0.002 to 0.004	16 to 32	1	8
1161412 GyrA S83F ParC E84K ampC	128	NA	256	NA	16	NA
1161412 GyrA S83F ParC E84K ampC ΔTolC	0.25-0.5	256 to 512	2	128	1	16
1162277 GyrA S83F D87V ParC S80I ESBL+	16-32	NA	64	NA	16	NA
1162277 GyrA S83F D87V ParC S80I ESBL+ ΔTolC	0.25-0.5	32 to 128	4	16	1 to 2	8 to 16
1162286 GyrA S83Y	16-32	NA	4	NA	4 to 8	NA
1162286 GyrA S83Y ΔTolC	0.25	64 to 128	0.032 to 0.063	64 to 128	1	4 to 8

Source: m5.3.5.4, GSK Study Report 2020N451222

Abbreviations: MIC, minimum inhibitory concentration; NA, not applicable

The table below shows gepotidacin MIC distribution data for isolates with higher gepotidacin MICs (≥16 mcg/mL against *E. coli* and ≥32 mcg/mL against other Enterobacterales) that were characterized for FQ-R genes and/or efflux from recent MIC, clinical and surveillance studies. Data for *K. pneumoniae* isolates with higher gepotidacin MICs (≥64 mcg/mL) is also shown. Regarding FQ-R genes in isolates against which gepotidacin had higher MICs, the Applicant reported the following: 90.8 % of *E. coli*, 85.2% of *K. pneumoniae*, 85.7% of *K. aerogenes*, 66.7% of *K. oxytoca*, 76.9% of *E. cloacae*, 100% of *C. freundii*, 15.5% of *P. mirabilis*, 33.3% of *P. stuartii*, 47.1% of *P. rettgeri* and 0% of *S. marcescens* carried one or more *qnr* gene.

Table 182. Summary of Isolates With Higher MICs From a 2020 MIC Study, the Phase 3 uUTI Study 206989 and EAGLE-3, the 2019 to 2021 and 2022 Gepotidacin Uropathogen Global Surveillance Studies (*E. coli*) and the 2019 to 2022 *K. pneumoniae* Gepotidacin Uropathogen Global Surveillance Study That Have Been Characterized for Potential Gepotidacin Resistance Mechanisms

GSK study report# [m5.3.5.4] (study description)	Bacteria	Distribution of higher gepotidacin MICs (µg/mL) against bacteria [number of isolates]						Total	Fold PAβN↓	FQ-R gene and efflux genotypes^ (N)
		16	32	64	>64	128	>128			
2022N522567 (characterization of nonclinical isolates from the 2020 N=4000 MIC study)	*C. freundii*		2			1		3	0 to 4	*qnrS* (1), *qnrB* + *acrR* (2)
	E. cloacae		10	24		6	3	43	0 to 64	*qnrA* (3), *qnrA*+*qnrS* (1), *qnrB* (10), *qnrE*(1), *qnrS* (14), *qnrS*+*acrR* (1), *qnrS*+qepA1 (1)
	E. coli	20	1	1				22	0 to 8	*qnrS* (15), *qnrS* + *acrR* (1), *qepA4* + *acrR* (2), *qnrB* + *qepA4*-like partial CDS + *acrR* (1), *acrR* + *marR* (1)
	K. aerogenes		5	1				6	0 to 16	*qnrS* (4), *qnrS*+*acrR* (1)
	K. oxytoca		1	1				2	2	*qnrS* +*marR*+*marB* (1)
	K.. pneumoniae		40	9		6	2	57	-2 to 16	*qnrB* (12), qnrB + acrR (1), *qnrB* + *ramR* (1), *qnrS* (17), *qnrS* + *qnrB* (3), *qnrS* + *acrR* (1) *qnrS* + *ramR* (1), *qnrS* + *qnrB* + *ramR* (1), *qnrS* + *marB* (2), *qnrS* + *oqxR* (2), *ramR* + *oqxR* (1),

GSK study report# [m5.3.5.4] (study description)	Bacteria	Distribution of higher gepotidacin MICs (µg/mL) against bacteria [number of isolates]						Total	Fold PAβN↓	FQ-R gene and efflux genotypes^ (N)
		16	32	64	>64	128	>128			
										ramR (2)
	P. mirabilis		13	6		3		22	-2 to 4	*qnrA* (2), *qnrD* (1), *qnrS* (1)
	P. rettgeri		4	5		5	3	17	-2 to 2	*qnrB* (1), *qnrD* (7)
2023N530778 (Study 204989 ITT Population, all visits)	*E. cloacae*		4		1			5	NT	*oqxB9* + *qnrS1* (2), *oqxB9*-like + *qnrS1*(3)
	E. coli	22	12	2	2			38	NT	*qnrS1* (23), *qnrS13* (2,) aac(6')-Ib-cr + *qnrB4* + *qnrS1*(1), *qepA8* + *qnrS1*(1), *qepA1*-like + *qnrS1* (3), *qnrB19* (1), *qnrB19* + *qnrS1* (4)
	K. aerogenes		1					1	NT	*oqxB9*-like + *qnrS1* (1)
	K. oxytoca			1				1	NT	*oqxB*-like + *qnrS1* (1)
	K. pneumoniae		14	3	9			26	NT	aac(6')-Ib-cr + *oqxA11* + *oqxB19* + *qnrB1* (4), *oqxA* + *oqxB20*-like + *qnrS1* (3), *oqxA* + *oqxB25* (2), *oqxA11* + *oqxB19* + *qnrS* (1), *oqxA*-like + *oqxB14* + *qnrS1* (1), *oqxA* + *oqxB20* + *qnrB4* (1), *oqxA* + *oqxB25* + *qnrS1* (1), *oqxA* + *oqxB* (1), *oqxA*-like + *oqxB9*-like (1), *oqxA10* + *oqxB19* (1), *oqxA* + *oqxB5* +*qnrS1* (2), *qnrB4* (1), *qnrA1* (1), *qnrS1* (3), *oqxA* + *oqxB*-like (1), *oqxA*-*like* + *oqxB19* + *qnrS1* (1)

GSK study report# [m5.3.5.4] (study description)	Bacteria	Distribution of higher gepotidacin MICs (µg/mL) against bacteria [number of isolates]						Total	Fold PAβN↓	FQ-R gene and efflux genotypes^ (N)
		16	32	64	>64	128	>128			
	P. stuartii		3					3	NT	*qnrA1* (1)
	P. mirabilis		12	7	10			29	NT	*qnrD1* (1), aac(6`)-Ib-cr-like + *qnrS1* (1), aac(6`)-Ib-cr7-like + *qnrA1* (1), *qnrVC5* (2)
2023N530778 (Study 212390 ITT Population, all visits)	*E. cloacae*		1	1	1			3	NT	*oqxB9*-like + *qnrS1* (2), *oqxB9*-like + *qnrD2* +*qnrS1*(1)
	E. coli	6	6					12	NT	aac(6`)-Ib-cr + *qnrS1* (1) *qnrS1* (11)
	K. pneumoniae		10	1	2			13	NT	*oqxA10* + *oqxB19*-like (2), *oqxA11* + *oqxB19* + *qnrS1* (1), *oqxA* + *oqxB19* (2), *oqxA* + *oqxB25* (1), *oqxA* + *oqxB5*-like + *qnrS1* (1), *oqxA10* + *oqxB19* (1), *oqxA* + *oqxB19* + *qnrS1* (2), aac(6`)-Ib-cr + *oqxA* + *oqxB25*-like + *qnrB1* (1), *oqxA10* + *oqxB25* +*qnrS1* (1)
2022N507183 (2019 to 2021 gepotidacin uropathogen global surveillance study)	*E. coli*	27	6					33	NT	*qnrS1* (28), *qnrS1* + *qepA5* (1), *qnrB4* (1), *qnrB19* (1), *qepA5* (1), *qepA8* (1)
2023N545083 2022 gepotidacin uropathogen global surveillance study	*E. coli*	11	4					15	NT	*qnrS1* (13), *qnrS4* + *qepA4* (1) *qepA4* (1)
2024N551074 2019 to 2022 gepotidacin uropathogen global surveillance study	*K. pneumoniae*			47	6			53	NT	*qnrS* (21), *qnrB* (14) *qnrB* + *qnrS* (2) aac(6`)-Ib-cr + *qnrS* (1) aac(6`)-Ib-cr + *qnrB* (6) aac(6`)-Ib-cr + *qnrS* + *qnrB* (2)

Source: This submission.
^Genotype was not determined in all isolates
Lab generated mutants were not included in these analyses.
Abbreviations: FQ-R, fluoroquinolone-resistance; MIC, minimum inhibitory concentration; N, number identified; NT, not tested; uUTI, uncomplicated urinary tract infection

Reviewer's Comments

The fluoroquinolone-resistance gene primarily associated with higher gepotidacin MICs was qnr.

E. coli isolates from the 2019 to 2021 and 2022 gepotidacin uropathogen global surveillance studies were screened for QRDR mutations, FQ-R genes, and expression of AcrA. None of the 48 isolates with higher gepotidacin MICs were reported by the Applicant to have QRDR mutations at gepotidacin specific residues. Refer to the table below:

Table 183. Molecular Characterization of *E. coli* Isolates From the 2019 to 2021 and 2022 Gepotidacin Global Surveillance Studies That Displayed Gepotidacin MICs Greater Than or Equal to 16 mcg/mL

Number	Year	Site	Country	MIC (µg/mL)			FQ resistance mechanism		
				GEP	CIP	LVX	FQ-R genes	AcrA expression[b]	GyrA, GyrB, ParC, ParE[a]
1197711	2021	481	USA	16	0.12	0.5	*qnrS1*	4.5	WT, WT, WT, WT
1124915	2019	97	Russia	16	0.25	0.25	*qnrS1*	3.3	WT, WT, WT, WT
1158119	2020	75	Italy	16	0.25	0.5	*qnrS1*	2.8	WT, WT, WT, WT
1197839	2021	115	Mexico	16	0.5	0.5	*qnrS1*	<0.1	WT, WT, WT, WT
1109661	2019	115	Mexico	16	0.5	0.5	*qnrS1*	4.5	WT, WT, WT, WT
1155714	2020	66	Spain	16	0.5	0.5	*qnrS1*	9.3	WT, WT, WT, WT
1194573	2021	149	USA	16	0.5	0.5	*qnrS1*	3.0	WT, WT, WT, WT
1093864	2019	122	USA	16	0.5	0.5	*qnrS1*	0.9	WT, WT, WT, WT
1179327	2020	376	France	16	0.5	1	*qnrS1*	1.2	WT, WT, WT, WT
1096816	2019	138	Portugal	16	0.5	1	*qnrS1*	2.6	WT, WT, WT, WT
1163297	2020	138	Portugal	16	0.5	1	*qnrS1*	2.5	WT, WT, WT, WT
1125400	2019	139	Russia	16	0.5	1	*qnrS1*	2.3	WT, WT, WT, WT
1177737	2020	68	Turkey	16	0.5	1	*qnrS1*	<0.1	WT, WT, WT, WT
1208220	2021	24	USA	16	0.5	1	*qnrS1*	<0.1	WT, WT, WT, WT
1202778	2021	130	USA	16	0.5	1	*qnrS1*	1.3	WT, WT, WT, WT
1156784	2020	448	USA	16	0.5	1	*qnrS1*	<0.1	WT, WT, WT, WT
1223109	2021	131	Belgium	16	1	0.5	*qnrS1*	2.7	WT, WT, WT, WT
1223108	2021	131	Belgium	16	1	1	*qnrS1*	0.4	WT, WT, WT, WT
1187089	2020	776	USA	16	1	2	*qnrB4*	3.3	WT, WT, WT, WT
1107249	2019	130	USA	16	1	4	*qnrS1*	1.3	WT, WT, WT, WT
1088163	2019	51	USA	16	>4	16	*qnrS1*	3.3	S83L, WT, S80I, WT
1110754	2019	376	France	16	>4	32	*qnrS1*	5.7	S83L/D87N, WT, S80I, WT
1114046	2019	43	Chile	16	>4	>32	*qnrB19*	8.8	S83L/D87N, WT, S80I, WT
1192751	2021	150	Germany	16	>4	>32	*qnrS1*	15.4	S83L/D87N, WT, S80I, WT
1167101	2020	502	Japan	16	>4	>32	*qnrS1*	4.4	S83L/D87E, WT, S80I, WT
1168145	2020	115	Mexico	16	>4	>32	*qepA8*	3.3	S83L/D87N, WT, S80I, WT
1163332	2020	138	Portugal	16	>4	>32	*qnrS1*	1.8	S83L/D87N, WT, S80I/E84V, WT
1127679	2019	57	Brazil	32	0.5	1	*qnrS1*	3.6	WT, WT, WT, WT
1163347	2020	303	UK	32	0.5	1	*qnrS1*	1.4	WT, WT, WT, WT
1177752	2020	68	Turkey	32	0.5	2	*qnrS1*	1.4	WT, WT, WT, WT
1216128	2021	137	USA	32	1	1	*qnrS1*	5.6	WT, WT, WT, WT
1090888	2019	115	Mexico	32	>4	>32	*qepA5*	1.2	S83L/D87N, WT, S80I, WT
1106660	2019	24	USA	32	>4	>32	*qnrS1, qepA5*	3.2	S83L/D87N, WT, S80I, WT
1249367	2022	11	USA	16	0.25	0.5	*qnrS1*	8.9	WT, WT, WT, WT
1250847	2022	329	Slovenia	16	0.25	0.5	*qnrS1*	6.7	WT, WT, WT, WT
1251423	2022	282	Romania	16	0.25	0.5	*qnrS1*	16.0	WT, WT, WT, WT
1236577	2022	153	Sweden	16	0.5	0.5	*qnrS1*	0.9	WT, WT, WT, WT
1231012	2022	472	USA	16	0.5	0.5	*qnrS1*	0.4	WT, WT, WT, WT
1243113	2022	126	Mexico	16	0.5	1	*qnrS1*	0.1	WT, WT, WT, WT
1241832	2022	470	USA	16	0.5	0.5	*qnrS1*	0.5	WT, WT, WT, WT
1241833	2022	470	USA	16	0.5	0.5	*qnrS1*	1.0	WT, WT, WT, WT
1250919	2022	112	Sweden	16	0.5	0.5	*qnrS1*	3.7	WT, WT, WT, WT
1267760	2022	57	Brazil	16	4	8	*qnrS1*	3.0	WT, WT, WT, WT
1234095	2022	478	USA	16	>4	>32	*qepA4*	14.4	S83L,D87N, WT, S80I, WT
1244297	2022	514	Japan	32	0.25	1	*qnrS1*	2.4	WT, WT, WT, WT
1231374	2022	728	USA	32	0.5	0.5	*qnrS1*	2.0	WT, WT, WT, WT
1235155	2022	115	Mexico	32	1	2	*qnrS1*	6.5	WT, WT, WT, WT
1233198	2022	24	USA	32	>4	>32	*qnrS4, qepA4*	15.1	S83L/D87N, WT, S80I, WT

Source:m5.3.5.4, GSK Study Report 2022N507183; m5.3.5.4, GSK Study Report 2023N545083

a. Mutations in GyrB were not observed

b. Expression levels (n-fold) were compared to a WT control *E. coli* strain with a basal expression of *ampC*. Expression results of <5-fold are considered similar to a baseline expression of the control strain; results of 5- to 10-fold are considered moderate expression; whereas results >10-fold are considered elevated expression

Abbreviation: MIC, minimum inhibitory concentration

K. pneumoniae isolates from the 2019 to 2022 gepotidacin uropathogen global surveillance study were screened for QRDR mutations, and FQ-R genes. For isolates with no QRDR mutations or PMQR genes, expression of efflux genes *oqxAB* and *acrA* were determined. Refer to the table below showing isolates with gepotidacin MIC ≥64 mcg/mL. Of the 53 isolates, 46 carried the *qnr* gene. Also, 20.8% of the isolates had QRDR variations known to reduce susceptibility to FQs. None of the 53 *K. pneumoniae* isolates with higher gepotidacin MICs were reported to have QRDR mutations at gepotidacin specific residues.

Table 184. Molecular Characterization of *K. pneumoniae* Isolates From the 2019 to 2022 Global Uropathogen Surveillance Study With Gepotidacin MICs Greater Than or Equal to 64 mcg/mL

Number	Year	Site	Country	MIC (µg/mL)			FQ resistance mechanism			
				GEP	CIP	LVX	*oqxAB* expression[b]	AcrA expression[b]	PMQR gene	GyrA/GyrB/ParC/ParE[a]
1124435	2019	476	USA	64	0.06	0.12	109.9	2.5	Negative	WT, WT, WT, WT
1124439	2019	476	USA	64	0.06	0.12	1.0	0.2	Negative	WT, WT, WT, WT
1240265	2022	349	Slovakia	64	0.5	0.5	NA	NA	*qnrS*	WT, WT, WT, WT
1261238	2022	63	Israel	64	1	1	NA	NA	*qnrS*	WT, WT, WT, WT
1189903	2021	51	USA	64	0.25	1	4.3	6.2	Negative	WT, WT, WT, WT
1225584	2021	69	Turkey	64	2	2	56.5	0.8	Negative	WT, WT, WT, WT
1092075	2019	455	USA	64	1	4	86.0	0.4	Negative	WT, WT, WT, WT
1097894	2019	462	USA	64	1	2	NA	NA	*qnrS*	WT, WT, WT, WT
1194710	2021	469	USA	64	0.25	1	190.3	13.1	Negative	WT, WT, WT, WT
1232443	2022	477	USA	64	2	1	NA	NA	*qnrB, aac(6')-Ib-cr*	WT, WT, WT, WT
1170702	2020	461	USA	64	2	2	NA	NA	*qnrS*	WT, WT, N304S, WT
1198706	2021	739	USA	64	0.5	2	235.3	5.0	Negative	WT, WT, WT, WT
1092110	2019	455	USA	64	2	4	NA	NA	*qnrS*	WT, WT, WT, WT
1118951	2019	606	Korea	>64	2	4	NA	NA	*qnrS*	WT, WT, WT, WT
1178157	2020	137	USA	64	2	4	NA	NA	*qnrS*	WT, WT, WT, WT
1195182	2021	131	Belgium	64	2	4	NA	NA	*qnrB*	WT, WT, WT, WT
1210230	2021	15	USA	64	2	4	NA	NA	*qnrB*	WT, WT, WT, WT
1232152	2022	51	USA	>64	2	4	NA	NA	*qnrS*	WT, WT, WT, WT
1251420	2022	282	Romania	64	2	4	NA	NA	*qnrS*	WT, WT, WT, WT
1157867	2020	115	Mexico	>64	2	32	NA	NA	*qnrS*	WT, WT, WT, WT
1088295	2019	425	USA	64	4	2	NA	NA	*qnrB*	WT, WT, WT, WT
1210027	2021	601	Malaysia	64	4	2	NA	NA	*qnrS, aac(6')-Ib-cr*	WT, WT, WT, WT
1195479	2021	63	Israel	64	4	4	NA	NA	*qnrB*	WT, WT, WT, WT
1210572	2021	616	Philippines	64	4	4	NA	NA	*qnrS*	WT, WT, WT, WT
1210613	2021	616	Philippines	>64	4	8	NA	NA	*qnrS*	WT, WT, WT, WT
1157874	2020	115	Mexico	64	>4	4	NA	NA	*qnrB*	WT, WT, WT, WT
1202516	2021	743	USA	64	>4	4	NA	NA	*qnrB, aac(6')-Ib-cr*	WT, WT, WT, WT
1089821	2019	75	Italy	64	>4	8	NA	NA	*qnrB*	WT, WT, WT, WT
1097094	2019	377	Italy	64	>4	8	NA	NA	*qnrB*	WT, WT, WT, WT
1099749	2019	115	Mexico	64	>4	8	NA	NA	*qnrB*	WT, WT, WT, WT
1161337	2020	263	Australia	64	>4	8	NA	NA	*qnrS*	WT, WT, WT, WT
1210585	2021	616	Philippines	64	>4	8	NA	NA	*qnrB/qnrS, aac(6')-Ib-cr*	WT, WT, WT, WT
1261250	2022	63	Israel	64	>4	8	NA	NA	*qnrB, aac(6')-Ib-cr*	WT, WT, WT, WT
1112796	2019	69	Turkey	>64	>4	16	NA	NA	*qnrS*	WT, WT, WT, WT
1154227	2020	728	USA	64	>4	16	NA	NA	*qnrS*	WT, WT, WT, WT
1166081	2020	133	UK	64	>4	16	NA	NA	*qnrB/qnrS*	WT, WT, WT, WT
1174978	2020	62	Greece	64	>4	16	NA	NA	*qnrB/qnrS*	WT, WT, WT, WT
1181997	2020	131	Belgium	64	>4	16	NA	NA	*qnrB*	WT, WT, WT, WT
1189624	2020	134	USA	64	>4	16	NA	NA	*qnrB*	WT, WT, WT, WT
1214368	2021	806	USA	64	>4	16	NA	NA	*qnrB*	WT, WT, WT, WT
1221561	2021	62	Greece	64	>4	16	NA	NA	*qnrB, aac(6')-Ib-cr*	WT, WT, WT, WT
1154503	2020	453	USA	64	>4	32	NA	NA	*qnrB*	S83Y, WT, WT, WT
1160604	2020	456	USA	64	>4	32	NA	NA	*qnrS*	S83I, WT, WT, WT
1219073	2021	100	UK	>64	>4	32	NA	NA	*qnrS*	WT, WT, WT, WT
1248414	2022	814	USA	64	>4	32	NA	NA	*qnrB, aac(6')-Ib-cr*	WT, WT, WT, WT
1102764	2019	65	Spain	64	>4	>32	NA	NA	*qnrB*	S83I, WT, S80I, WT

Number	Year	Site	Country	MIC (µg/mL)			FQ resistance mechanism			
				GEP	CIP	LVX	*oqxAB* expression[b]	AcrA expression[b]	PMQR gene	GyrA/GyrB/ParC/ParE[a]
1112765	2019	69	Turkey	64	>4	>32	NA	NA	*qnrS*	S83I, WT, S80I, WT
1177466	2020	346	Panama	64	>4	>32	NA	NA	*qnrB*	S83I, WT, S80I, WT
1199535	2021	336	Hungary	64	>4	>32	NA	NA	*qnrB*, *aac*(6')-*Ib-cr*	S83I, WT, S80I, WT
1218754	2021	377	Italy	64	>4	>32	NA	NA	*qnrS*	S83I, WT, S80I, WT
1234850	2022	75	Italy	64	>4	>32	NA	NA	*qnrS*	S83I, WT, S80I, WT
1242453	2022	467	USA	64	>4	>32	NA	NA	*qnrS*	S83I, WT, S80I, WT
1264303	2022	616	Philippines	64	>4	>32	NA	NA	*qnrB*/*qnrS*, *aac*(6')-*Ib-cr*	S83I, WT, WT, WT

Source:m5.3.5.4, GSK Study Report 2024N551074

a. Mutations in GyrB were not observed

b. Expression levels (n-fold) only performed on isolates that did not carry PMQR genes and had WT sequences for QRDR. Expression levels were compared to a WT control *K. pneumoniae* strain with a basal expression of *acrAB* and *oqxAB*. Expression results of <5-fold are considered similar to a baseline expression of the control strain; results of 5- to 10-fold and >10-fold are considered moderate and elevated expression levels.

Abbreviation: MIC, minimum inhibitory concentration

The Applicant reported that while isogenic strains showed a decrease in gepotidacin MICs in the absence of efflux, disruption of negative regulators of efflux (*acrR, marR, soxR, ramR and oqxR*), expression of *acrA* and broth microdilution (BMD) MIC testing in the presence of efflux inhibitor PAβN showed a varying effect of efflux and a range of gepotidacin MICs.

The Applicant has stated that mechanisms responsible for higher gepotidacin MICs against isolates with QRDR variations in residues not associated with gepotidacin activity are likely linked to the presence of a *qnr* gene or expression of plasmid and/or chromosomally mediated efflux. Gepotidacin specific single residue variations within the QRDR have been observed and are described in the table below.

Table 185. Summary of Isolates From the 2020 MIC Study, Phase 3 Study EAGLE-2 and Study EAGLE-3 and the 2019 to 2021, Gepotidacin Uropathogen Global Surveillance Study With Variations in Type II Topoisomerase Residues Known to be Involved in Gepotidacin Activity

GSK study report# [m5.3.5.4] (study description)	Uropathogen species/mutation*	Number of isolates	Gepotidacin involvement	Gepotidacin MIC (µg/mL)	Gepotidacin MIC90 for the species from that study (µg/mL)
2022N522567 (characterization of nonclinical isolates from the 2020 N=4000 MIC study)	*K. pneumoniae* GyrA D82N	1	Binding pocket, contact with gepotidacin [Bax, 2010; Szilli, 2019; Lahiri, 2015]	8 to 16	64
2022N522567 (characterization of nonclinical isolates from the 2020 N=4000 MIC study)	*K. oxytoca* ParC T178A	1	GSK proposed interaction; unpublished	1	8
2022N522567 (characterization of nonclinical isolates from the 2020 N=4000 MIC study)	*P. mirabilis* ParE D421N	4	Binding pocket, contact with DNA [GSK unpublished data; Lahiri, 2015]	16 to 128	64
2022N522567 (characterization of nonclinical isolates from the 2020 N=4000 MIC study)	*P. mirabilis* ParE P440S	5	Binding pocket, contact with DNA [GSK unpublished data; Lahiri, 2015]	16 to 128	64
2022N522567 (characterization of nonclinical isolates from the 2020 N=4000 MIC study)	*P. rettgeri* D421N ParE	2	Binding pocket, contact with DNA [GSK unpublished data; Lahiri, 2015]	128	128
2022N507183 (2019 to 2021 gepotidacin uropathogen global surveillance study)	*E. coli* GyrA D82N	1	Binding pocket, contact with gepotidacin [Bax, 2010; Szilli, 2019; Lahiri, 2015]	8	4
2023N530778 (Study 204989)	*E. coli* ParC D79G	3*	Binding pocket, contact with gepotidacin [Bax, 2010; Szilli, 2019; Lahiri, 2015]	>64	4

*1 isolate was collected outside the FU collection window
Abbreviation: MIC, minimum inhibitory concentration

The Applicant reported that among isolates recovered in phase 3 Study EAGLE-2 and Study EAGLE-3, the only type II topoisomerase variation known to be associated higher gepotidacin MICs was ParC D79G. This mutation was observed in 3 *E. coli* isolates from different collection time points (including one time points outside follow up) from subject 401298. This isolate had gepotidacin MICs of >64 mcg/mL, and the *E. coli* isolate from baseline had a gepotidacin MIC of 16 mcg/mL and no ParC D79 mutation. The Applicant states that no double gepotidacin specific QRDR residue variations were observed in the clinical studies. The Applicant concluded that an "off-target" mechanism is responsible for the higher gepotidacin MICs against isolates with single gepotidacin specific amino acid mutations. Studies with isogenic mutants were recommended for final conclusions. Please refer to this reviewer's analysis of the genetic characterization of isolates from clinical studies.

From a spontaneous frequency of resistance study (GSK Study Report 2021N485364), a subset of gepotidacin mutants from each species were selected for whole-genome sequencing and characterized for variations in target genes, *par*C/E and *gyr*A/B in comparison to their parent isolates. No target-specific mutations were detected among the 23 mutants tested from gram-negative isolates. Two mutants from *E. faecalis* were found to have a single amino acid substitution in the target genes (GyrA, A34V and GyrB, D437V) The Applicant suggests that this means that the inhibition by gepotidacin of both enzymes is not balanced in this organism. In other words, a single mutation in GyrA led to a higher gepotidacin MIC. GyrA residue 34 is in a region known to be involved in DNA bending and GyrB residue 437 is part of binding pocket that contacts DNA.

Reviewer's Comments

The data from this study of spontaneous resistance on 4XMIC agar plates with E. faecalis are an example of a uUTI pathogen that had an increase in MICs to gepotidacin with a mutation in one amino acid residue. The MIC at baseline was 0.25 mcg/mL and one isolate resulted in MIC of 4 mcg/mL, while the other resulted in an MIC of 2 mcg/mL. Refer to the table below for additional information.

Potential gepotidacin resistance mechanisms of *E. coli* mutants from in vitro dose ranging studies with gepotidacin MICs greater than or equal to 16 mcg/mL were determined. Efflux was named as the potential gepotidacin resistance mechanism. From in vitro hollow-fiber infection model studies, 13 *E. coli* isolates with gepotidacin MIC values ≥16 mcg/mL were selected for whole genome sequencing to identify mutations associated with gepotidacin reduced susceptibility. Mutations associated with efflux, stress response, and RNA/DNA replication were all identified as having this potential, but isogenic mutants were not constructed to provide definitive conclusions.

Cross-Resistance

Mutants selected by gepotidacin from the following species displayed cross-resistance to LVX: *E. cloacae* species complex, (4/11 were also resistant to azithromycin and tetracycline), *K. pneumoniae* (3/5), *P. mirabilis* (1/1), and *P. rettgeri* (30/30). No target-based variations were observed for any of the Enterbacterales mutants recovered in the study. Mutants selected by LVX were not tested for cross-resistance to gepotidacin or comparators.

Table 186. Observed BMD MIC Values for Gepotidacin and Comparator Agents for Isolates Recovered on 4XMIC Agar Plates From a Spontaneous Frequency of Resistance Study

Isolate	Exposure	MIC (µg/mL)								
		GEP	LVX	AZI	CAZ	NTF	TET	SXT	ATM	MEM
C. freundii										
1091286	Baseline	1	0.03	4	0.25	32	1	≤0.12	0.12	≤0.03
161	4xAgar	**8**	0.015	4	0.25	16	1	≤0.12	0.06	≤0.03
162	4xAgar	**16**	0.015	2	0.25	32	1	≤0.12	0.06	≤0.03
163	4xAgar	**8**	0.015	4	0.25	16	1	≤0.12	0.06	≤0.03
164	4xAgar	**8**	0.015	8	0.25	16	1	≤0.12	0.06	≤0.03
165	4xAgar	**8**	0.015	4	0.25	16	1	≤0.12	0.12	≤0.03
166	4xAgar	**8**	0.015	8	0.5	16	1	≤0.12	0.06	≤0.03
167	4xAgar	**16**	0.03	8	0.25	16	≤0.5	≤0.12	0.12	≤0.03
168	4xAgar	**8**	0.015	8	0.25	16	1	≤0.12	0.12	≤0.03
169	4xAgar	**8**	0.015	4	0.25	16	1	≤0.12	0.06	≤0.03
170	4xAgar	**8**	0.015	2	0.25	16	1	≤0.12	0.06	≤0.03
1116313	Baseline	16	8	64	1	32	>128	>16	0.25	≤0.03
222	4xAgar	**>64**	8	32	1	32	8	1	0.25	≤0.03
1130512	Baseline	2	0.03	16	64	16	1	≤0.12	16	≤0.03
158	4xAgar	2	0.06	16	>64	16	1	≤0.12	16	≤0.03
E. cloacae										
1092279	Baseline	4	0.03	8	64	32	1	≤0.12	32	≤0.03
137	4xAgar	**64**	**0.5**	**64**	64	64	**16**	0.25	32	0.06
139	4xAgar	**32**	**0.5**	**32**	64	64	**16**	0.25	32	≤0.03
141	4xAgar	**32**	**0.25**	**32**	64	64	**16**	≤0.12	32	≤0.03
143	4xAgar	**32**	0.03	16	64	32	2	≤0.12	32	≤0.03
146	4xAgar	**16**	**0.25**	**32**	32	64	**16**	≤0.12	16	0.06
147	4xAgar	**32**	0.03	16	64	32	2	≤0.12	32	≤0.03
148	4xAgar	**64**	0.03	16	64	32	2	≤0.12	32	≤0.03
149	4xAgar	**32**	0.06	16	64	64	2	≤0.12	32	0.06
150	4xAgar	**32**	0.03	16	64	32	2	≤0.12	32	≤0.03
153	4xAgar	**32**	0.03	16	>64	64	2	≤0.12	32	≤0.03
1098581	Baseline	4	0.06	8	0.25	32	1	≤0.12	0.06	≤0.03
182	4xAgar	**32**	0.12	16	0.5	64	2	0.25	0.12	≤0.03
K. pneumoniae										
1124085	Baseline	32	8	8	0.25	>128	4	2	0.12	≤0.03
205	10xAgar	64	8	8	0.5	>128	4	2	0.12	≤0.03
206	10xAgar	64	8	8	0.5	>128	4	2	0.12	≤0.03
207	10xAgar	32	8	8	0.25	>128	4	2	0.12	≤0.03
208	10xAgar	32	8	8	0.5	>128	4	2	0.12	≤0.03
210	4xAgar	**>64**	**64**	4	0.25	>128	4	4	0.12	0.06

Isolate	Exposure	MIC (µg/mL)								
		GEP	LVX	AZI	CAZ	NTF	TET	SXT	ATM	MEM
211	4xAgar	**>64**	**64**	4	0.25	>128	4	4	0.12	0.06
212	4xAgar	64	8	8	0.25	>128	4	2	0.12	≤0.03
213	4xAgar	**>64**	16	8	0.5	>128	4	1	0.12	≤0.03
214	4xAgar	64	8	8	0.25	>128	4	2	0.12	≤0.03
215	4xAgar	**>64**	16	8	0.25	>128	4	4	0.12	0.06
216	4xAgar	64	8	8	0.25	>128	4	2	0.12	≤0.03
218	4xAgar	**>64**	**32**	8	0.25	>128	4	4	0.06	0.06
219	4xAgar	64	8	8	0.25	>128	4	2	0.25	≤0.03
P. mirabilis										
1091952	Baseline	16	0.06	64	0.06	128	32	2	≤0.03	0.12
224	4xAgar	**>64**	**0.5**	64	0.06	128	32	2	≤0.03	0.06
P. rettgeri										
1089529	Baseline	4	0.12	128	0.06	32	64	≤0.12	≤0.03	≤0.03
172	4xAgar	**>64**	**1**	128	0.06	32	64	≤0.12	≤0.03	≤0.03
173	4xAgar	**>64**	**1**	128	0.06	32	128	≤0.12	≤0.03	≤0.03
174	4xAgar	**>64**	**1**	128	0.06	32	128	0.25	≤0.03	≤0.03
175	4xAgar	**>64**	**1**	128	0.06	32	64	0.25	≤0.03	≤0.03
176	4xAgar	**>64**	**1**	128	0.06	32	64	0.25	≤0.03	≤0.03
177	4xAgar	**>64**	**2**	>128	0.06	32	64	0.25	≤0.03	0.06
178	4xAgar	**>64**	**1**	128	0.06	32	128	≤0.12	≤0.03	≤0.03
179	4xAgar	**>64**	**1**	128	0.12	32	128	0.25	≤0.03	≤0.03
180	4xAgar	**>64**	**1**	128	0.06	32	128	≤0.12	≤0.03	≤0.03
181	4xAgar	**>64**	**1**	128	0.06	32	128	≤0.12	≤0.03	≤0.03
1090192	Baseline	4	16	64	>64	>128	64	>16	16	≤0.03
184	4xAgar	**64**	**64**	64	>64	>128	64	>16	16	≤0.03
185	4xAgar	**64**	**64**	64	>64	>128	64	>16	16	≤0.03
186	4xAgar	**64**	**64**	64	>64	>128	64	>16	16	≤0.03
187	4xAgar	**64**	**64**	64	>64	>128	64	>16	16	≤0.03
188	4xAgar	**>64**	**>64**	>128	>64	>128	128	>16	32	≤0.03
189	4xAgar	**64**	**>64**	64	>64	>128	64	>16	32	≤0.03
190	4xAgar	**64**	**64**	64	>64	>128	64	>16	16	≤0.03
191	4xAgar	**64**	**64**	64	>64	>128	32	>16	16	≤0.03
192	4xAgar	**>64**	**>64**	64	>64	>128	64	>16	32	≤0.03
193	4xAgar	**>64**	**>64**	64	>64	>128	64	>16	16	≤0.03
194	4xAgar	**>64**	**>64**	64	>64	>128	64	>16	16	≤0.03
203	4xAgar	**>64**	**64**	64	>64	>128	64	>16	16	≤0.03
1118004	Baseline	4	8	64	0.06	>128	64	>16	≤0.03	0.06
195	4xAgar	8	8	**>128**	0.06	>128	32	>16	≤0.03	0.06
196	4xAgar	**>64**	**>64**	64	0.12	>128	64	>16	≤0.03	≤0.03
197	4xAgar	**>64**	**>64**	64	0.06	>128	64	>16	≤0.03	≤0.03
198	4xAgar	**>64**	**>64**	128	0.06	>128	128	>16	≤0.03	0.06
199	4xAgar	**>64**	**>64**	64	0.06	>128	64	>16	≤0.03	≤0.03
200	4xAgar	**>64**	**>64**	64	0.06	>128	64	>16	≤0.03	≤0.03
201	4xAgar	**>64**	**>64**	64	0.06	>128	64	>16	≤0.03	≤0.03
202	4xAgar	**>64**	**>64**	64	0.06	>128	64	>16	≤0.03	≤0.03
225	4xAgar	**64**	**32**	32	0.06	64	16	>16	≤0.03	≤0.03
E. faecalis										
									LZD	VAN
1103850	Baseline	0.25	0.5	>128	>64	≤8	32	0.25	1	1
135	4xAgar	**4**	0.5	>128	>64	≤8	32	0.25	1	1
136	4xAgar	**2**	0.5	>128	>64	16	32	≤0.12	1	1

Source Data: m5.3.5.4, GSK Study Report 2021N485364
Antibacterial agent abbreviations: AZI, azithromycin; TET, tetracycline; LZD, linezolid
Bold values denote a ≥4-fold increase compared to the parent baseline MIC values

Abbreviations: BMD, broth microdilution; MIC, minimum inhibitory concentration

Cross-Resistance With the Fluoroquinolone Class

The *E. coli* K-12 isolates with mutations associated with fluoroquinolone resistance that had stepwise mutations demonstrated increased ciprofloxacin MICs (4-to 2000- fold) and a 2-fold decrease in gepotidacin MICs. The *K. pneumoniae* ATCC 10031 isolate carrying mutations associated with fluoroquinolone resistance with stepwise mutations demonstrated increased ciprofloxacin MICs (20- to 1000-fold) and a 2- to 8-fold increase in gepotidacin MICs. The results are shown in the table below:

Table 187. MICs Against *E. coli* and *K. pneumoniae* FQ-R Target Isogenic Mutants

Strain	FQ-R mutation		MIC (µg/mL)			
	GyrA	ParC	Gepotidacin	Fold change in MIC	CIP	Fold change in MIC
E. coli K-12 M1655	WT	WT	0.25	NA	0.016	NA
	S83L	WT	0.125	2↓	0.063	4↑
	S83L, D87N	WT	0.25	0	0.25	16↑
	S83L, D87N	S80I	0.125	2↓	20	1250↑
	S83L, D87Y	S80I, E84G	0.125	2↓	32	2000↑
K. pneumoniae spp. ATCC 10031	WT	WT	0.063	NA	0.004	NA
	S83F	WT	0.5	8↑	0.08	20↑
	S83F, D87G	WT	0.25	4↑	0.125	32↑
	S83F, D87G	S80I	0.063	0	2	500↑
	S83F, D87G	S80I, E84G	0.31	5↑	4	1000↑

Source: Szilli, 2019; m5.3.5.4, GSK Study Report 2020N451222
NA=not applicable
Abbreviation: CIP, ciprofloxacin; FQ-R, fluoroquinolone resistance; MIC, minimum inhibitory concentration

The Applicant studied the cross-resistance between the fluoroquinolone class of antibacterials and gepotidacin using isogenic strains of *K. pneumoniae* (refer to the table below). No target-based cross-resistance to fluoroquinolones was reported by the Applicant. Results showed that the FQ-R target mutations conferred 16- to 1024-fold increases in ciprofloxacin MICs, but minimal changes in gepotidacin MICs (4-fold increases or decreases). In a *tolC* knockout, isolates with fluoroquinolone target mutations had a 2000-fold increase in ciprofloxacin MIC in comparison to the fluoroquinolone susceptible isolate, and a 2-fold increase in gepotidacin MIC.

Table 188. MICs Against *K. pneumoniae* 1161486 FQ-R Isogenic Mutants

K. pneumoniae strain	MIC (µg/mL)					
	Gepotidacin	Fold	CIP	Fold ↑	Azithromycin	Fold↑
1161486	8 to16	NA	0.063	NA	8	NA
1161486 GyrA S83F	16 to 32	0 to 4↑	1	16	8 to 16	0 to2↑
1161486 GyrA S83Y	8 to 16	0 to 2	1	16	8	0
1161486 GyrA S83I	2 to 4	2 to 8↓	1-2	16 to 32	8	0
1161486 GyrA S83I ParC S80I	4	2 to 4↓	16	256	8	0
1161486 GyrA S83F D87V ParC S80I	8 to 16	0 to 2↑	64	1024	8	0

Source: m5.3.5.4, GSK Study Report 2020N451222
Abbreviation: CIP, ciprofloxacin; MIC, minimum inhibitory concentration; NA, not applicable

Development of Resistance

The following sections will summarize development of resistance data from in vitro studies (frequency of spontaneous mutation, serial passage, and a hollow-fiber infection model) and from the gepotidacin clinical studies.

Frequency of Spontaneous Mutation Studies

To evaluate the potential of gepotidacin to select for spontaneous resistance in select gram-negative and gram-positive bacterial isolates, high inoculums were plated on Mueller-Hinton agar plates containing gepotidacin at 4X and 10X their MICs. Mutation frequencies ranged from 10^{-8} to 10^{-10}. Refer to the table below.

Table 189. Summary of Spontaneous Mutation Frequencies for 4X MIC and 10X MIC Gepotidacin Against Gram-Negative and Gram-Positive Species Commonly Associated With uUTI

Organism (N)	Gepotidacin	
	4x MIC	10x MIC
E. coli (3)[a]	$<9.1\times10^{-10}$ to $<6.7\times10^{-10}$	$<9.1\times10^{-10}$ to $<6.7\times10^{-10}$
K. pneumoniae (3)[b]	2.7×10^{-8} to $<6.6\times10^{-10}$	$<5.5\times10^{-9}$ to $<5.7\times10^{-10}$
C. freundii (3)[b]	2.7×10^{-8} to $<5.0\times10^{-9}$	$<5.4\times10^{-9}$ to $<8.3\times10^{-10}$
E. cloacae (3)[b]	6.1×10^{-8} to $<2.5\times10^{-10}$	$<6.5\times10^{-10}$ to $<2.5\times10^{-10}$
K. aerogenes (3)[b]	$<4.7\times10^{-10}$ to $<3.7\times10^{-10}$	$<4.7\times10^{-10}$ to $<3.7\times10^{-10}$
P. mirabilis (3)[b]	7.1×10^{-10} to $<5.4\times10^{-10}$	$<7.1\times10^{-10}$ to $<5.4\times10^{-10}$
P.rettgeri (3)[b]	7.8×10^{-9} to 3.9×10^{-9}	$<5.4\times10^{-10}$ to $<4.3\times10^{-10}$
E. faecalis (3)[b]	1.7×10^{-8} to $<3.2\times10^{-10}$	$<8.3\times10^{-9}$ to $<3.2\times10^{-10}$
S. saprophyticus (3)[b]	$<9.2\times10^{-10}$ to $<5.9\times10^{-10}$	$<9.2\times10^{-10}$ to $<5.9\times10^{-10}$

Source: a. m5.3.5.4, GSK Study Report 2015N226372; b. m5.3.5.4, GSK Study Report 2021N485364

Abbreviation: MIC, minimum inhibitory concentration; uUTI, uncomplicated urinary tract infection

Four additional *E. coli* isolates were subjected to 2.5X and 4X MIC of gepotidacin in a frequency of resistance study conducted to inform the dose fractionation/dose ranging/hollow-fiber study. At 2.5 × MIC, mutants were recovered at mutation frequencies of 4.5×10^{-9} to $<1.1 \times 10^{-9}$.

Serial Passage Studies

In *S. aureus* WCUH29, reduction in susceptibility to gepotidacin reportedly occurs with a gepotidacin MIC increase of 256-fold over the 10-day period, giving a final MIC of 64 mcg/mL. This is higher than for moxifloxacin and azithromycin which had 16-fold increases in MIC. No serial passage studies were conducted for gepotidacin and *E. coli*.

Hollow-Fiber Infection Model

Duplicate 10-day hollow-fiber infection models against *E. coli* NCTC 13441 were used to measure the impact of a range of gepotidacin exposures on the amplification of a drug-resistant subpopulation in *E. coli*. The gepotidacin MIC values of isolates ranged from 8 -32 mcg/mL but returned to baseline values in the presence of a broad-spectrum efflux pump inhibitor.

Development of Resistance During Clinical Studies

No development of reduced susceptibility was seen in the phase 2 Study 206899. Development of reduced susceptibility to gepotidacin was observed from the phase 3 Studies EAGLE-2 and EAGLE-3. It was noted that there was also some development of resistance to gepotidacin from the phase 2 GC and phase 2 ABSSSI studies that are not described in this review. In the phase 2 GC study, 3 microbiological failures had preexisting mutations at ParC D86N (based on *N. gonorrhoeae* numbering) which is a critical residue for gepotidacin binding. Two isolates had an MIC increase of ≥32-fold increase with an additional GyrA A93T at the TOC visit. This was a second mutation thought to be involved in gepotidacin binding. In the phase 2 ABSSSI Study BTZ116704, the data were not considered by the Applicant to be development of resistance, but MRSA isolates recovered from baseline lesion samples of 2 subjects with gepotidacin MICs of 8 and >32 mcg/mL had mutations known to occur in quinolone-resistance (GyrA S84L, ParC S80Y, and ParE D422E) or implicated in gepotidacin binding (GyrA D83N, both isolates; ParC V67A, 1 isolate). These are by *S. aureus* numbering.

19.3. Susceptibility Test Methods and Interpretive Criteria

The Applicant has stated that all studies were conducted in accordance with CLSI and/or European Committee on Antimicrobial Susceptibility Testing approved standards and guidelines.

Disk Manufacturers

10-mcg disks were manufactured (b) (4) and determined to be the best disk concentration for zone diameter susceptibility testing against bacteria. Lot numbers were tested against relevant indicated pathogens and *N. gonorrhoeae* which is not an indicated pathogen but is a quality control organism. Manufacturers and lot numbers for uUTI pathogens are listed below:

10 mcg GSK2140944 disk (b) (4) lot # 2340189

10 mcg GSK2140944 disk (b) (4) group lot #309972

10 mcg GSK 2140944 disk (b) (4) lot #142383767

10 mcg GSK 2140944 disk (b) (4) lot # 2265052

Reviewer's Comments

Disk quality control (QC) performance was evaluated and found to be acceptable. Disc QC criteria have also been accepted and published by CLSI in M100.

Disk stability reports were not provided in the original submission of the gepotidacin NDA but were provided by the Applicant on request. The studies were found to be acceptable.

Quality Control for Susceptibility Testing

The Applicant's proposed MIC and disk diffusion QC ranges for gepotidacin are shown in the table below. They have been approved by CLSI.

Table 190. CLSI-Approved QC Ranges for Gepotidacin

QC strain	MIC range (µg/mL)[a]	Disk diffusion zone diameter range (mm)
CLSI approved QC Ranges (CLSI.M100)		
E. coli ATCC 25922	1 to 4	18 to 26[c]
E. faecalis ATCC 29212	1 to 4	NA
S. aureus ATCC 29213	0.12 to 1	NA
S. aureus ATCC 25923	NA	23 to 29
S. pneumoniae ATCC 49619	0.06 to 0.25	22 to 28
H. influenzae ATCC 49247	0.25 to 1	NA[d]
N. gonorrhoeae ATCC 49226	0.25 to 1[b]	32 to 40

Source: m5.3.5.4, GSK Study Report 2011N128061; m5.3.5.4, GSK Study Report 2013N170310; m5.3.5.4, GSK Study Report 2015N261571; m5.3.5.4, GSK Study Report 2018N369201; m5.3.5.4, GSK Study Report 2020N451836

a. Determined by BMD, unless otherwise specified
b. Range approved for AD only
c. Final CLSI approved range differs from report by 1 mm (18 to 26 mm vs 19 to 26 mm)
d. While a range is indicated in the report, a range was not approved by CLSI.

Abbreviations: AD, agar dilution; ATCC, American type culture collection; BMD, broth microdilution; CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration; NA, not available; QC, quality control

Reviewer's Comments

The Applicant described QC testing using data from the uropathogen global surveillance study 2019-2021 and phase 3 clinical studies. QC results were analyzed to ensure the gepotidacin BMD and disk diffusion results were within the approved CLSI reference ranges. Quality control testing described by the Applicant was done according to CLSI guidelines and had a high percentage of quality control results that were in range. Quality Control Ranges have been published by the CLSI in M100 for MIC and disk. This reviewer agrees with the Quality Control published by the CLSI in M100 and that the published quality control values and isolates are referenced on the Agency's breakpoint website.

Disk Development

Disk development for gepotidacin was conducted according to CLSI M23 guidelines. To determine an appropriate gepotidacin disk concentration for disk diffusion, a preliminary study was conducted to narrow the range of disk content options for further study. A total of 50 isolates were tested using BMD and 5 disk concentrations (2 mcg, 5 mcg, 10 mcg, 15 mcg and 30 mcg) by the disk diffusion method. A disk concentration of 10 mcg was determined to be the most appropriate for disk diffusion testing of gepotidacin against the bacteria tested.

Effect of Culture Conditions

The effect of various testing parameters on BMD, agar dilution, and disk diffusion methods was assessed for gepotidacin against *E. coli* and some respiratory pathogens. The variables that were shown to impact gepotidacin MIC results by ≥2-dilutions for BMD were pH and high inoculum concentration, for all species tested. The addition of lung surfactant did not have a significant effect on gepotidacin in vitro activity. An additional study determined the effect of different concentrations of urine at varying pH levels on the in vitro activity of gepotidacin. Overall, the effect of urine on the gepotidacin and LVX MIC results was about 1- to 2-dilutions higher for certain strains.

Another study was conducted to determine the effect of testing parameters on the in vitro activity of gepotidacin against 65 Enterobacterales, 10 *S. saprophyticus* and 10 *E. faecalis*. The following variables were studied by BMD: temperature, incubation time, atmospheric conditions, inoculum concentration, pH, calcium, magnesium, zinc, potassium, urine, polysorbate 80, albumin, and serum. All quality control results were within recommended CLSI ranges. Gepotidacin mean MIC results from the reference BMD method varied by approximately 1-dilution over multiple days for all species tested. Day-to-day variation was eliminated in this study by performing reference and variable BMD MICs on the same day. Variables that were shown to impact gepotidacin MIC results the most for the Enterobacterales and gram-positive species tested were high inoculum concentration, pH, and urine.

Comparison of Agar Dilution to Broth Microdilution

In accordance with CLSI M23 guidelines, the equivalency of MIC values obtained by 2 reference antimicrobial susceptibility testing methods, agar dilution (AD) and BMD, were determined for gepotidacin against *E. coli, K. pneumoniae, K. aerogenes, E. cloacae* species complex, *P. mirablis, C. koseri, S. saprophyticus, E. faecalis, K. oxytoca, P. rettgeri, C. freundii, N. gonorrhoeae,* and other respiratory and skin pathogens. An essential agreement rate of >95% was obtained for *E. coli, K. pneumoniae, K. aerogenes, E. cloacae* species complex, *P. mirabilis*,

and *C. koseri*; however, for *N. gonorrhoeae, S. saprophyticus, E. faecalis, K. oxytoca, P. rettgeri,* and *C. freundii,* equivalency between the 2 methods was not established.

Equivalency of Dried Panels With CLSI Reference Methods

The Sensititre Dried Susceptibility plate technology was tested to determine the MIC values for gepotidacin in comparison with frozen plate reference method (CLSI M07). The 200 isolates tested included gram-positive, gram-negative, and fastidious bacteria. Testing for reproducibility used 10 isolates in triplicate on 3 separate days and testing of the standard ATCC quality control strains for BMD testing by both methodologies. Essential agreements for the 200 isolates and the reproducibility isolates were calculated using the +/-1 log2 dilution standard for comparison studies. The essential agreement rates for testing of the 200 isolates and for reproducibility testing were both >99%.

19.3.1. Antibacterial Interactions

The potential interactions between gepotidacin and other agents (e.g., synergy, antagonism, indifference) were investigated by the Applicant through in vitro fractional inhibitory concentrations studies. Potential interactions were also investigated by time-kill kinetic analysis of the antibacterial agents in combination. Fractional inhibitory concentration was evaluated using a checkerboard panel in which the combination agents are tested alone or together at varying concentrations and no instances of antagonism were noted. The most common interaction was indifference (82.6%). All other interactions, except one, were not determinable due to the presence of resistance to comparator agents with off-scale MIC results. Synergy was noted in the in vitro checkerboard test for the combination of gepotidacin and moxifloxacin against one *N. gonorrhoeae* strain, however, this was not confirmed in an in vitro time kill study.

Clinical isolates of *Citrobacter* species, *E. cloacae* complex, *E. coli, K. aerogenes, K. pneumoniae, P. mirabilis, P. rettgeri, E. faecalis*, and *S. saprophyticus* (five isolates each) were also tested by the Applicant using BMD checkerboard assays of gepotidacin in combination with eight other antibacterial agents. Of 360 organisms/combinations tested, synergy was demonstrated in 25 (6.9%) organism/combinations. For Enterobacterales, the greatest number of synergistic combinations with gepotidacin were observed with the beta-lactams MEM (14.3%), CAZ (14.3%), and ATM (11.4%). Synergy was observed at least once for each gram-negative species. Examples include *E. cloacae* (12.5%), *P. rettgeri* (12.5%), *Citrobacter species* (7.5%), and *P. mirabilis* (7.5%). For other species tested, synergy was reported in 1-2 organism/combinations tested. The synergistic activity between gepotidacin and vancomycin (VAN) against *S. saprophyticus* was confirmed by time kill at 1 × MIC concentrations of the drugs.

Reviewer's Comments

In cross resistance studies, the most common interaction observed in the organism/combinations tested was indifference. No instances of antagonism were observed by the Applicant for the gepotidacin and comparator combinations tested.

19.4. Activity In Vivo (Animal Studies)

19.4.1. Proof of Concept

Gepotidacin has been tested by the Applicant for in vivo efficacy against *E. coli, K. pneumoniae, S. pneumoniae, H. influenzae, S. aureus, N. gonorrhoeae, Y. pestis, F. tularensis*, and *B. anthracis* in various animal models. Not all these models are relevant to the indication of uUTI. Pyelonephritis studies were done with uropathogens through the injection of log-phase *E. coli* directly into both kidneys via nonsurgical palpation of the organ. Treatment with gepotidacin was administered 1 to 2 hours post-infection. In the rat pyelonephritis model, gepotidacin at ≥50 mg/kg demonstrated >2-log10 reduction in kidney or bladder CFUs compared with baseline controls. The pyelonephritis model was also used by the Applicant to establish humanized dosing of gepotidacin and LVX against MDR *E. coli* isolates. Refer to the table below.

Table 191. Summary of Gepotidacin (MIC 2 to 4 mcg/mL) and LVX (MICs 16 to 32 mcg/mL) Efficacy Using Humanized Exposure Profiles Against 4 MDR *E. coli* (LVX-R ST-131 and NDM-1 Producing Isolates) Using a Pyelonephritis Model in Cannulated Rates

Targeted Human Oral Doses	Mean log10 change in CFU vs 2 h baseline controls in kidneys (mean CFU in 2 h controls were 5.0 to 6.5 log10 CFU/kidneys)			
	E. coli NCTC 13441 (GEP MIC = 4 µg/mL)	*E. coli* 5649 (GEP MIC = 2 µg/mL)	*E. coli* IR5 (GEP MIC = 4 µg/mL)	*E. coli* ALL (GEP MIC = 4 µg/mL)
GEP 800 mg q12h	-4.9**	-3.3**	-2.9**	-2.4**
GEP 1500 mg q12h	-4.9**	-3.6**	-4.3**	-2.9**
LVX 500 mg q24h	-0.7NS	-0.1NS	-0.4NS	+0.2

Source: m5.3.5.4, GSK Study Report 2016N299037
**Significant reduction in CFU compared with 2 h baseline controls ($p \leq 0.01$)
NS = CFU not significantly reduced compared with 2 h baseline controls

Abbreviations: CFU, colony forming units; GEP, gepotidacin; LVX, levofloxacin; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; NDM-1, New Delhi metallo-β-lactamase-1 enzyme

Reviewer's Comments

These data show proof of concept of the efficacy of gepotidacin against uropathogenic E. coli in a UTI model (pyelonephritis in rats), including against drug-resistant strains.

19.4.2. In Vivo PK-PD Studies With Uropathogens

The PK-PD properties of gepotidacin were characterized by the Applicant against 17 *E. coli* and 7 *K. pneumoniae* strains, including those resistant to existing antibacterial agents using a thigh infection model in neutropenic mice and a kidney infection model in immunocompetent and neutropenic mice. The statistics of *f*AUC/MIC required for gepotidacin to achieve stasis, 1 log10 or 2 log 10 reductions in bacterial burden compared to baseline were provided. See clinical pharmacology review for further evaluation of PK-PD targets. The Applicant's data are summarized in the table below:

Table 192. Summary of Statistics of fAUC/MIC Required for Gepotidacin to Achieve Stasis, 1 log10 or 2 log10 Reductions in Bacterial Burden Compared With Baseline Against all Strains Combined (17 *E. coli* and 7 *K. pneumoniae*), Representing General Enterobacterales PK/PD Targets, as Studied in a Thigh Infection Model in Neutropenic Mice

	fAUC/MIC ratios		
	Stasis	1 log10 reduction	2 log10 reduction
Summary statistics including all strains			
Mean ± SD	5.6 ± 6.7	11 ± 10	20 ± 16
50th percentile (Median)	2.9	6.2	14
75th percentile	7.3	18	32
Range (Min – Max)	0 – 23	0.8 – 37	2.1 - 63
Subset analysis excluding strains with <1 log10 of growth[a]			
Mean ± SD	7.0 ± 7.1	12 ± 11	22 ± 17
50th percentile (Median)	4.2	8.1	15
75th percentile	11	20	38
Range (Min – Max)	0.6 – 23	1.4 – 37	2.9 – 63
Summary using 1 log10 reduction endpoint for strains with ≥1 log10 of growth and 2 log10 reduction endpoint for strains with <1 log10 of growth[a]			
Mean ± SD	13 ± 11		
50th percentile (Median)	10		
75th percentile	18		
Range (Min – Max)	1.4 – 37		

Source: m5.3.5.4, GSK Study Report 2021N489444
a. See Table 108 and Table 109 for strain growth

Abbreviations: fAUC/MIC, area under the free-drug concentration-time curve to minimum inhibitory concentration ratio; max, maximum; min, minimum; PK/PD, pharmacokinetic-pharmacodynamic; SD, standard deviation

19.5. Pharmacokinetics/Pharmacodynamics

In summary, *f*AUC/MIC is the primary PK-PD index predictive of gepotidacin efficacy. The PK-PD data provided by the Applicant was deemed not sufficient to inform breakpoints for gepotidacin. Please refer to the clinical pharmacology review for additional information.

19.6. Clinical Microbiology Analysis of Efficacy

Study EAGLE-2 and Study EAGLE-3 were phase 3 studies with 4 visits over a 28-day period: Screening and Randomization (Day 1), OT (Days 2 through 4), TOC (Days 10 through 13) and follow-up (FU) (Day 28 ±3). Subjects provided a urine sample for bacteriology at every visit. The primary endpoint was composite response (combined subject-level clinical and microbiological response) at TOC.

19.6.1. Microbiology Procedures

Microbiology procedures and analyses were performed at the investigator sites and the central laboratory (b) (4) in Study EAGLE-2 and Study EAGLE-3. Molecular analyses, nitrofurantoin BMD and fosfomycin AD testing were performed at a third-party laboratory (b) (4)

Isolates were identified to the genus and species level by Matrix-assisted Laser Desorption/ionization Time-of-Flight mass-spectrometer. Antimicrobial susceptibility testing (AST) was conducted by BMD using custom dried microdilution panels (b) (4) and by disk diffusion according to CLSI procedures. Gepotidacin disk diffusion was performed using disks from two different manufacturers (b) (4) A gepotidacin gradient strip (b) (4) was also conducted as part of AST. All uropathogens

were stored at the central laboratory. Confirmatory nitrofurantoin susceptibility testing was not performed on uropathogens that were intrinsically resistant to nitrofurantoin (e.g., *P. mirabilis*).

The Applicant described that based on specific resistant phenotypes, selected uropathogens underwent genetic characterization, including whole-genome sequencing to screen for antibacterial resistance markers such as beta-lactamase genes (extended-spectrum beta-lactamases), mutations in the QRDR regions of *gyrA* and *gyrB*, and *parC* and *parE*, and the presence of PMQR genes. Selected *E. coli* uropathogens were evaluated for multilocus sequence typing (MLST) or pulsed-field gel electrophoresis (PFGE), and O:H serotyping. The ST131 isolates, were also tested for *fimH*. *E. coli* uropathogens with gepotidacin MICs of ≥8 mcg/mL were selected for screening of QRDR, PMQR genes, expression of *acrAB* and MLST. Participants with uropathogens that were microbiological failures were evaluated for MLST or PFGE.

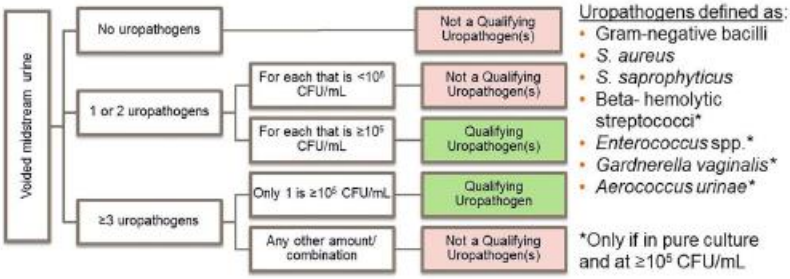
Reviewer's Comments

ST131, or sequence type 131, is an E. coli clonal group, that is predominant among extraintestinal pathogenic E. coli isolates worldwide and commonly produces ESBLs and is fluoroquinolone resistant.

19.6.2. Microbiology Analysis in Clinical Studies

The algorithm for determining qualifying uropathogens based on microbiology laboratory quantitative culture results is provided in Figure 25 below.

Figure 25. Baseline Algorithm for Determining Qualifying Uropathogens



For the 204989 and 212390 studies, only the following uropathogen species/groups were considered for inclusion in the microbiological populations: gram-negative bacilli (e.g., *E. coli*, *K. pneumoniae*, *P. mirabilis*), *S. saprophyticus*, and *Enterococcus* spp.

Abbreviation: CFU, colony forming units

Efficacy Analysis and Endpoints

Exploratory Efficacy Endpoints Specific to Microbiology Provided by the Applicant Included:

Gram stain, quantitative bacteriology culture, and in vitro AST results at Baseline, OT, TOC, and FU

Therapeutic response, clinical outcome and response, and microbiological outcome and response by uropathogen at TOC and FU

Microbiological outcome by uropathogen at OT

Clinical outcome by uropathogen at OT

Genetic relatedness of qualifying uropathogens from microbiological failures

Reduced susceptibility of uropathogens

Microbiological outcome based on new qualifying uropathogens

Subgroup analyses for efficacy as they related to microbiology were performed, including:

- Participant infection category (phenotypic categories)

ESBL+ infection (any baseline qualifying uropathogen is ESBL+)

Non-ESBL infection (no baseline qualifying uropathogen is ESBL+)

FQ-R infection (any baseline qualifying uropathogen is FQ-R)

FQ-S infection (all qualifying baseline qualifying uropathogen are FQ-S)

Qualifying uropathogen species/group isolated at baseline, including phenotypic genotypic subcategories

Characterization of Uropathogens From Clinical Studies

The following sections present baseline microbiology data at the uropathogen level for pooled Study EAGLE-2 and Study EAGLE-3.

Reviewer's Comments

P. mirabilis is intrinsically resistant to nitrofurantoin, the comparator used in clinical studies discussed here. As a result, this organism was not included in the efficacy population, which required susceptibility to nitrofurantoin.

Gram Stain and Culture

The most common bacterial morphology observed was gram-negative bacilli.

The most prevalent qualifying uropathogens in the micro-ITT Population were *E. coli*, followed by *K. pneumoniae* and *P. mirabilis* and were observed at similar percentages in both treatment groups. A summary of baseline qualifying uropathogens is below:

Table 193. Summary of Baseline Qualifying Uropathogens in the Micro-ITT NTF-S Population in Pooled Study EAGLE-2 and Study EAGLE-3

Qualifying uropathogen/phenotypic or genotypic subcategory	Number of isolates (n=)	Gepotidacin (n/%)	Nitrofurantoin (n/%)
All qualifying uropathogens	1225	642	583
Gram-negative organisms			
E. coli	1097	573 (89%)	524 (90%)
Non-ESBL	948	489 (85%)	459 (88%)
ESBL+	149	84 (15%)	65 (12%)
FQ-S	773	395 (69%)	378 (72%)
FQ-R	294	166 (29%)	128 (24%)
SXT-R	295	161 (28%)	134 (26%)
MDR	288	161 (28%)	127 (24%)
GEN-R	96	50 (9%)	46 (9%)
AMC-R	45	29 (5%)	16 (3%)
AMP-R	510	273 (48%)	237 (45%)
CFZ-R	170	97 (17%)	73 (14%)
CRO-R	135	75 (13%)	60 (11%)
FOF-R	9	5 (1%)	4 (1%)
MEC-R	25	13 (2%)	12 (2%)
TZP-R	20	12 (2%)	8 (2%)
FOS-R and ESBL+	5	3 (1%)	2 (<1%)
FQ-R and ESBL+	103	61 (11%)	42 (8%)
FQ-R and ESBL+ and SXT-R	54	31 (5%)	23 (4%)
FQ-R and SXT-R	131	71 (12%)	60 (11%)
SXT-R and ESBL+	78	47 (8%)	31 (6%)
Beta-lactamase gene-positive	167	92 (16%)	75 (14%)
Narrow spectrum beta-lactamases	57	34 (6%)	23 (4%)
EC-5	17	11 (2%)	6 (1%)
TEM-1	34	20 (3%)	14 (3%)
ESBLs	134	76 (13%)	58 (11%)
CTX-M-15	37	23 (4%)	14 (3%)
CTX-M-15, OXA-1_OXA-30	30	17 (3%)	13 (2%)
CTX-M-27	43	24 (4%)	19 (4%)
Extended spectrum AmpC	92	54 (9%)	38 (7%)
EC-6	72	45 (8%)	27 (5%)
EC-6-like	17	7 (1%)	10 (2%)
Uncategorized spectrum beta-lactamases	54	26 (5%)	28 (5%)
QRDR mutations	305	170 (30%)	135 (26%)
GyrA mutations	305	170 (30%)	135 (26%)
GyrA S83L	27	16 (3%)	11 (2%)
GyrA S83L, D87N	275	153 (27%)	122 (23%)
ParC mutations	285	160 (28%)	125 (24%)
ParC S80I	168	92 (16%)	76 (15%)
ParC S80I, E84V	108	62 (11%)	46 (9%)
ParE mutations	95	50 (9%)	45 (9%)
ParE L416F	95	50 (9%)	45 (9%)
PMQR gene-positive	77	47 (8%)	30 (6%)

Qualifying uropathogen/phenotypic or genotypic subcategory	Number of isolates (n=)	Gepotidacin (n/%)	Nitrofurantoin (n/%)
aac(6')-Ib-cr	34	20 (3%)	14 (3%)
qnrB19	11	5 (<1%)	6 (1%)
qnrS1	16	11 (2%)	5 (1%)
K. pneumoniae	32	15 (2%)	17 (3%)
Non-ESBL	27	13 (87%)	14 (82%)
ESBL+	5	2 (13%)	3 (18%)
FQ-S	23	12 (80%)	11 (65%)
FQ-R	8	2 (13%)	6 (35%)
CFZ-R	5	2 (13%)	3 (18%)
SXT-R	7	4 (27%)	3 (18%)
MDR	7	3 (20%)	4 (24%)
FQ-R and ESBL+	5	2 (13%)	3 (18%)
FQ-R and ESBL+ and SXT-R	1	0 (0%)	1 (6%)
FQ-R and SXT-R	1	0 (0%)	1 (6%)
SXT-R and ESBL+	1	0 (0%)	1 (6%)
Beta-lactamase gene-positive	5	2 (13%)	3 (18%)
Narrow spectrum beta-lactamases	5	2 (13%)	3 (18%)
PMQR gene-positive	9	3 (20%)	6 (35%)
Other *Klebsiella* spp.[a]	14	7 (1%)	7 (1%)
E. cloacae complex	5	1 (<1%)	4 (<1%)
MDR	5	1 (100%)	4 (100%)
C. freundii complex	17	12 (2%)	5 (<1%)
FQ-S	16	11 (92%)	5 (100%)
Other *Citrobacter* spp.[b]	9	4 (<1%)	5 (<1%)
Gram-positive organisms			
S. saprophyticus	29	15 (2%)	14 (2%)
E. faecalis	21	14 (2%)	7 (1%)
E. faecium	1	1 (<1%)	0 (0%)

Source: PDAP Table 1.0730; PDAP Table 1.0820; PDAP post-hoc Table 92.02302; PDAP post-hoc Table 92.02305; PDAP post-hoc Table 92.02308

Note: Percentage of each baseline qualifying uropathogen/uropathogen group was calculated using the number of all qualifying uropathogens at Baseline within the treatment group as the denominator. Percentage of each phenotypic or genotypic subcategory was calculated using the number of each respective Baseline qualifying uropathogen as the denominator.

a. other *Klebsiella* species (n=14): 8 *K. oxytoca*/*R. omithinolytica*, 5 *K. aerogenes*, 1 *K. variicola*
b. other *Citrobacter* species (n=9): 7 *C. koseri*, 2 *C. amalonaticus* group

Abbreviations: AMC-R, amoxicillin-clavulanic acid-resistant; AMP-R, ampicillin-resistant; CFZ-R, ceftazidime-resistant; CRO-R, ceftriaxone-resistant; ESBL, extended-spectrum beta-lactamase; FOF-R, fosfomycin-resistant; FQ-R, fluoroquinolone-resistance; FQ-S, fluoroquinolone-susceptible; MDR, multidrug-resistant; MEC-R, mecillinam-resistant; micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; PMQR, plasmid-mediated quinolone resistance genes; SXT-R, trimethoprim-sulfamethoxazole-resistant; TZP-R, piperacillin tazobactam-resistant

Polymicrobial Infections

In the micro-ITT Population, there were 41 (5%) subjects in Study EAGLE-2 and 24 (4%) in Study EAGLE-3 with 2 baseline qualifying uropathogens, some of which were of the same genus and species (e.g., 2 morphologically different *E. coli*), recovered from urine cultures. The percentages of these polymicrobial infections were similar across treatment groups.

Susceptibility to Gepotidacin and Comparators

Gepotidacin activity for genotypic subcategories of baseline *E. coli* and *K. pneumoniae* isolates in the micro-ITT population from the pooled studies EAGLE-2 and EAGLE-3 are shown in the table below.

Table 194. Gepotidacin Activity for Genotypic Subcategories of Baseline *E. coli* (n=1159) and *K. pneumoniae* (n=114) Isolates From Both Treatment Groups in the Micro-ITT Population From Pooled Study EAGLE-2 and Study EAGLE-3

Uropathogen/Genotypic subcategory	Number of isolates (n=)	Gepotidacin MIC (µg/mL)			
		min	max	MIC50	MIC90
E. coli	1159	≤0.03	32	1	4
Narrow spectrum beta-lactamases	66	0.5	16	1	4
TEM-1	43	0.5	16	1	4
ESBLs	155	0.12	16	2	4
CTX-M-15	42	0.25	16	2	8
CTX-M-15, OXA-1_OXA-30	40	0.5	16	2	2
CTX-M-27	44	0.12	8	2	4
Extended-spectrum AmpC	105	0.5	16	2	4
EC-6	84	0.5	8	2	4
Uncategorized spectrum beta-lactamases	63	0.25	16	2	8
QRDR mutations	342	≤0.03	16	1	4
GyrA mutations	342	≤0.03	16	1	4
GyrA S83L	29	0.5	16	2	4
GyrA S83L, D87N	310	≤0.03	16	1	4
ParC mutations	320	≤0.03	16	1	4
ParC S80I	186	≤0.03	16	1	2
ParC S80I, E84V	124	0.5	8	2	4
ParE mutations	98	≤0.03	4	0.5	1
ParE L416F	98	≤0.03	4	0.5	1
PMQR gene-positive	95	0.5	32	2	8
aac(6')-Ib-cr	47	0.5	4	2	4
K. pneumoniae	114	1	32	4	16
PMQR gene-positive	25	2	32	8	32

Source: PDAP Table 2.2220
Note: n=number of uropathogens with non-missing MIC values

Abbreviations: ESBL, extended-spectrum beta-lactamase; MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; PMQR, plasmid-mediated quinolone resistance genes

The most prevalent MLST for *E. coli* reported by the Applicant was ST131 and ST1193 in the micro-ITT and ITT Populations and the most prevalent O:H type in both populations was O25b:H4. Similar percentages of ST131, ST1193, and O25b:H4 were identified in both treatment groups in the micro-ITT and ITT Population for the subset of *E. coli* that were characterized by the Applicant.

Table 195. Gepotidacin Activity for Specific MLST, O:H Types and *fimH* Alleles of Baseline *E. coli* Isolates From Both Treatment Groups in the Micro-ITT Population From Pooled Study EAGLE-2 and Study EAGLE-3

Epidemiological type	Number of isolates (n=)	Gepotidacin MIC (µg/mL)			
		min	max	MIC50	MIC90
ST131	111	0.5	8	2	4
ST1193	53	≤0.03	4	0.5	1
ST10	24	0.25	16	1	4
ST69	30	0.5	8	1	2
ST73	36	0.5	4	2	4
ST95	24	1	4	1	2
O25b:H4	76	0.5	8	2	4
fimH 30	72	0.5	8	2	4

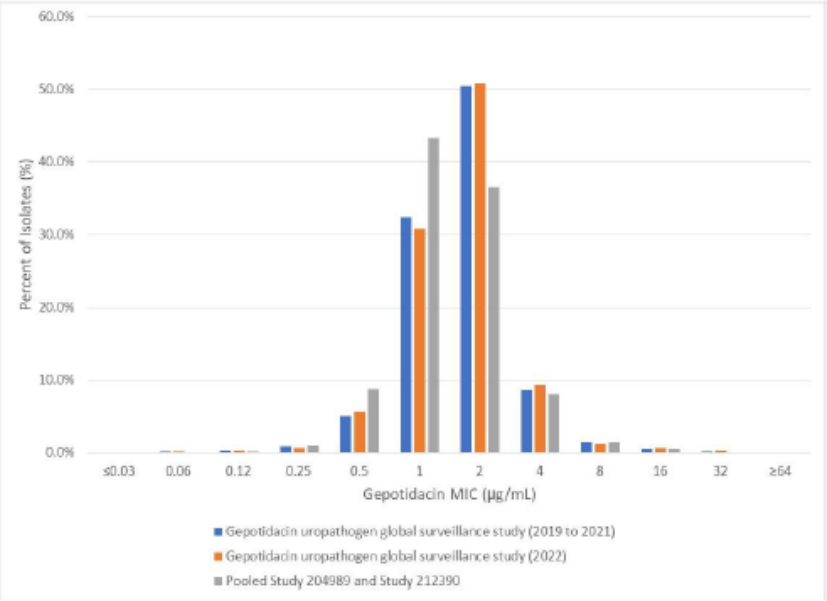
Source: PDAP Table 2.2220
Note: n=number of uropathogens with non-missing MIC values

Abbreviations: MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; max, maximum; min, minimum

The following figures show the MIC frequency distribution histograms of isolates (*E. coli*, *K. pneumoniae*, and *S. saprophyticus*) from global surveillance studies compared with baseline isolates from both treatment groups in the micro-ITT population from pooled studies EAGLE-2 and EAGLE-3.

Figure 26. Gepotidacin MIC Frequency Distribution Histograms for *E. coli* Isolates From the 2019 to 2021 and 2022 Gepotidacin Uropathogen Global Surveillance Studies Compared With Baseline

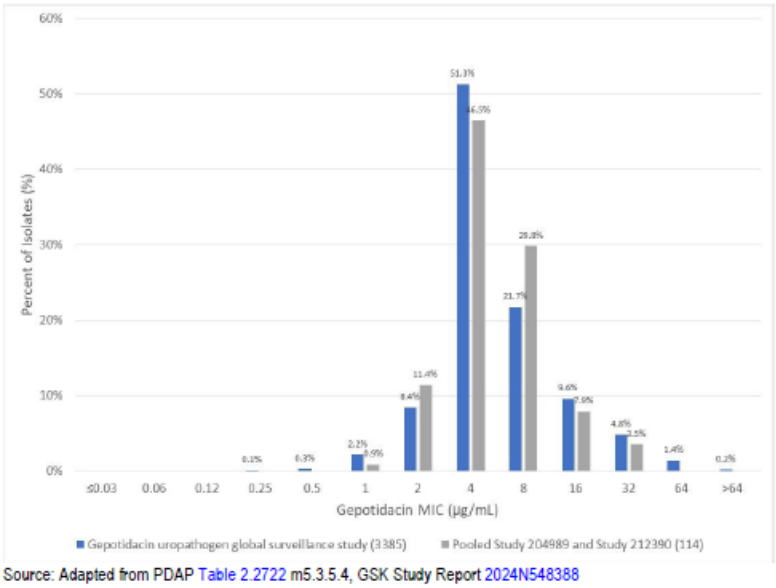
***E. coli* Isolates From Both Treatment Groups in the Micro-ITT Population From Pooled Study EAGLE-2 and Study EAGLE-3**



Source: Adaped from PDAP Table 2.2720; m5.3.5.4, GSK Study Report 2022N507182; m5.3.5.4, GSK Study Report 2023N545082

Abbreviation: MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat

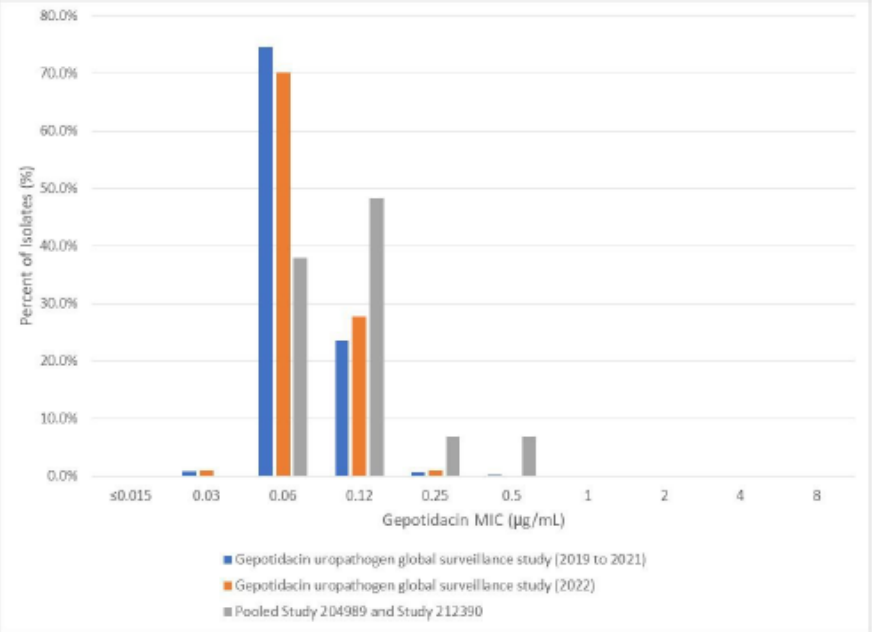
Figure 27. Gepotidacin MIC Frequency Distribution Histogram Against *K. pneumoniae* Isolates From the 2019 to 2022 Gepotidacin Uropathogen Global Surveillance Study Compared With Baseline *K. pneumoniae* Isolates From Both Treatment Groups in the Micro-ITT Population From Pooled Study EAGLE-2 and Study EAGLE-3



Source: Adapted from PDAP Table 2.2722 m5.3.5.4, GSK Study Report 2024N548388

Abbreviations: MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat

Figure 28. Gepotidacin MIC Frequency Distribution Histogram for *S. saprophyticus* From 2019 to 2021 and 2022 Gepotidacin Uropathogen Global Surveillance Studies Compared With Baseline *S. saprophyticus* Isolates From Both Treatment Groups in the Micro-ITT Population From Pooled Study EAGLE-2 and Study EAGLE-3



Abbreviations: MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat

Composite, Clinical, and Microbiological Response by Uropathogen and Genotype

Only uropathogens that met pre-specified phenotypic screening criteria had additional molecular characterization by the Applicant to determine resistance mechanisms and epidemiological typing. The table below shows the therapeutic, clinical, and microbiological success at TOC in the micro-ITT nitrofurantoin susceptible (NTF-S) population of pooled phase 3 Studies EAGLE-2 and EAGLE-3 by uropathogen and genotype.

Table 196. Composite Response, and Clinical, and Microbiological Success at TOC by Uropathogen and Genotype for Pooled Study EAGLE-2 and Study EAGLE-3 (Micro-ITT NTF-S Population)

Baseline qualifying uropathogen Genotype	Clinical success (participant-level)		Microbiological success (uropathogen-level)		Therapeutic success (participant-level)	
	GEP n/N1 (%) N=628	NTF n/N1 (%) N=573	GEP n/N1 (%) N=628	NTF n/N1 (%) N=573	GEP n/N1 (%) N=628	NTF n/N1 (%) N=573
E. coli	387/566 (68.4)	337/520 (64.8)	412/573 (71.9)	322/524 (61.5)	312/566 (55.1)	234/520 (45.0)
Beta-lactamase gene-positive	65/92 (70.7)	45/75 (60.0)	57/92 (62.0)	46/75 (61.3)	50/92 (54.3)	31/75 (41.3)
Narrow spectrum beta-lactamases	24/34 (70.6)	14/23 (60.9)	20/34 (58.8)	12/23 (52.2)	19/34 (55.9)	8/23 (34.8)
EC-5	11/11 (100)	6/6 (100)	10/11 (90.9)	3/6 (50.0)	10/11 (90.9)	3/6 (50.0)
TEM-1	11/20 (55.0)	6/14 (42.9)	9/20 (45.0)	6/14 (42.9)	8/20 (40.0)	3/14 (21.4)
ESBLs	53/76 (69.7)	29/58 (50.0)	48/76 (63.2)	33/58 (56.9)	41/76 (53.9)	19/58 (32.8)
CTX-M-15	14/23 (60.9)	9/14 (64.3)	15/23 (65.2)	10/14 (71.4)	11/23 (47.8)	8/14 (57.1)
CTX-M-15, OXA-1_OXA-30	12/17 (70.6)	3/13 (23.1)	9/17 (52.9)	7/13 (53.8)	8/17 (47.1)	3/13 (23.1)
CTX-M-27	19/24 (79.2)	12/19 (63.2)	17/24 (70.8)	12/19 (63.2)	16/24 (66.7)	7/19 (36.8)
Extended-spectrum AmpCs	36/54 (66.7)	20/38 (52.6)	32/54 (59.3)	23/38 (60.5)	27/54 (50.0)	14/38 (36.8)
EC-6	32/45 (71.1)	12/27 (44.4)	28/45 (62.2)	16/27 (59.3)	25/45 (55.6)	9/27 (33.3)
EC-6-like	3/7 (42.9)	7/10 (70.0)	3/7 (42.9)	6/10 (60.0)	2/7 (28.6)	4/10 (40.0)
Uncategorized spectrum beta-lactamases	18/26 (69.2)	16/28 (57.1)	15/26 (57.7)	17/28 (60.7)	13/26 (50.0)	11/28 (39.3)
QRDR mutations	116/165 (70.3)	84/134 (62.7)	110/170 (64.7)	74/135 (54.8)	82/165 (49.7)	53/134 (39.6)
GyrA mutations	116/165 (70.3)	84/134 (62.7)	110/170 (64.7)	74/135 (54.8)	82/165 (49.7)	53/134 (39.6)
GyrA S83L	14/16 (87.5)	8/11 (72.7)	10/16 (62.5)	5/11 (45.5)	10/16 (62.5)	5/11 (45.5)
GyrA S83L, D87N	102/149 (68.5)	75/122 (61.5)	99/153 (64.7)	67/122 (54.9)	71/149 (47.7)	46/122 (37.7)
ParC mutations	108/155 (69.7)	77/125 (61.6)	105/160 (65.6)	69/125 (55.2)	77/155 (49.7)	48/125 (38.4)
ParC S80I	64/89 (71.9)	54/76 (71.1)	61/92 (66.3)	40/76 (52.6)	43/89 (48.3)	32/76 (42.1)
ParC S80I, E84V	40/61 (65.6)	23/46 (50.0)	40/62 (64.5)	29/46 (63.0)	30/61 (49.2)	16/46 (34.8)
ParE mutations	34/49 (69.4)	33/45 (73.3)	33/50 (66.0)	20/45 (44.4)	23/49 (46.9)	17/45 (37.8)
ParE L416F	34/49 (69.4)	33/45 (73.3)	33/50 (66.0)	20/45 (44.4)	23/49 (46.9)	17/45 (37.8)
PMQR gene-positive	33/46 (71.7)	11/30 (36.7)	29/47 (61.7)	13/30 (43.3)	25/46 (54.3)	5/30 (16.7)
aac(6')-Ib-cr	12/19 (63.2)	4/14 (28.6)	12/20 (60.0)	7/14 (50.0)	9/19 (47.4)	3/14 (21.4)
qnrS1	9/11 (81.8)	4/5 (80.0)	9/11 (81.8)	3/5 (60.0)	8/11 (72.7)	2/5 (40.0)
ST10	6/11 (54.5)	8/13 (61.5)	5/11 (45.5)	4/13 (30.8)	3/11 (27.3)	3/13 (23.1)
ST1193	18/25 (72.0)	18/26 (69.2)	13/25 (52.0)	5/26 (19.2)	11/25 (44.0)	4/26 (15.4)
ST127	3/4 (75.0)	5/10 (50.0)	2/4 (50.0)	3/10 (30.0)	2/4 (50.0)	2/10 (20.0)
ST131	35/53 (66.0)	20/43 (46.5)	32/54 (59.3)	18/43 (41.9)	26/53 (49.1)	11/43 (25.6)
ST69	9/11 (81.8)	16/19 (84.2)	5/11 (45.5)	9/19 (47.4)	4/11 (36.4)	8/19 (42.1)
ST73	14/18 (77.8)	13/18 (72.2)	12/18 (66.7)	8/18 (44.4)	9/18 (50.0)	6/18 (33.3)
ST95	6/10 (60.0)	9/14 (64.3)	5/10 (50.0)	6/14 (42.9)	3/10 (30.0)	3/14 (21.4)
O25b:H4	26/38 (68.4)	12/26 (46.2)	23/38 (60.5)	16/26 (61.5)	20/38 (52.6)	9/26 (34.6)
H30	23/43 (67.6)	12/26 (46.2)	20/34 (58.8)	16/26 (61.5)	18/34 (52.9)	9/26 (34.6)

Source: PDAP Table 2.1120; PDAP Table 2.1720; PDAP Table 2.0420

Note: For clinical and therapeutic response, a participant is counted once under a uropathogen category if multiple qualifying uropathogens within that category are isolated at Baseline for the participant. Participants who do not eradicate all pathogens and symptoms are considered therapeutic failures for all pathogens. For microbiological response, a participant is counted more than once under a uropathogen category if multiple qualifying uropathogens within that category are isolated at Baseline for the Participant. n/N1 = (n) the number of participants within the category with a response of success / (N1) the total number of participants within the category and is the denominator for corresponding percentages. The 'N' in the header represents the total number of participants in the treatment group. Only phenotypic subgroups with ≥10 participants in either treatment group based on pooled Study 204989 and Study 212390 data are presented.

Abbreviations: ESBL, extended-spectrum beta-lactamase; GEP, gepotidacin; micro-ITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; PMQR, plasmid-mediated quinolone resistance genes

Composite, Clinical, and Microbiological Response by Uropathogen and Demographic Subgroup

In the micro-ITT population, composite response, clinical, and microbiological success rates at TOC were higher in the gepotidacin treatment group in comparison to the nitrofurantoin treatment group (data not shown). The success rates were generally consistent across demographic subgroups for subjects with *E. coli*, *K. pneumoniae*, and *E. faecalis*. For *S. saprophyticus*, composite response, and clinical, and microbiological success rates at TOC were lower in the gepotidacin treatment group in comparison to the nitrofurantoin treatment group but were generally consistent within the gepotidacin treatment group across all demographic subgroups. Numbers of subjects in some of the subgroups were too small to make definitive conclusions. Among *E. coli* isolates with two qualifying uropathogens in the micro-ITT NTF-S population, 66.7% had composite response success, and among *E. coli* isolates with recurrent infection, 67.9% had microbiological success.

In the micro-ITT Population for subjects with *E. coli*, therapeutic success rates were higher in subjects with non-recurrent infections versus recurrent infections, by approximately 10% for both treatment groups, and isolates from the Europe subgroup had the highest overall composite response success rate among regions (data not shown). Among subjects with *K. pneumoniae*, higher composite response success was also seen in non-recurrent infections compared to recurrent infections. Among regions of the United States, microbiological success rates for *E. coli* at TOC in the micro-ITT NTF-S population were 73.3% in the Midwest region, 94.4% in the Northeast region, 73.5% in the South region, and 66.1% in the West region (gepotidacin arm).

Genetic Relatedness of Qualifying Uropathogens From Microbiological Failures

The Applicant used genetic relatedness to determine if isolates from microbiological failures were the same as baseline isolates, however based on precedence from other recent approvals of antibacterial drugs for uUTI, relatedness by methods such as MLST and PFGE will not be accepted. The reason for this approach is that *E. coli* are known to have rearrangements of their genetic material and form hetero-resistance populations. Clinical microbiology analyzed a subset of the isolates identified during clinical studies that had a ≥4-fold increase in MIC to gepotidacin on therapy and were microbiological failures at the TOC visit. Refer also to the statistical review for additional information. Some of these isolates had plasmid mediated fluoroquinolone-resistance genes (*qnrS*) or mutations in target proteins (GyrA D87N, S83L:ParC S80L).

Analysis of Reduced Susceptibility of Uropathogens

Overall, for pooled Study EAGLE-2 and Study EAGLE-3, the most common baseline qualifying uropathogen detected was *E. coli* (78%). The Applicant reported that among 1159 baseline *E. coli* isolates, 28% were FQ-R, 28% were SXT-R, 15% were ESBL+, and 28% were MDR. The most prevalent ESBL genotypes among the baseline *E. coli* isolates that met phenotypic criteria for molecular testing were CTX-M-15, CTX-M-15_OXA-1_OXA-30, and CTX-M-27. The most prevalent QRDR mutations were GyrA S83L D87N, ParC S80I and ParC S80I E84V. In the micro-ITT Population, the most prevalent MLSTs for *E. coli* were ST131 and ST1193 in both studies and the most prevalent O:H type was O25b:H4. Other common baseline qualifying uropathogens detected in the micro-ITT Population from pooled Study EAGLE-2 and Study EAGLE-3 for both treatment groups combined, were *K. pneumoniae* (8%), *P. mirabilis* (5%) *C. freundii* complex (1.3%), *S. saprophyticus* (2%), and *E. faecalis* (1.4%). Gepotidacin was active in vitro against the uropathogen species with MIC90s ranging from 0.25 to 16 mcg/mL. Isolates with ≥4-fold increase in gepotidacin MIC were identified and characterized for genotypic and phenotypic characteristics. Please also see the statistical review for additional information.

19.7. Susceptibility Test Interpretive Criteria

The Applicant's proposed MIC and zone diameter breakpoints and interpretive categories were developed in accordance with CLSI M23 guidance and are shown in the table below. The Applicant's breakpoints and interpretive criteria were based on an analysis of epidemiological cutoff values (ECVs), nonclinical PK-PD cutoff values, clinical-exposure response (CER) cutoffs, and clinical cutoffs. For ECVs, ECOFFFinder_XL_2010_v2.0-xlsm, an Excel-based software was used. The MIC distribution was from at least 100 isolates and 6 laboratories.

Table 197. Applicant's Gepotidacin Clinical MIC Breakpoint Proposal

Uropathogen	ECV (µg/mL)		Nonclinical PK/PD cutoff (µg/mL)	Clinical cutoff (µg/mL)	Proposed clinical MIC breakpoints (µg/mL)		
	97.5%	99.0%			S	I	R
Enterobacterales	ND	ND	≤32	≤16	≤16	32	≥64
E. coli	8	16	≤32	≤16			
K. pneumoniae	32	128	≤32	≤16			
P. mirabilis	32	128	≤32	≤16			
C. freundii complex	32	128	≤32	≤8			
S. saprophyticus	0.25	0.25	≤8	≤0.25	≤0.25	-	-
E. faecalis	8	16	ND	≤4	≤4	-	-

ND=not determined
ECVs are showin in Section 9.1.1, nonclinical PK/PD cutoffs in Section 9.1.2.4 and clinical cutoffs in Section 9.1.3.3

Source: This submission.
Abbreviations: ECV, epidemiologic cutoff values; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic–pharmacodynamic

Reviewer's Comments

The Applicant's proposed ECVs trended higher than what was seen in global surveillance studies, but the cause of this difference was unknown. Also, the Applicant's proposed breakpoints split the Applicant's identified wild-type populations. For reasons described in the information request to the Applicant below (1/2025), the FDA clinical microbiology reviewer used the combined clinical study data and surveillance data for analysis of ECVs and requested further explanation from the Applicant:

"The proposed MIC breakpoints for gepotidacin fall within the proposed wild-type population according to the stated epidemiological cutoff values (ECVs) and may lead to issues with MIC interpretation and testing. For example, the susceptible breakpoint for K. pneumoniae is ≤ 16 mcg/mL while the ECV is 32 mcg/mL at 97.5%. Additionally, table 40 of the Special Studies Microbiology document, shows K. pneumoniae isolates with potential resistance factors at MIC90s of ≥16 mcg/mL, while those that were ESBL screen negative and FQ MIC screen negative had MIC values of 8 mcg/mL. This suggests that isolates with MIC ≥16 mcg/mL may not represent the wild-type population. Additionally, it is unclear why the MIC frequency distributions for the ECV studies varied from the surveillance studies for similar years. Please clarify this discrepancy between the proposed breakpoints and the wild-type population/ECVs."

The Applicant's tables showing composite response, and microbiological, and clinical success by baseline gepotidacin MIC at TOC for the Micro-ITT population are below. Refer also to the efficacy section of this review for additional information on clinical success and composite response. The highest MIC value with adequate supportive data was evaluated for the Agency's MIC breakpoint.

Table 198. Summary of Gepotidacin Composite Response Participant-Level) at TOC by Baseline Gepotidacin MIC for Enterobacterales in Pooled Study EAGLE-2 and Study EAGLE-3 (Micro-ITT Population)

Baseline gepotidacin MIC (µg/mL)	Enterobacterales (731)	*E. coli* (598)	Non-*E. coli* Enterobacterales[a] (133)	*K. pneumoniae* (56)	Other *Klebsiella* spp.[b] (10)	*Citrobacter* spp.[c] (17)	*P. mirabilis* (34)	Other Enterobacterales[d] (16)
≤0.12		-	-	-	-	-	-	-
0.25	2/5 (40.0%)	2/5 (40.0%)	-	-	-	-	-	-
0.5	26/50 (52.0%)	26/49 (53.1%)	0/1 (0%)	-	-	0/1 (0%)	-	-
1	142/263 (54.0%)	136/252 (54.0%)	6/11 (54.5%)	-	1/2 (50.0%)	3/6 (50.0%)	1/1 (100%)	1/2 (50.0%)
2	135/247 (54.7%)	123/223 (55.2%)	12/24 (50.0%)	1/6 (16.7%)	4/5 (80.0%)	5/6 (83.3%)	1/2 (50.0%)	1/5 (20.0%)
4	53/102 (52.0%)	29/55 (52.7%)	24/47 (51.1%)	11/25 (44.0%)	0/1 (0%)	2/3 (66.7%)	7/10 (70.0%)	4/8 (50.0%)
8	24/43 (55.8%)	6/9 (66.7%)	18/34 (52.9%)	7/17 (41.2%)	0/2 (0%)	1/1 (100%)	9/13 (69.2%)	1/1 (100%)
16	11/16 (68.8%)	3/4 (75.0%)	8/12 (66.7%)	2/5 (40.0%)	-	-	6/7 (85.7%)	-
32	2/5 (40.0%)	1/1 (100%)	1/4 (25.0%)	1/3 (33.3%)	-	-	0/1 (0%)	-
Total	**395/731 (54.0%)**	**326/598 (54.5%)**	**69/133 (51.9%)**	**22/56 (39.3%)**	**5/10 (50.0%)**	**11/17 (64.7%)**	**24/34 (70.6%)**	**7/16 (43.8%)**
MIC range	0.25 to 32	0.25 to 32	0.5 to 32	2 to 32	1 to 8	0.5 to 8	1 to 32	1 to 8
MIC50	2	1	4	4	2	2	8	4
MIC90	4	4	16	16	8	4	16	4

Source: PDAP Table 2.4310

Note: Microbiological response is uropathogen-level response. Clinical and therapeutic responses are participant-level responses. MIC is referring to the baseline visit MIC for the compound in that respective treatment group. The denominator is the number of participants with the specified uropathogen and baseline MIC result, and the numerator is the number of success responses. A participant with more than 1 specified uropathogen and baseline MIC result is counted more than once for clinical, microbiological, and therapeutic response. MICs are based on the BMD MICs.

a. For Study 204989 includes *K. pneumoniae* (32), *K. oxytoca / R. ornithinolytica* (3), *K. variicola* (2), *P. mirabilis* (21), *C. freundii* complex (7), *E. cloacae* (3), *M. morganii* (5), *P. rettgeri* (1) and *S. luquefaciens* (1). For Study 212390 includes *K. pneumoniae* (24), *K. oxytoca/R. ornithinolytica* (2), *K. variicola* (1), *K. aerogenes* (2), *P. mirabilis* (13), *C. koseri* (2), *C. freundii* complex (6), *C. amalonaticus* (2), *E. cloacae* (3) and *M. morganii* (3) [PDAP Table 1.0810]
b. For Study 204989 includes *K. oxytoca/R. ornithinolytica* (3) and *K. variicola* (2). In Study 212390 includes *K. oxytoca/R. ornithinolytica* (2), *K. variicola* (1) and *K. aerogenes* (1) [PDAP Table 1.0810]
c. For Study 204989 includes *C. freundii* complex (7). For Study 212390 includes *C. koseri* (2), *C. freundii* complex (6) and *C. amalonaticus* (2) [PDAP Table 1.0810]
d. For Study 204989 includes *E. cloacae* (3), *M. morganii* (5), *P. rettgeri* (1) and *S. luquefaciens* (1). For Study 212390 includes *E. cloacae* (3) and *M. morganii* (3) [PDAP Table 1.0810]

Abbreviations: BMD, broth microdilution; MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; TOC, test-of-cure

Table 199. Summary of Gepotidacin Clinical Success (Participant-Level) at TOC by Baseline Gepotidacin MIC for Enterobacterales in Pooled Study EAGLE-2 and Study EAGLE-3 (Micro-ITT Population)

Baseline gepotidacin MIC (µg/mL)	Enterobacterales (731)	*E. coli* (598)	Non-*E. coli* Enterobacterales[a] (133)	*K. pneumoniae* (56)	Other *Klebsiella* spp.[b] (10)	*Citrobacter* spp.[c] (17)	*P. mirabilis* (34)	Other Enterobacterales[d] (16)
≤0.12		-	-	-	-	-	-	-
0.25	2/5 (40.0%)	2/5 (40.0%)						
0.5	35/50 (70.0%)	35/49 (71.4%)	0/1 (0%)			01 (0%)		
1	176/263 (66.9%)	169/252 (67.1%)	7/11 (63.6%)		2/2 (100%)	3/6 (50.0%)	1/1 (100%)	1/2 (50.0%)
2	166/247 (67.2%)	154/223 (69.1%)	12/24 (50.0%)	1/6 (16.7%)	4/5 (80.0%)	5/6 (83.3%)	1/2 (50.0%)	1/5 (20.0%)
4	65/102 (63.7%)	38/55 (69.1%)	27/47 (57.4%)	13/25 (52.0%)	0/1 (0%)	2/3 (66.7%)	8/10 (80.0%)	4/8 (50.0%)
8	28/43 (65.1%)	6/9 (66.7%)	22/34 (64.7%)	9/17 (52.9%)	0/2 (0%)	1/1 (100.0%)	11/13 (84.6%)	1/1 (100.0%)
16	13/16 (81.3%)	4/4 (100%)	9/12 (75.0%)	3/5 (60.0%)			6/7 (85.7%)	
32	3/5 (60.0%)	1/1 (100%)	2/4 (50.0%)	2/3 (66.7%)			0/1 (0%)	
Total	**488/731 (66.8%)**	**409/598 (68.4%)**	**79/133 (59.4%)**	**28/56 (50.0%)**	**6/10 (60.0%)**	**11/17 (64.7%)**	**27/34 (79.4%)**	**7/16 (43.8%)**
MIC range	0.25 to 32	0.25 to 32	0.5 to 32	2 to 32	1 to 8	0.5 to 8	1 to 32	1 to 8
MIC50	2	1	4	4	2	2	8	4
MIC90	4	4	16	16	8	4	16	4

Source: PDAP Table 2.4310

Note: Microbiological response is uropathogen-level response. Clinical and therapeutic responses are participant-level responses. MIC is referring to the baseline visit MIC for the compound in that respective treatment group. The denominator is the number of participants with the specified uropathogen and baseline MIC result, and the numerator is the number of success responses. A participant with more than 1 specified uropathogen and baseline MIC result is counted more than once for clinical, microbiological, and therapeutic response. MICs are based on the BMD MICs.

a. For Study 204989 includes *K. pneumoniae* (32), *K. oxytoca / R. ornithinolytica* (3), *K. variicola* (2), *P. mirabilis* (21), *C. freundii* complex (7), *E. cloacae* (3), *M. morganii* (5), *P. rettgeri* (1) and *S. luquefaciens* (1). For Study 212390 includes *K. pneumoniae* (24), *K. oxytoca/R. ornithinolytica* (2), *K. variicola* (1), *K. aerogenes* (2), *P. mirabilis* (13), *C. koseri* (2), *C. freundii* complex (6), *C. amalonaticus* (2), *E. cloacae* (3) and *M. morganii* (3) [PDAP Table 1.0810]
b. For Study 204989 includes *K. oxytoca/R. ornithinolytica* (3) and *K. variicola* (2). In Study 212390 includes *K. oxytoca/R. ornithinolytica* (2), *K. variicola* (1) and *K. aerogenes* (1) [PDAP Table 1.0810]
c. For Study 204989 includes *C. freundii* complex (7). For Study 212390 includes *C. koseri* (2), *C. freundii* complex (6) and *C. amalonaticus* (2) [PDAP Table 1.0810]
d. For Study 204989 includes *E. cloacae* (3), *M. morganii* (5), *P. rettgeri* (1) and *S. luquefaciens* (1). For Study 212390 includes *E. cloacae* (3) and *M. morganii* (3) [PDAP Table 1.0810]

Abbreviations: MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; TOC, test-of-cure

Table 200. Summary of Gepotidacin Microbiological Success (Uropathogen-Level) at TOC by Baseline Gepotidacin MIC for Enterobacterales in Pooled Study EAGLE-2 and Study EAGLE-3 (Micro-ITT Population)

Baseline gepotidacin MIC (µg/mL)	Enterobacterales (731)	*E. coli* (598)	Non-*E. coli* Enterobacterales[a] (133)	*K. pneumoniae* (56)	Other *Klebsiella* spp.[b] (10)	*Citrobacter* spp.[c] (17)	*P. mirabilis* (34)	Other Enterobacterales[d] (16)
≤0.12		-	-	-	-	-	-	-
0.25	5/5 (100%)	5/5 (100%)						
0.5	36/50 (72.0%)	35/49 (71.4%)	1/1 (100%)			1/1 (100%)		
1	198/263 (75.3%)	188/252 (74.6%)	10/11 (90.9%)		2/2 (100%)	5/6 (83.3%)	1/1 (100%)	2/2 (100%)
2	178/247 (72.1%)	156/223 (70.0%)	22/24 (91.7%)	6/6 (100%)	5/5 (100%)	5/6 (83.3%)	2/2 (100%)	4/5 (80.0%)
4	73/102 (71.6%)	35/55 (63.6%)	38/47 (80.9%)	17/25 (68.0%)	1/1 (100%)	3/3 (100%)	9/10 (90.0%)	8/8 (100%)
8	34/43 (79.1%)	8/9 (88.9%)	26/34 (76.5%)	11/17 (64.7%)	1/2 (50.0%)	1/1 (100%)	12/13 (92.3%)	1/1 (100%)
16	13/16 (81.3%)	3/4 (75.0%)	10/12 (83.3%)	3/5 (60.0%)			7/7 (100%)	
32	3/5 (60.0%)	1/1 (100%)	2/4 (50.0%)	1/3 (33.3%)			1/1 (100%)	
Total	**540/731 (73.9%)**	**431/598 (72.1%)**	**109/133 (82.0%)**	**38/56 (67.9%)**	**9/10 (90.0%)**	**15/17 (88.2%)**	**32/34 (94.1%)**	**15/16 (93.8%)**
MIC range	0.25 to 32	0.25 to 32	0.5 to 32	2 to 32	1 to 8	0.5 to 8	1 to 32	1 to 8
MIC50	2	1	4	4	2	2	8	4
MIC90	4	4	16	16	8	4	16	4

Source: PDAP Table 2.4310

Note: Microbiological response is uropathogen-level response. Clinical and therapeutic responses are participant-level responses. MIC is referring to the baseline visit MIC for the compound in that respective treatment group. The denominator is the number of participants with the specified uropathogen and baseline MIC result, and the numerator is the number of success responses. A participant with more than 1 specified uropathogen and baseline MIC result is counted more than once for clinical, microbiological, and therapeutic response. MICs are based on the BMD MICs.

a. For Study 204989 includes *K. pneumoniae* (32), *K. oxytoca / R. ornithinolytica* (3), *K. variicola* (2), *P. mirabilis* (21), *C. freundii* complex (7), *E. cloacae* (3), *M. morganii* (5), *P. rettgeri* (1) and *S. luquefaciens* (1). For Study 212390 includes *K. pneumoniae* (24), *K. oxytoca/R. ornithinolytica* (2), *K. variicola* (1), *K. aerogenes* (2), *P. mirabilis* (13), *C. koseri* (2), *C. freundii* complex (6), *C. amalonaticus* (2), *E. cloacae* (3) and *M. morganii* (3) [PDAP Table 1.0810]

b. For Study 204989 includes *K. oxytoca/R. ornithinolytica* (3) and *K. variicola* (2). In Study 212390 includes *K. oxytoca/R. ornithinolytica* (2), *K. variicola* (1) and *K. aerogenes* (1) [PDAP Table 1.0810]

c. For Study 204989 includes *C. freundii* complex (7). For Study 212390 includes *C. koseri* (2), *C. freundii* complex (6) and *C. amalonaticus* (2) [PDAP Table 1.0810]

d. For Study 204989 includes *E. cloacae* (3), *M. morganii* (5), *P. rettgeri* (1) and *S. luquefaciens* (1). For Study 212390 includes *E. cloacae* (3) and *M. morganii* (3) [PDAP Table 1.0810]

Abbreviations: BMD, broth microdilution; MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; TOC, test-of-cure

Table 201. Summary of Gepotidacin Clinical, Microbiological and Composite Response Success at TOC by Baseline Gepotidacin MIC for *S. saprophyticus* in Pooled Study EAGLE-2 and Study EAGLE-3 (Micro-ITT Population)

Baseline gepotidacin MIC (µg/mL)	Clinical Success (participant-level)	Microbiological Success (uropathogen-level)	Therapeutic Success (participant-level)
≤0.03			
0.06	5/10 (50.0%)	7/10 (70.0%)	5/10 (50.0%)
0.12	3/4 (75.0%)	4/4 (100%)	3/4 (75.0%)
0.25	1/1 (100%)	1/1 (100%)	1/1 (100%)
0.5			
1			
2			
4			
8			
Total	**9/15 (60.0%)**	**12/15 (80.0%)**	**9/15 (60.0%)**
MIC range	0.06 to 0.25		
MIC50	0.06		
MIC90	0.12		

Source: PDAP Table 2.4310

Note: Microbiological response is uropathogen-level response. Clinical and therapeutic responses are participant-level responses. MIC is referring to the baseline visit MIC for the compound in that respective treatment group. The denominator is the number of participants with the specified uropathogen and baseline MIC result, and the numerator is the number of success responses. A participant with more than 1 specified uropathogen and baseline MIC result is counted more than once for clinical, microbiological, and therapeutic response. MICs are based on the BMD MICs.

Abbreviations: BMD, broth microdilution; MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; TOC, test-of-cure

Table 202. Summary of Gepotidacin Clinical, Microbiological, and Composite Response at TOC by Baseline Gepotidacin MIC for *E. faecalis* in Pooled Study EAGLE-2 and Study EAGLE-3 (Micro-ITT Populations)

Baseline gepotidacin MIC (µg/mL)	Clinical Success (participant-level)	Microbiological Success (uropathogen-level)	Therapeutic Success (participant-level)
≤0.03			
0.06			
0.12			
0.25			
0.5	2/2 (100%)	2/2 (100.0%)	2/2 (100.0%)
1	2/6 (33.3%)	5/6 (83.3%)	2/6 (33.3%)
2	2/4 (50.0%)	3/4 (75.0%)	2/4 (50.0%)
4	2/2 (100%)	2/2 (100%)	2/2 (100%)
8			
Total	8/14 (57.1%)	12/14 (85.7%)	8/14 (57.1%)
MIC range	0.5 to 4		
MIC50	1		
MIC90	2		

Source: PDAP Table 2.4310

Note: Microbiological response is uropathogen-level response. Clinical and therapeutic responses are participant-level responses. MIC is referring to the baseline visit MIC for the compound in that respective treatment group. The denominator is the number of participants with the specified uropathogen and baseline MIC result, and the numerator is the number of success responses. A participant with more than 1 specified uropathogen and baseline MIC result is counted more than once for clinical, microbiological, and therapeutic response. MICs are based on the BMD MICs.

Abbreviations: MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; TOC, test-of-cure

For *S. saprophyticus* and *E. faecalis*, the number of isolates at each MIC was limited and the microbiological success trended higher than or equal to the clinical and therapeutic success.

Response by Baseline Susceptibility to Other Antimicrobials

There were decreases in gepotidacin microbiological and therapeutic success rates for several of the isolate groups, but this was most apparent for the amoxicillin-clavulanic acid-resistant (AMC-R) and FQ-R *E. coli* isolates, respectively, compared to the amoxicillin-clavulanic acid-susceptible (AMC-S) and FQ-S *E. coli* isolates at FU.

Table 203. Applicant's Proposed Gepotidacin MIC and Zone Breakpoints and Interpretive Criteria

Uropathogen	Proposed MIC breakpoints (µg/mL)			Tentative zone diameter breakpoints (mm)		
	S	I	R	S	I	R
Enterobacterales	≤16	32	≥64	≥12	8-11	≤7
S. saprophyticus	≤0.25	-	-	≥23	-	-
E. faecalis	≤4	-	-	≥14	-	-

Source: This submission
Abbreviation: I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible

Agency's Proposed Breakpoints

The Agency accepts the Applicant's proposed MIC and disk diffusion breakpoints based on their own analysis of in vitro surveillance studies, ECVs, activity in vivo, and clinical studies. The Applicant's proposed disk diffusion breakpoints agree with CLSI recommendations except that the Applicant's proposal has Very Major error rates for *S. saprophyticus* that are outside of CLSI recommendations in one MIC Range. The Agency was not able to determine an acceptable

alternative proposal for disk diffusion breakpoints for *S. saprophyticus* that would reduce these error rates.

Reviewer's Comments

When the final breakpoints are determined, there should be footnote to Enterobacterales in the breakpoint table in the Susceptibility Test Interpretive Criteria website that says, "clinical efficacy was shown for E. coli, K. pneumoniae, and C. freundii complex."

Conclusions: From a clinical microbiological perspective, approval of gepotidacin is recommended with the breakpoints modified and listed as below.

Table 204. Final Agency MIC and Disk Breakpoint Recommendations

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (Zone Diameter in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacterales[a]	≤ 16	32	≥ 64	≥ 12	8-11	≤ 7
S. saprophyticus	≤0.25	___	___	≥ 23	___	___
E. faecalis	≤4	___	___	≥ 14	___	___

Source: Modified from Applicant's submission
[a] Clinical efficacy was shown for *E. coli, K. pneumoniae, and C. freundii complex.*
Abbreviations: I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible

20. Mechanism of Action/Drug Resistance

See Section 19, Clinical Microbiology.

21. Other Drug Development Considerations

Not applicable

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Drs. Garev, Kester, Ajani, and Lambert, as well as the Applicant, GlaxoSmithKline, LLC, were inspected in support of this application, covering studies EAGLE-2 and EAGLE-3. No significant good clinical practice deficiencies or regulatory violations were observed for any of the four CIs or the Applicant. The data generated by the four inspected CIs and submitted by the Sponsor appear to be acceptable in support of the proposed indication.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted on July 26, 2024 (Table 205). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

The Established Pharmacologic Class (EPC) in the Indications and Usage section of the Highlights of the Prescribing information was modified to triazaacenaphthylene bacterial type II topoisomerase inhibitor as this provides a more complete EPC that includes mode of action and chemical structure that is scientifically valid and clinically meaningful. This EPC modification was based on the labeling recommendations in the Guidance for Industry: Labeling for Human Prescription Drug and Biological Products-Determining Established Pharmacological Class for Use in the Highlights of Prescribing Information. Refer to Section 19.2 of the IAMA for additional details.

Table 205. Key Labeling Changes and Considerations

Full Prescribing Information Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	Not applicable.
1 INDICATIONS AND USAGE	Indication statement edited to restrict use of gepotidacin to treatment of uncomplicated urinary tract infections (uUTI); claim of (b) (4) was removed from the usage statement. This part of the language under 21 CFR 201.24 is not appropriate to include in the BLUJEPA PI. (b) (4) was removed from the indication statement to be consistent with other recently approved labeling for drugs with this indication. (b) (4) was removed from the indication statement (b) (4) Refer to Sections 6 and 19 of the IAMA for additional details.
2 DOSAGE AND ADMINISTRATION	Subsection 2.2 Recommendations Regarding Missed Dose(s): Added statement not to double the dose to make up for a missed dose due to the potential for QT prolongation at higher exposure at higher doses. Refer to Sections 5.2 and 7.7.3 of the IAMA for additional details.
4 CONTRAINDICATIONS	Added severe hypersensitivity to BLUJEPA as a contraindication. Refer to Sections 7.6 and 7.7.2 of the IAMA for additional details.
5 WARNINGS AND PRECAUTIONS	Subsection 5.1 QTc Prolongation: Specific drug names were removed as an exhaustive list of potential QTc prolonging drugs cannot be included in the label. Addition of clinical monitoring and management instructions for patients at risk of QTc prolongation if BLUJEPA must be administered. Refer to Sections 7.6 and 7.7.3 of the IAMA for additional details. Subsection 5.2 Acetylcholinesterase Inhibition:

Full Prescribing Information Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	Addition of dysarthria, nausea, vomiting, abdominal pain, diarrhea, hypersalivation, presyncope, muscle spasms, and hyperhidrosis as acetylcholinesterase inhibition adverse reactions reported with BLUJEPA. Refer to Sections 7.6 and 7.7.1 of the IAMA for additional details. Subsection 5.3 Hypersensitivity Reactions was added as hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving BLUJEPA. Refer to Sections 7.6 and 7.7.2 of the IAMA for additional details. Subsection 5.4 *Clostridioides difficile*-associated Diarrhea, (CDAD) changed to *Clostridioides difficile* Infection (CDI) as this is the current terminology used in the field. This change was also supported by the fact that CDI is the term used in the draft FDA guidance for industry entitled *Clostridioides difficile* Infection: Developing Drugs for Treatment, Reduction of Recurrence, and Prevention (October 2022).
6 ADVERSE REACTIONS	Subsection 6.1 Clinical Trials Experience: Added demographic ethnicity details and study arm comparator details. Expanded Common Adverse Reactions to >1% of patients receiving BLUJEPA. Dizziness and vulvovaginal candidiasis were added to Table 1. Adverse Reactions Occurring in Less than 1% of Patients Receiving BLUJEPA in Trials 1 and 2 (pooled): Addition of muscle spasms to *Musculoskeletal and Connective Tissue Disorders* listing. (b) (4) was removed from the Gastrointestinal Disorders section and placed in a separate heading of Select Adverse Reactions Occurring in Patients Receiving BLUJEPA in Phase 1 and 2 Clinical Studies. Refer to Section 7 of the IAMA for additional details.
7 DRUG INTERACTIONS	Subsection 7.1 Effects of Other Drugs on BLUJEPA: Added a statement about avoiding coadministration of BLUJEPA and CYP3A4 strong inducers with cross-reference to subsections 5.1 and 12.3. When co-administered with rifampicin (CYP3A4 inducer), the BLUJEPA plasma exposures were reduced by ≥50%. Refer to Section 8.2.2 of the IAMA for additional details.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Subsection 8.1 Pregnancy: Added a statement regarding a pregnancy exposure registry that will be established to monitor pregnancy outcomes in women exposed to BLUJEPA during pregnancy. Added a statement under the Risk Summary subheading indicating that there are no available data on the use of BLUJEPA during pregnancy instead of the Applicant's proposal stating that "(b) (4)" Refer to the Division of Pediatric and Maternal Health (DPMH) review in DARRTS dated January 29, 2025. Study descriptions were simplified with details in the animal data section. Margins were extrapolated using toxicokinetic data from repeat-dose studies at the same dose in the same species. Negative data were removed from the summary.

Full Prescribing Information Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	Animal data language was edited to reflect the data, with margins adjusted to reflect exposure comparisons using the mean clinical AUC exposure in this label and animal exposures from other repeat-dose animal studies with toxicokinetic data at the same dose. Subsection 8.2 Lactation: Description of transfer of gepotidacin based on the study in lactating mice in the risk summary was simplified. Margins (i.e., multiples of exposure to the maximum recommended human dose (MRHD)) were clarified in the data section. Refer to Section 8.4 or Section 13.1.4.4 of the IAMA for additional details. Subsection 8.6 Renal Impairment: The renal impairment study used modification of diet in renal disease equation to estimate renal function and classify renal status; therefore, the section was revised by replacing the terminology creatinine clearance with estimated glomerular filtration rate. Refer to Section 8.1.2 of the IAMA for additional details.
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	Added a recommendation to contact the Poison Help Line (1-800-222-1222) or medical toxicologist for additional overdose management recommendations. Removed language that does not directly assist in cases of overdose.
12 CLINICAL PHARMACOLOGY	Subsection 12.3 Pharmacokinetics: Table 2 which describes the ADME was included to improve readability and clarity. Specific Populations subsections (e.g., age, sex, race, body weight) were condensed to a sentence, since no clinically significant differences were observed. In the Patients with Renal Impairment subsection, plasma exposure differences between normal renal function and various degrees of renal impairment were revised since the previous comparison was based on indexed eGFR instead of eGFR individualized based on body surface area. In the Patients with Renal Impairment and Patients with Hepatic Impairment subsections, (b) (4) was removed as it was not considered clinically informative. The following revisions were made to the Drug Interactions subsection: • A subheading was added for clarity (clinical drug interaction studies). • (b) (4) information was removed for lack of clinical relevance. • A sentence (b) (4) was removed since it was not considered clinically informative (see Sections 6.1, 8.2.2) of the IAMA for additional details.

Full Prescribing Information Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	• The subsection "In vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically" was added to provide clarity to prescribers. Refer to Section 5.2 and Section 8.2.2 of the IAMA for additional details. Subsection 12.4 Microbiology: This section was edited in accordance with the FDA guidance document, "Microbiological Data for Systemic Antibacterial Drugs-Development, Analysis and Presentation-Guidance for Industry". For example, some information was removed (b) (4) Mechanism of Action: edited to clarify bacterial Type II topoisomerases. Resistance: information was added on amino acids in the target site that may be important for gepotidacin activity. Edited for clarity and scientific accuracy including a more accurate description of resistance findings. Deleted information in this section to focus on resistance characteristics that are relevant to gepotidacin. Refer to Section 19 of the IAMA for additional details.
13 NONCLINICAL TOXICOLOGY	Subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: Subheadings were added for clarity. Descriptions of studies were edited to reflect the data and remove commentary. Subsection 13.2 was deleted. The information on (b) (4) was not pivotal. The information on (b) (4) was not considered generally informative to clinical practice based on the lack of consistency and severity. Refer to Section 7.1 of the IAMA for additional details.
14 CLINICAL STUDIES	Results for each study were presented in the micro-ITT NTF-S set with complete study data rather than the micro-ITT NTF-S [interim analysis (IA) set] or other analysis sets, to provide more complete results. (b) (4) was removed for Study EAGLE-3 (b) (4). To streamline presentation of results, subgroup analysis by baseline pathogen was only shown for the primary composite endpoint rather than for the separate clinical and microbiological components of this endpoint. (b) (4) were removed that were considered exploratory. Refer to Section 6 of the IAMA for additional details.
17 PATIENT COUNSELING INFORMATION	Revised language to be consistent with QTc Prolongation, Acetylcholinesterase Inhibition, Hypersensitivity Reactions, *Clostridioides difficile* infection Warning statements. Added Pregnancy Exposure Registry reporting language as well.

Full Prescribing Information Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	In the DESCRIPTION section, the salt equivalency statement was adjusted to not include (b) (4) in the calculation. Refer to the Product Quality Review in DARRTS dated February 20, 2025.

Source: Reviewer
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC, area under the concentration-time curve; BID, twice daily; CDAD, *Clostridioides difficile*-associated Diarrhea; CDI, *Clostridioides difficile* Infection; CFR, Code of Federal Regulations; C_{max}, maximum plasma concentration; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; IA, interim analysis; IV, intravenous; micro-ITT NTF-S, microbiological intent to treat nitrofurantoin susceptible; PI, Prescribing Information; QT, interval from the start of the Q wave to the end of the T wave; QTc, QT interval corrected for heart rate; uUTI, uncomplicated urinary tract infection

Medication Guide

To mitigate the potential risks of adverse reactions associated with cholinergic effects, such as dysarthria, the Applicant's proposed Patient Package Insert will be replaced by a Medication Guide which is required to be given to patients along with the medication.

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide
- Container Labeling

24. Postmarketing Requirements and Commitments

The following postmarketing requirements have been requested by FDA and agreed to by the Applicant. Please refer to the approval letter for the final PMR language and timelines.

Required pediatric assessments:

1. Conduct an open-label, add-on, non-comparator study to evaluate the pharmacokinetics and safety of a single dose of oral gepotidacin administered in addition to antibacterial standard of care, in pediatric patients aged 2 years to less than 12 years with suspected or confirmed bacterial infection or who are receiving antibacterial prophylaxis.

   The study milestone dates are as follows:

   - Draft Protocol submission: May 2025
   - Final Protocol Submission: October 2025
   - Study Completion: December 2027
   - Final Report Submission: June 2028

2. Conduct an open-label, active-controlled comparator study to evaluate the safety and tolerability of oral gepotidacin in pediatric patients aged 2 years to less than 12 years with a confirmed or suspected uncomplicated UTI.

   The study milestone dates are as follows:

   - Draft Protocol submission: March 2027
   - Final Protocol Submission: August 2027
   - Study Completion: September 2032
   - Final Report Submission: March 2033

PMRs under 505(o):

3. Collect data from a prospective pregnancy exposure registry, preferably a disease- based multiproduct pregnancy registry, using a registry-based cohort study design that compares the maternal, fetal, and infant outcomes of women exposed to gepotidacin during pregnancy with comparator population(s) unexposed to gepotidacin. Align the study protocol with protocol(s) outside the U.S. to reach a target sample size.

   The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

   The milestone dates are as follows:

   - Draft Protocol Submission: October 2025
   - Final Protocol Submission: April 2026
   - Interim Report Submission: April 2029
   - Study Completion: April 2032
   - Final Report Submission: October 2032

4. Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess small- for-gestational-age births, spontaneous abortions, major congenital malformations, stillbirths, and preterm births in individuals exposed to gepotidacin during pregnancy compared to appropriate comparator population(s).

   The milestone dates are as follows:

   - Draft Protocol Submission: October 2025
   - Final Protocol Submission: April 2026
   - Interim Report Submissions: April 2028, April 2029, April 2030
   - Study Completion: April 2032
   - Final Report Submission: October 2032

5. Perform a clinical lactation study (milk only or mother-infant pair study) in lactating women who have received gepotidacin to measure concentrations of gepotidacin in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on the study population.

   The study milestone dates are as follows:

   - Draft Protocol Submission: October 2025
   - Final Protocol Submission: April 2026
   - Study Completion: April 2028
   - Final Report Submission: October 2028

6. Conduct a United States surveillance study, or studies as appropriate, for 5 years from the date of marketing to determine if resistance to gepotidacin has developed in those organisms specific to the indication in the label.

   The milestone dates are as follows:

   - Draft Protocol Submission: May 2025
   - Final Protocol Submission: September 2025
   - Interim Report Submission: September 2026
   - Interim Report Submission: September 2027
   - Interim Report Submission: September 2028
   - Interim Report Submission: September 2029
   - Interim Report Submission: September 2030
   - Study Completion: June 2031
   - Final Report Submission: September 2031

25. Financial Disclosure

Table 206. Covered Clinical Studies: [EAGLE-2, EAGLE-3]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1323		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: CFR, Code of Federal Regulations; FDA, Food and Drug Administration

26. References

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27. Review Team

Table 207. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Christopher Davi
Nonclinical reviewer	Leah Rosenfeld
Nonclinical team leader	Amy Nostrandt
OCP reviewer(s)	Anthony Nicasio, Elyes Dahmane
OCP team leader(s)	Dakshina Chilukuri, Justin Earp
Clinical reviewer	Rebecca Levorson
Clinical team leader	Brittany Goldberg
Biometrics reviewer	Jie Cong
Biometrics team leader	Daniel Rubin
Clinical microbiology reviewer	Kerian Grande Roche
Clinical microbiology team leader	Avery Goodwin
Cross-discipline team leader; Deputy director for safety	Mukil Natarajan
Deputy division director (pharm/tox)	Terry Miller
Division director (OCP)	Kellie Reynolds
Associate director for labeling	Abimbola Adebowale
Deputy division director (clinical)	Dmitri Iarikov
Division director (clinical)	Peter Kim
Office director (or designated signatory authority)	Adam Sherwat

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 208. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Dorota Matecka, Juliana Quarterman
OPDP	Qumer Syed
OSI	John Lee
OSE/DEPI	Ikponmwosa Osaghae
OSE/DMEPA	Deborah Myers
DPMH	Kevin Clark, Tamara Johnson

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-209 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Microbiology Discipline Secondary Reviewer	Avery Goodwin OID DAI	Sections: 19	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Avery Goodwin

Digitally signed by Avery Goodwin

Date: 3/20/2025 10:43 AM EDT
GUID: 2025320144359

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Terry Miller OID DPTID	Sections: 5.2, 7.1, 8.4, 13, 23, 24	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Terry Miller

Digitally signed by Terry Miller

Date: 3/20/2025 10:45 AM EDT
GUID: 202532014457

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Daniel Rubin OB DBIV	Sections: 6, 15 - 16, 23 - 26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Daniel Rubin

Digitally signed by Daniel Rubin

Date: 3/20/2025 10:46 AM EDT
GUID: 2025320144632

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Elyes Dahmane OCP DPM	Sections: 5, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Elyes Dahmane

Digitally signed by Elyes Dahmane

Date: 3/20/2025 10:48 AM EDT
GUID: 2025320144829

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Elyes Dahmane OCP DPM	Sections: 5,14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elyes Dahmane			**Digitally signed by Elyes Dahmane** **Date: 3/20/2025 10:50 AM EDT** **GUID: 202532014501**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Wen Lin OCP DPM	Sections: 14.5.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Wen Lin			**Digitally signed by Wen Lin** **Date: 3/20/2025 10:59 AM EDT** **GUID: 2025320145921**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Gregory Dibernardo ORO DROID	Sections: 3	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Gregory Dibernardo

Digitally signed by Gregory Dibernardo

Date: 3/20/2025 11:04 AM EDT
GUID: 202532015423

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Dakshina Chilukuri OCP DIDP	Sections: 5, 6, 8, 14 and 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Dakshina Chilukuri

Digitally signed by Dakshina Chilukuri

Date: 3/20/2025 11:07 AM EDT
GUID: 202532015750

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Anthony Nicasio OCP DIDP	Sections: 5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Anthony Nicasio

Digitally signed by Anthony Nicasio

Date: 3/20/2025 11:08 AM EDT
GUID: 202532015841

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Christina Won OCP DIDP	Sections: 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Christina Won

Digitally signed by Christina Won

Date: 3/20/2025 11:12 AM EDT
GUID: 2025320151250

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Christina Won OCP DIDP	Sections: 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Christina Won

Digitally signed by Christina Won

Date: 3/20/2025 11:14 AM EDT
GUID: 202532015147

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Microbiology Discipline Primary Reviewer	Kerian Grande Roche OID DAI	Sections: 19, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Kerian Grande Roche

Digitally signed by Kerian Grande Roche

Date: 3/20/2025 11:14 AM EDT
GUID: 2025320151444

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Mukilan Natarajan OID DAI	Sections: 1, 2, 3, 4, 7, 15, 17, 22, 23, 24, 25, 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Mukilan Natarajan**			**Digitally signed by Mukilan Natarajan** **Date: 3/20/2025 11:29 AM EDT** **GUID: 2025320152920**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Brittany Goldberg OID DAI	Sections: 1 - 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Brittany Goldberg**			**Digitally signed by Brittany Goldberg** **Date: 3/20/2025 11:57 AM EDT** **GUID: 2025320155715**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Primary Reviewer	Abimbola Adebowale OID DAI	Sections: 23, 23.1	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abimbola Adebowale			**Digitally signed by Abimbola Adebowale** **Date: 3/20/2025 12:03 PM EDT** **GUID: 20253201633**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Secondary Reviewer	Abimbola Adebowale OID DAI	Sections: 23, 23.1	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abimbola Adebowale			**Digitally signed by Abimbola Adebowale** **Date: 3/20/2025 12:08 PM EDT** **GUID: 20253201682**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Kellie Reynolds OCP DIDP	Sections: 5, 6, 8, 14, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Kellie Reynolds

Digitally signed by Kellie Reynolds

Date: 3/20/2025 12:30 PM EDT
GUID: 2025320163029

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Leah Rosenfeld OID DPTID	Sections: 5.2, 7.1, 8.4, 13, 23, 24	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Leah Rosenfeld

Digitally signed by Leah Rosenfeld

Date: 3/20/2025 1:18 PM EDT
GUID: 2025320171846

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Amy Nostrandt OID DPTID	Sections: 5.2, 7.1, 8.4, 13, 23, 24	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Amy Nostrandt			**Digitally signed by Amy Nostrandt** **Date: 3/20/2025 1:22 PM EDT** **GUID: 2025320172244**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Jie Cong OB DBIV	Sections: 2, 6, 16, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jie Cong			**Digitally signed by Jie Cong** **Date: 3/20/2025 1:27 PM EDT** **GUID: 2025320172758**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Rebecca Levorson OID DAI	Sections: module4, section 7	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Rebecca Levorson			**Digitally signed by Rebecca Levorson** **Date: 3/20/2025 2:08 PM EDT** **GUID: 202532018821**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Dorota Matecka OPQAI DPQAIII	Sections: 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Signing on behalf of OPQ Review Team
Signature: Dorota Matecka			**Digitally signed by Dorota Matecka** **Date: 3/20/2025 2:19 PM EDT** **GUID: 2025320181933**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Dorota Matecka OPQAI DPQAIII	Sections: 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Signing on behalf of OPQ Review Team

Signature: Dorota Matecka

Digitally signed by Dorota Matecka

Date: 3/20/2025 2:20 PM EDT
GUID: 2025320182052

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Justin Earp OCP DPM	Sections: 5, 14, 5, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Justin Earp

Digitally signed by Justin Earp

Date: 3/20/2025 11:08 PM EDT
GUID: 2025321381

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Justin Earp OCP DPM	Sections: 5,6,14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Justin Earp

Digitally signed by Justin Earp

Date: 3/20/2025 11:12 PM EDT
GUID: 20253213120

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Joseph Davi ORO DROID	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Joseph Davi

Digitally signed by Joseph Davi

Date: 3/21/2025 1:39 PM EDT
GUID: 2025321173952

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Tertiary Reviewer	Maureen Dillon Parker ORO DRO-ID	Sections: 3	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Maureen Dillon Parker			**Digitally signed by Maureen Dillon Parker** **Date: 3/21/2025 2:15 PM EDT** **GUID: 2025321181549**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Yuching Yang OCP DPM	Sections: section 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuching Yang			**Digitally signed by Yuching Yang** **Date: 3/21/2025 2:16 PM EDT** **GUID: 2025321181646**	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUKILAN NATARAJAN
03/21/2025 08:35:11 PM

PETER W KIM
03/23/2025 02:16:27 PM

ADAM I SHERWAT
03/24/2025 08:57:21 AM