Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	218230/S-001
Priority or standard	Priority
Submit date	6/11/2025
Received date	6/11/2025
PDUFA goal date	12/11/2025
Division/office	Division of Anti-Infectives (DAI)
Review completion date	11/10/2025
Established/proper name	Gepotidacin
(Proposed) proprietary name	Blujepa
Pharmacologic class	Triazaacenaphthylene bacterial type II topoisomerase inhibitor
Other product name(s)	GSK 2140944
Applicant	GSK
Dosage form/formulation	Tablet
Dosing regimen	3,000 mg (four 750 mg tablets) taken orally followed by a second dose of 3,000 mg approximately 12 hours later.
Applicant-proposed indication/ populations	Treatment of adult and pediatric patients 12 years of age and older weighing more than 45 kilograms (kg) with uncomplicated urogenital gonorrhea caused by susceptible strains of *Neisseria gonorrhoeae* (b) (4)
SNOMED CT code for proposed indication disease term(s)[1]	15628003 | Gonorrhea (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	3,000 mg (four 750 mg tablets) taken orally followed by a second dose of 3,000 mg approximately 12 hours later.
Approved indication(s)/ population(s) (if applicable)	Adult and pediatric patients 12 years of age and older weighing at least 45 kilograms (kg) who have limited or no alternative options for the treatment of uncomplicated urogenital gonorrhea caused by susceptible strains of *Neisseria gonorrhoeae*.
SNOMED CT code for approved indication disease term(s)[1]	15628003 | Gonorrhea (disorder)

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

Table of Contents

Table of Tables

Table of Figures

Glossary

AChE-I	acetylcholinesterase inhibition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BID	twice daily
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	cross-discipline team leader
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	clinician-reported outcome
CSR	clinical study report
DEPI	Division of Epidemiology
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eCTD	electronic common technical document
EFD	embryo-fetal development
EOP2	end-of-phase 2
EPC	established pharmacologic class
E-R	exposure-response
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IND	investigational new drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat

LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOA	mechanism of action
MRHD	maximum recommended human dose
NG	*Neisseria gonorrhoeae*
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OB	Office of Biostatistics
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PD	pharmacodynamic
PFDD	patient-focused drug development
PI	Prescribing Information
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PT	preferred term
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T_{max}	time to maximum concentration
TQT	thorough QT
uGC	uncomplicated urogenital gonorrhea
ULN	upper limit of normal

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On June 11, 2025, GlaxoSmithKline limited liability company (LLC), (the Applicant) submitted a supplemental new drug application (sNDA) for Blujepa (gepotidacin) 750 mg tablets, a triazaacenaphthylene bacterial type II topoisomerase inhibitor antibacterial drug, intended to treat uncomplicated urogenital gonorrhea (uGC) in adult and pediatric patients 12 years of age and older, weighing greater than 45 kg. Gepotidacin has Qualified Infectious Disease Product (QIDP) designation qualifying for Priority Review. The Prescription Drug User Fee Act goal date is December 11, 2025.

Gepotidacin was approved on March 25, 2025, for the treatment of 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. It 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 several bacteria causing uUTI and also *Neisseria gonorrhoeae* which causes uGC.

In this supplemental application, clinical efficacy data were provided from a phase 3, randomized, multicenter, open-label (sponsor-blinded), active-controlled, noninferiority clinical study, EAGLE-1, in which two oral doses (four pills each) of gepotidacin 3000 mg taken 10 to 12 hours apart were compared to a combination of a single intramuscular (IM) 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin for the treatment of uGC caused by *N. gonorrhoeae*.

The primary analysis population was the microbiologic intent-to-treat (micro-ITT) population. The trial met the prespecified 10% non-inferiority margin for the primary efficacy endpoint of culture-confirmed bacterial eradication (i.e., microbiological success) of *N. gonorrhoeae* from the urogenital body site at Test of Cure in the micro-ITT population. Specifically, the microbiological success rates for gepotidacin and ceftriaxone/azithromycin were 187/202 (92.6%) and 186/204 (91.2%), respectively. The gepotidacin minus ceftriaxone/azithromycin treatment difference (95% confidence interval) was -0.1% (-5.6%, 5.5%) in the micro-ITT population. Confirmatory evidence was obtained from Study BTZ116576, a phase 2, multicenter, randomized, dose-ranging study that enrolled adult participants with uncomplicated urogenital gonorrhea to receive single oral dose of gepotidacin 1500 mg or 3000 mg. The phase 2 study results were supportive, with cure rates at urogenital sites of 96.7% (29/30) and 94.9% (37/39) for the 1500 mg and 3000 mg gepotidacin doses, respectively.

The safety database was composed of 309 study participants enrolled in the phase 3 clinical study 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 uGC in adult and pediatric patients 12 years of age and older, weighing at least 45 kg.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

One randomized, active-controlled phase 3 clinical study in patients with uGC titled EAGLE-1 provided SEE, with confirmatory evidence based on the results from a phase 2 uGC clinical study. The phase 3 clinical study met the primary endpoint, demonstrating that gepotidacin was non-inferior to ceftriaxone and azithromycin for treating uGC.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Gonorrhea is caused by the bacterium *Neisseria gonorrhoeae*. • The bacterium is strictly a human pathogen transmitted primarily by sexual contact and may cause symptomatic and asymptomatic infections.[1] • Gonorrhea is the second most commonly reported bacterial sexually transmitted infection in the United States with over 600,000 cases reported in 2023.[2] • Due to underreporting, the Center for Disease Control and Prevention (CDC) estimates about 1.6 million new infections occur each year.[3] • If left untreated, gonorrhea can cause serious and permanent health problems in women and men, such as pelvic inflammatory disease (PID), ectopic pregnancy, infertility, and disseminated infections.[4]	Gonorrhea is primarily a sexually transmitted infection that impacts both males and females. If left untreated, this infection can lead to lifelong complications including PID and infertility.

[1] WHO. "Gonorrhoea (*Neisseria gonorrhoeae* infection)." 4 July 2024. https://www.who.int/news-room/fact-sheets/detail/gonorrhoea-(neisseria-gonorrhoeae-infection)#:~:text=*%20vaginal%20discharge.%20*%20pain%20or%20burning,bleeding%20between%20periods%20or%20during%20sexual%20intercourse.

[2] CDC. "National Overview of STIs in 2023." November 12, 2024. https://www.cdc.gov/sti-statistics/annual/summary.html.

[3] Workowski, K. A., Bachmann, L. H., Chan, P. A., Johnston, C. M., Muzny, C. A., Park, I., Reno, H., Zenilman, J. M., & Bolan, G. A. (2021). Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep, 70(4), 1-187. https://doi.org/10.15585/mmwr.rr7004a1

[4] Quilter LAS, St Cyr SB, Barbee LA. The Management of Gonorrhea in the Era of Emerging Antimicrobial Resistance: What Primary Care Clinicians Should Know. Med Clin North Am. 2024 Mar;108(2):279-296. doi: 10.1016/j.mcna.2023.08.015. Epub 2023 Sep 14. PMID: 38331480; PMCID: PMC11150008.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• The first line treatment for gonococcal infections is one intramuscular dose of ceftriaxone.[5] • If ceftriaxone is unavailable, a single oral dose of cefixime is an alternative regimen. However, cefixime is less effective than ceftriaxone for pharyngeal gonorrhea.[6] • For individuals with a cephalosporin allergy, treatment with one intramuscular dose of gentamicin and one dose of oral azithromycin is recommended. • In 2013, the CDC classified cephalosporin-resistant *N. gonorrhoeae* as an urgent public health threat.[7] • The first multi-drug resistant (MDR) *N. gonorrhoeae* strain was identified in Japan in 2015 and has been reported in several European and Asian countries.[8] • Antimicrobial resistance may complicate selection of appropriate antibacterial treatment for gonorrhea.	There is one recommended first-line treatment option for gonococcal infections. *N. gonorrhoeae* antimicrobial resistance is on the rise with limited effective treatment options available.

[5] CDC. "Gonococcal Infections Among Adolescents and Adults." September 21, 2022. https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm.

[6] Yang KJ, Kojima N, Bristow CC, Klausner JD. Effectiveness of Cefixime for the Treatment of *Neisseria gonorrhoeae* Infection at 3 Anatomic Sites: A Systematic Review and Meta-Analysis. Sex Transm Dis. 2023 Mar 1;50(3):131-137. doi: 10.1097/OLQ.0000000000001742. Epub 2022 Dec 13. PMID: 36729626; PMCID: PMC9906985.

[7] CDC. "Drug-resistant Gonorrhea." https://www.cdc.gov/gonorrhea/hcp/drug-resistant/index.html.

[8] Raccagni AR, Ranzenigo M, Bruzzesi E, Maci C, Castagna A, Nozza S. *Neisseria gonorrhoeae* Antimicrobial Resistance: The Future of Antibiotic Therapy. Journal of Clinical Medicine. 2023; 12(24):7767. https://doi.org/10.3390/jcm12247767

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Clinical efficacy of gepotidacin was demonstrated in one adequate and well controlled trial (EAGLE-1). • The primary efficacy endpoint was the microbiological cure rate using a pre-specified noninferiority (NI) margin of 10% in the microbiologic intent-to-treat (Micro-ITT) population. • In EAGLE-1, gepotidacin met the prespecified 10% NI margin for the primary efficacy endpoint at test of cure in the micro-ITT population. The microbiological success rates for gepotidacin and ceftriaxone/azithromycin were 187/202 (92.6%) and 186/204 (91.2%), respectively. Compared to ceftriaxone/azithromycin, the treatment difference was -0.1% (-5.6%, 5.5%). • Confirmatory evidence was obtained from Study BTZ116576, a phase 2, multicenter, randomized, dose-ranging study that demonstrated microbiologic cure rates at urogenital sites of 96.7% (29/30) and 94.9% (37/39) for single doses of 1500 mg and 3000 mg gepotidacin, respectively.	Gepotidacin was demonstrated to be effective for the treatment of uncomplicated urogenital gonorrhea infections in one adequate and well-controlled clinical study. Confirmatory evidence was obtained from the phase 2 uGC study. Gepotidacin provides an additional oral option for the treatment of uGC in adult and pediatric patients 12 years of age and older with limited or no other treatment option.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The safety database for gepotidacin contained 309 participants exposed to at least one dose of gepotidacin 3000 mg in the EAGLE-1 study. • Another 60 healthy phase 1 participants were exposed to an equivalent gepotidacin dosing regimen. • There were no deaths in the phase 3 clinical trial. One serious adverse event (lower extremity fracture) occurred in the phase 3 clinical trial but it was not felt to be related to gepotidacin exposure. • Frequent mild to moderate grade adverse reactions included diarrhea, nausea, abdominal pain, and vomiting occurred in gepotidacin exposed participants. • AEs potentially associated with acetylcholinesterase inhibition were observed in 64% of gepotidacin recipients with most adverse reactions consisting of gastrointestinal events (diarrhea, abdominal pain and nausea), but nongastrointestinal events (e.g., dizziness, headache, fatigue, hyperhidrosis, blurred vision, myalgias, and 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* infection (CDI) was observed in gepotidacin recipients in the development program.	The safety profile for gepotidacin is acceptable for the treatment of uncomplicated urogenital gonorrhea in adult and pediatric patients 12 years of age and older weighing at least 45 kg who have limited or no alternative treatment options. 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. Of note, labeling already includes a warning in the prescribing information and a Medication Guide which will communicate the risk to healthcare providers and patients, respectively. Warnings are also included in labeling to communicate the risk of: (1) hypersensitivity reactions; (2) QTc prolongation, including approaches to risk mitigation if the use of gepotidacin cannot be avoided; and (3) CDI, including approaches to risk mitigation. The safety database at the uGC dosing was small and the rates of adverse reactions high, which warrants accumulating a larger safety database to evaluate the frequency of common and more rare adverse reactions. A PMR for a safety trial will be issued.

2.2. Conclusions Regarding Benefit-Risk

In this sNDA, the Applicant submitted safety and effectiveness data to support the use of gepotidacin for the treatment of uncomplicated urogenital gonorrhea infections in adult and pediatric patients 12 years of age and older who weigh at least 45 kilograms. Gepotidacin is a novel triazaacenaphthylene type II topoisomerase inhibitor that inhibits bacterial DNA gyrase and topoisomerase IV.

Clinical effectiveness data were provided from one adequate and well-controlled randomized clinical study of gepotidacin at the proposed dose of 3000 mg given as two doses approximately twelve hours apart. The study utilized microbiologic cure as the primary efficacy endpoint and met the 10% noninferiority margin. Compared to ceftriaxone and azithromycin, the treatment difference was -0.1% (-5.6%, 5.5%) in the efficacy population. Confirmatory evidence was obtained from a phase 2, multicenter, randomized, dose-ranging study of gepotidacin in uGC patients.

The safety database included 309 participants who received at least one dose of gepotidacin at the 3000 mg dose, plus an additional sixty participants in the phase 1 studies who received comparable dosing. The available data indicate that gepotidacin's safety profile is acceptable for its intended use (i.e., the treatment of uGC in patients who have limited or no other treatment options). Adverse reactions observed in the clinical studies were generally mild or moderate 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 participants in clinical trials. Additional warnings in the prescribing information include those for hypersensitivity reactions, CDI, and dose- and concentration-dependent prolongation of the QTc interval. 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 uGC in adult and pediatric patients 12 years of age and older weighing at least 45 kilograms who have limited or no other treatment options.

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. The proposed dose is 3000 mg given orally as two doses 12 hours apart to treat uncomplicated urogenital gonorrhea (uGC) in adult and pediatric patients 12 years of age and older who weigh at least 45 kilograms. Uncomplicated urogenital gonorrhea is generally treated by a single dose of intramuscular ceftriaxone, but antimicrobial resistance increasingly threatens successful treatment of *N. gonorrhoeae* infections. Clinicians typically base treatment on nucleic acid amplification testing (NAAT), whereas they rarely perform *N. gonorrhoeae* culture and antimicrobial susceptibility testing prior to initial treatment.

The Applicant conducted a single phase 3, randomized, multicenter, open-label, active-controlled noninferiority clinical study comparing gepotidacin to intramuscular ceftriaxone and oral azithromycin for treating uGC due to ceftriaxone-susceptible *N. gonorrhoeae* to assess gepotidacin's safety and effectiveness. The study met the prespecified noninferiority margin of 10% by assessing culture confirmed bacterial eradication of urogenital *N. gonorrhoeae* at the test of cure visit (microbiologic success). The safety database included 309 individuals who received at least one dose of gepotidacin. Most adverse events were mild or moderate and self-limited, and the overall safety assessment was favorable.

Reviewers identified several key safety review issues during the review of this supplemental new drug application (sNDA), 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. Limited Safety Database

3.1.2.2. Acetylcholinesterase Inhibition

3.1.2.3. QTc Prolongation

3.2. Approach to the Clinical Review

The primary evidence of effectiveness and safety for gepotidacin for the treatment of uGC was generated by a single clinical trial (EAGLE-1) in adult and pediatric patients 12 years of age and older. Efficacy and safety data were evaluated from this phase 3 trial. The submitted safety database from this clinical trial did not include a minimum of 500 participants exposed to gepotidacin at the proposed dose and duration as recommended in the FDA guidance for industry. However, the safety database, taken together with the prior uUTI trials, were adequate to evaluate the safety and efficacy of gepotidacin for a limited indication. Details on the EAGLE-1 trial are summarized in the table 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.

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

   Adult and pediatric patients 12 years of age and older weighing at least 45 kilograms (kg) who have limited or no alternative treatment options for the treatment of uncomplicated urogenital gonorrhea caused by susceptible strains of *Neisseria gonorrhoeae*.

2. 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[9,10,11]

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]

3. Complete response, if applicable

a. ☒ SEE was established
b. ☐ SEE was not established *(if checked, omit item 2)*

[9] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019)*

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

[11] 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 Participants Planned; Actual Randomized	Number of Centers and Countries
EAGLE-1 (NCT04010539)	Male and female participants 12 years of age and older with uGC	Control type: active, concurrent Randomization: standard, 1:1 ratio Blinding: open label, Applicant blinded Biomarkers: none Innovative design features: none	Drug: Gepotidacin Dosage: 3000 mg PO twice Number treated: 309 Duration (quantity and units): 1 d Drug: Ceftriaxone and azithromycin Dosage: 500 mg IM and 1000 mg PO, respectively Number treated: 313 Duration (quantity and units): 1 d	Primary: microbiological success (culture confirmed bacterial eradication of *N. gonorrhoeae* from the urogenital site at test of cure) Secondary: microbiological success (culture confirmed bacterial eradication of *N. gonorrhoeae* from rectal and pharyngeal body sites at test of cure)	620, 628	49 sites in 6 countries

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Participants Planned; Actual Randomized	Number of Centers and Countries
BTZ116576 (NCT02294682)	Male and female participants 18 years of age and older with uGC	Control type: active, concurrent Randomization: standard, 1:1 ratio Blinding: open label Biomarkers: none Innovative design features: none	Drug: Gepotidacin Dosage: 1500 mg PO Number treated: 53 Duration (quantity and units): 1 dose Drug: Gepotidacin Dosage: 3000 mg PO Number treated: 53 Duration (quantity and units): 1 dose	Primary: culture-confirmed bacterial eradication of urogenital *N. gonorrhoeae* at test of cure Secondary: culture-confirmed bacterial eradication of rectal or pharyngeal *N. gonorrhoeae* at test of cure	60; 106	12 centers in 2 countries

Source: Reviewer.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: NCT, national clinical trial; d, day; IM, intramuscular; PO, orally

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	
☐	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

The nonclinical assessment of gepotidacin's potential effectiveness against uGC was primarily informed by in vitro data, animal models of infection, and hollow-fiber infection model studies.

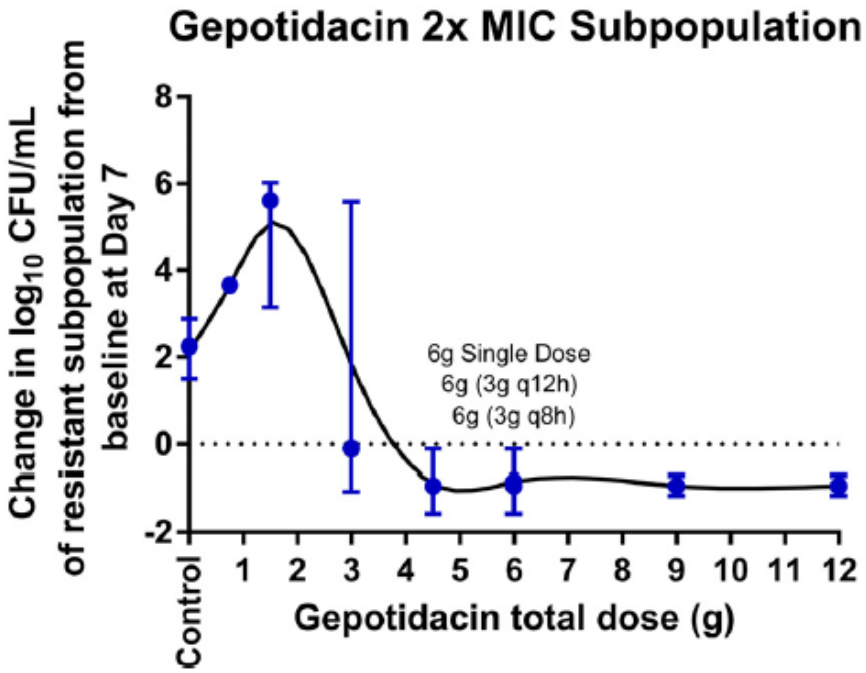
The Applicant provided an analysis of gepotidacin in vitro antibacterial activity against United States and global *N. gonorrhoeae* isolates from the Gonococcal Global Surveillance Study. This included isolates with phenotypic drug resistance to other antibacterial drugs, isolates from different body sites, and isolates characterized for mutations in target sites or with other

genotypic testing. The intracellular bactericidal activity of gepotidacin, the impact of resistance mechanisms on the gepotidacin MIC, and the frequency of spontaneous mutations were also assessed for *N. gonorrhoeae*. The in vivo efficacy model showed proof-of-concept for gepotidacin's efficacy against *N. gonorrhoeae* in a vaginal colonization model, a model that is acceptable for exploratory studies. Therefore, the determination of efficacy against *N. gonorrhoeae* relied primarily on nonclinical microbiology data and the data from human clinical trials. Refer to the Clinical Microbiology section of this review for additional information on the nonclinical microbiology assessment of potential effectiveness of gepotidacin against *N. gonorrhoeae.*

A 7-day hollow fiber infection model was conducted against a clinical *N. gonorrhoeae* isolate with a gepotidacin MIC of 1 µg/mL that carried the resistance patterns observed in the phase 2 clinical study BTZ116576 to specifically address the resistance observed in that study. The model demonstrated that gepotidacin daily dosing regimens ≥4.5 g (corresponding to *f*AUC0-24/MIC values ≥46) were necessary to successfully prevent amplification of resistant subpopulations in the tested clinical isolate harboring GyrA S91F:D95A and ParC D86N mutations.

To translate this finding into a clinically practical dosing strategy, the Applicant evaluated a regimen of 3 g administered twice (with the second dose given 12 hours post-treatment initiation) in the phase 3 study, which provides a total daily dose of 6 g that exceeds the 4.5 g threshold identified in the hollow-fiber model.

Figure 1. Relationship Between Gepotidacin Total Dose and Median (min, max) Change in log10CFU/mL From Baseline of the Gepotidacin 2×MIC Subpopulation for *N. gonorrhoeae* GSK #8 on Day 7.



5.2. Clinical Pharmacology/Pharmacokinetics

The clinical pharmacology properties of gepotidacin were comprehensively evaluated in the original review. See original review for uUTI for details. The clinical pharmacology review focused on optimizing dose selection to achieve resistance suppression and characterizing QT prolongation risk in special populations with increased drug exposure due to intrinsic and extrinsic factors (table below).

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Gepotidacin is a first in class triazaacenaphthylene bacterial type II topoisomerase inhibitor.
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 Cmax of 7.3 µg/mL) and 1800 mg (mean Cmax of 13.6 µg/mL), which exhibited mean ΔΔQTc of 12 msec and 22 msec, respectively. There was no disproportionate increase in the frequency of cardiovascular adverse events of special interest in uGC patients treated with the recommended dose of gepotidacin compared to counterparts treated with standard of care (ceftriaxone plus azithromycin) in the pivotal study (EAGLE-1). Only 1 event of grade 1 tachycardia was observed among 302 patients receiving gepotidacin (< 1%). Based on the QT consults, because the observed Cmax,ss of gepotidacin (11.6 µg/mL) does not exceed the exposure at a single IV dose of 1800 mg (13.6 µg/mL) in the QT assessment study, there is no need for reassessing the risk of QT prolongation for this new indication. However, there is concern for adverse events related to QTc prolongation and arrhythmias in clinical scenarios with increased gepotidacin exposure in specific populations with increased dose exposure, because of the higher 3000 mg dose for this indication. (See Sections 7.7.3, and 8 for details.)
General Information	
Bioanalysis	Validated UHPLC-MS/MS was used to determine gepotidacin concentrations in human plasma in the phase 2 Study BTZ116576. However, due to the use of a non-commercial dosage form and the limited sampling (single plasma concentration). No additional bioanalysis review was needed for this sNDA.

Characteristic	Drug Information
Healthy participants versus patients	No significant differences in Cmax and AUC between healthy and infected participants.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Post-Hoc Steady State Plasma Gepotidacin PK Parameters in Healthy Participants (3000 mg in 12-hour interval for 1 day)** **Parameter** — **Mean±SD** C_{max} (µg/mL)[a] — 11 (28.1) AUC_{0-T} (µg*hour/mL)[a,b] — 44.4 (22.8) Source: Table 16 in clinical study report 2019N422403_00 AUC_{0-T} and Cmax, were estimated where 2 doses were administered. Abbreviations: AUC_{0-t}, from time 0 to last quantifiable timepoint; Cmax, maximum plasma concentration
Range of effective dose(s) or exposure	Dose ranging study: • The phase 2 dose-ranging study (BTZ116576) evaluated single doses of 1500 mg and 3000 mg and demonstrated successful treatment of urogenital *N. gonorrhoeae*. However, resistance to gepotidacin emerged in 2 of the 3 microbiological failures for isolates with baseline MIC of 1 µg/mL. • Results from a 7-day in vitro hollow fiber infection model informed the clinical dose selection of 2 oral doses of 3000 mg taken 12 hours apart to prevent resistance amplification (See 5.1). Effective dosage: The phase 3 study (EAGLE-1) only evaluated one gepotidacin dosage (3000 mg×2 in 12-hour interval for 1 day). Effective exposure range: An exposure-response relationship was not established for uGC since no plasma concentrations were measured in the phase 3 study (EAGLE-1).
Maximally tolerated dose or exposure	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.
Dose proportionality	Gepotidacin AUCinf and Cmax were dose proportional within the dose range of 1500 mg to 3000 mg.
Accumulation	Accumulation is minimal due to the short treatment duration for uGC. Based on the PK study results from Study 209611 in healthy adults receiving 3000 mg BID, the mean Cmax for the first dose was 9.94 µg/mL, while the mean Cmax for the second dose was 10.9 µg/mL.
Time to achieve steady-state	Steady state was not achieved because the treatment consisted of only two doses administered in one day.
Bridge between to-be-marketed and clinical trial/study formulations	The final to-be-marketed oral formulation (gepotidacin mesylate tablet (b) (4) is the same formulation used in the phase 3 clinical studies EAGLE-1.
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)	No clinically meaningful food effect when administered with a moderate fat meal (table below). However, gepotidacin was not evaluated with a high fat meal.

Characteristic	Drug Information
Geometric least square mean and 90% CI	**Effect of Moderate Fat Meal on Plasma PK Parameters of Gepotidacin Oral Tablet** **Dosage Form** | **$AUC_{0-\infty}$** | **C_{max}** | **T_{max}** Mesylated Tablet | Geometric LS Mean Ratio (90% CI) | | Difference from fast 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: AUC0-∞, area under the concentration-time curve estimated to infinity; CI, confidence interval; Cmax, maximum plasma concentration; LS, least squares; PK, pharmacokinetic; Tmax, time to maximum concentration
Distribution	
Volume of distribution	The Vss from simulations in adult uGC patients was 188 L and was generally comparable with healthy adults and uUTI patients.
Plasma protein binding	25% 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	The geometric mean CL from simulations in adult urogenital uGC patients was 34.8 L/hr and was similar to that in adult uUTI patients with normal renal function.
Half-life	The $t_{1/2}$ from simulations in adult urogenital uGC patients was 9.4 hrs and was generally comparable with healthy adults and uUTI patients.
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).
Intrinsic Factors and Specific Populations	***Refer to Section 8 for a discussion of clinical considerations when multiple risk factors for increased gepotidacin exposure are combined.***
Body weight	No dosage adjustments are needed based on body weight differences because 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 uGC patients based on age ranging from 18 to 64 years in phase 3 study; 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.

Characteristic	Drug Information
Drug Interaction Liability (Drug as Perpetrator)	
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 DDI study of gepotidacin and midazolam (a CYP3A4 substrate) indicated gepotidacin is a weak CYP3A4 inhibitor.
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 Cmax 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; AUCinf, area under the concentration-time curve estimated to infinity; BMI, body mass index; Cmax, maximum plasma concentration; CI, confidence interval; DDI, drug-drug interaction; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; fAUC, area under the free-drug concentration-time curve; fAUC/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; Tmax, 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 final dosing regimen of 3000 mg BID for one day was evaluated in the phase 3 clinical trial. The dose for phase 3 was based on clinical study results from phase 2 and subsequent hollow fiber infection modeling.

The phase 2 study (BTZ116576) demonstrated that both 1500 mg and 3000 mg single doses achieved ≥95% efficacy against urogenital *N. gonorrhoeae* infection with no unexpected safety signals. However, resistance analysis revealed that among 5 participants with baseline MIC of 1 μg/mL, 2 achieved microbiological cure while 3 did not respond to treatment, with all non-responders having ciprofloxacin resistance and pre-existing ParC D86N mutations. Importantly, 2/3 of these failures developed additional GyrA A92T substitutions post-treatment, representing a ≥4-fold increase in gepotidacin MIC (from 1 μg/mL to ≥32 μg/mL). To address these resistance concerns, an in vitro 7-day hollow fiber infection model was conducted, using a single strain of *N. gonorrhoeae*, which identified fAUC/MIC ≥46 as the target for resistance suppression and confirmed that total daily doses ≥4,500 mg prevented resistance amplification.

The phase 3 study (BTZ116577) used a dosing regimen of 3000 mg twice daily for one day, which demonstrated a 92.6% microbiological success rate for uncomplicated urogenital *N. gonorrhoeae* (non-inferior to ceftriaxone plus azithromycin) with no reduction in susceptibility to gepotidacin observed at any body site, and zero culture-confirmed bacterial persistence at the urogenital site, validating the dosing regimen developed to address resistance concerns identified in phase 2.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Results of Pooled Analyses

In this sNDA for the indication of treatment of uncomplicated urogenital gonorrhea, one phase 3 clinical trial, EAGLE-1 (BTZ116577), provides the primary efficacy data for gepotidacin, with the phase 2 clinical trial (BTZ116576) providing confirmatory evidence. Due to the differences in dosages and study designs, a pooled analysis was not conducted.

6.2.2. Study EAGLE-1 (BTZ116577)

6.2.2.1. Design, Study EAGLE-1

Study EAGLE-1 was a phase 3, multicenter, randomized, open-label, comparator-controlled noninferiority study that enrolled adolescent and adult participants with uncomplicated

urogenital gonorrhea. Eligible patients were randomized 1:1 to receive two oral doses of gepotidacin 3 g on Day 1, or a single IM dose of ceftriaxone 500 mg and a single oral dose of azithromycin 1 g on Day 1. The randomization was stratified by sex and sexual orientation combination (men who have sex with men, men who have sex with women, or female) and age (<18 years, ≥18 to 65 years, or >65 years). Safety, efficacy, and microbiological assessments were conducted at Baseline (Day 1) and repeated at the TOC (test-of-cure, protocol window Day 4 to 8, Analysis Day 4 to 10) and FU (follow-up, Analysis Day 13 to 24) Visits. The study enrolled 627 participants between October 21, 2019, and September 26, 2023, from Europe, Australia, United States, and Mexico.

The primary efficacy endpoint was microbiological success as determined by culture at the urogenital site at TOC in the microbiological intent-to-treat (micro-ITT) population. The study utilized a non-inferiority design with a pre-defined non-inferiority margin of 10%, in accordance with the FDA Guidance, *Uncomplicated Gonorrhea: Developing Drugs for Treatment* (August 2015).

6.2.2.2. Eligibility Criteria, Study EAGLE-1

Participants were eligible to be included in the study only if all of the following criteria applied:

1. The participant was ≥12 years at the time of signing the informed consent/assent and had a body weight >45 kg.
2. The participant had clinical suspicion of a urogenital gonococcal infection (which could include sexual contact within the past 14 days with a partner who had a confirmed gonococcal infection) with or without pharyngeal and/or rectal gonococcal infection and had 1 of the following:
   - male participants with purulent yellow, green, or white urethral discharge or female participants with abnormal cervical or vaginal mucopurulent discharge upon physical examination, or
   - a prior positive culture for NG from up to 5 days before Screening (as long as the participant had not received any treatment for this infection), or
   - a Gram or equivalent stain (urogenital specimens only) positive or presumptive for intracellular diplococci from up to 5 days before Screening (as long as the participant had not received any treatment for this infection), or
   - a prior positive NAAT assay for NG from up to 7 days before Screening (as long as the participant had not received any treatment for this infection).
3. The participant must be willing to abstain from anal, oral, and vaginal sexual intercourse or use condoms for all forms of intercourse from the Baseline Visit through the TOC Visit.
4. Male or female and must have his or her original urogenital anatomy at birth
   a. Male participants: A male participant must agree to use contraception from the Baseline Visit through completion of the TOC Visit.
   b. Female participants: A female participant was eligible to participate if she was a woman of childbearing potential (WOCBP) who was not pregnant as confirmed by a high sensitivity urine pregnancy text at Baseline (Day 1) regardless of current or prior contraception use or abstinence, was not breastfeeding, or was not a WOCBP

5. The participant was capable of giving signed informed consent/assent.

Participants were excluded from the study if any of the following criteria applied:

1. The participant was a male with a current diagnosis of epididymitis and/or orchitis at the time of the Baseline Visit.
2. The participant was suspected or confirmed to have a *C. trachomatis* infection and per the investigator's judgement standard-of-care treatment for this infection cannot be safely postponed until the TOC Visit.
3. The participant had a body mass index ≥40 kg/m^2 or had a body mass index ≥35.0 kg/m^2 and is experiencing obesity-related health conditions such as uncontrolled high blood pressure or uncontrolled diabetes.
4. The participant had a history of sensitivity to the study treatments, or components thereof, or a history of a drug allergy (including erythromycin and any macrolide or ketolide drug) or other allergy that, in the opinion of the investigator or medical monitor, contraindicated his or her participation.
5. The participant was immunocompromised or had altered immune defenses that might predispose the participant to a higher risk of treatment failure and/or complications (e.g., participants with uncontrolled diabetes, renal transplant recipients, participants with clinically significant persistent granulocytopenia [absolute neutrophil count <1000/µL], and participants receiving immunosuppressive therapy, including corticosteroid therapy [>40 mg/day prednisolone or equivalent for >1 week, ≥20 mg/day prednisolone or equivalent for >2 weeks, or prednisolone or equivalent ≥10 mg/day for >6 weeks]). Participants with a known CD4 count of <200 cells/mm^3 should not be enrolled.
6. The participant had any of the following:
   - Medical condition that required medication that may be impacted by inhibition of acetylcholinesterase, such as:
     − Poorly controlled asthma or chronic obstructive pulmonary disease at the Baseline Visit and, in the opinion of the investigator, not stable on current therapy
     − Acute severe pain, uncontrolled with conventional medical management
     − Active peptic ulcer disease
     − Parkinson disease
     − Myasthenia gravis
     − A history of seizure disorder requiring medications for control (this did not include a history of childhood febrile seizures)

   OR
   - Any surgical or medical condition (active or chronic) that might interfere with drug absorption, distribution, metabolism, or excretion of the study treatment (e.g., ileostomy or malabsorption syndrome).
7. The participant had known anuria, oliguria, or severe impairment of renal function (creatinine clearance <30 mL/min or clinically significant elevated serum creatinine as determined by the investigator).
8. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up.
9. The participant had a serious underlying disease that could be imminently life threatening, or the participant was unlikely to survive for the duration of the study period.
10. The participant had congenital long QT syndrome or known prolongation of QTc.

11. The participant had uncompensated heart failure.
12. The participant had severe left ventricular hypertrophy.
13. The participant had a family history of QT prolongation or sudden death.
14. The participant had a recent history of vasovagal syncope or episodes of symptomatic bradycardia or bradyarrhythmia within the last 12 months.
15. The participant was taking QT-prolonging drugs or drugs known to increase the risk of torsades de pointes (TdP) per the www.crediblemeds.org "Known Risk of TdP" category at the time of his or her Baseline Visit, which cannot be safely discontinued from the Baseline Visit to the TOC Visit; or the participant was taking a strong CYP3A4 inhibitor.
16. For any participant ≥12 to <18 years, the participant had an abnormal ECG reading.
17. The participant had a QTc >450 msec or a QTc >480 msec for participants with bundle-branch block.
18. The participant had a documented or recent history of uncorrected hypokalemia within the past 3 months.
19. The participant had a known history of cholestatic jaundice or hepatic dysfunction associated with prior use of azithromycin.
20. The participant had a known alanine aminotransferase (ALT) value >2 × upper limit of normal (ULN).
21. The participant had a known bilirubin value >1.5 × ULN (isolated bilirubin >1.5 × ULN was acceptable if bilirubin was fractionated and direct bilirubin <35%).
22. The participant had a current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), including symptomatic viral hepatitis or moderate-to-severe liver insufficiency (Child Pugh class B or C).
23. The participant had been previously randomized in this study or had previously been treated with gepotidacin.
24. The participant had participated in a clinical trial and had received an investigational product within 30 days or 5 half-lives, whichever was longer.
25. The participant had any of the following gonococcal infections that required a different dose or duration of treatment:
    - Suspected or confirmed pelvic inflammatory disease
    - Suspected or confirmed gonococcal arthritis
    - Suspected or confirmed gonococcal conjunctivitis
    - Suspected or confirmed gonococcal endocarditis
    - Other evidence of disseminated gonococcal infection
26. The participant had received any antibacterial therapy for the treatment of a gonococcal infection within 14 days before the Baseline Visit.
27. The participant had received any systemic, topical, or intravaginal antibacterials or any systemic antifungals within 7 days before the Baseline Visit.
28. The participant must not use St John's wort or ergot derivatives from within 14 days before the Baseline Visit through the TOC Visit.

6.2.2.3. Statistical Analysis Plan, Study EAGLE-1

The following analysis populations were included in the study:

- Screened Population: All participants who were screened for eligibility.

- Intent-to-Treat (ITT) Population: All participants randomly assigned to study treatment.
- Microbiological ITT (micro-ITT) Population: All participants randomly assigned to study treatment who received at least 1 dose of study treatment and had confirmed NG isolated that was ceftriaxone-susceptible from baseline culture of their urogenital specimen.
- Micro-ITT Rectal Population: Participants who met the definition of the micro-ITT Population and had confirmed NG isolated that was ceftriaxone-susceptible from baseline culture of their rectal specimen.
- Micro-ITT Pharyngeal Population: Participants who meet the definition of the micro-ITT Population and have confirmed NG isolated that is ceftriaxone-susceptible from baseline culture of their pharyngeal specimen.
- Microbiologically Evaluable (ME) Population: Participants who met the definition of the micro-ITT Population and followed important components of the study (i.e., [1] received all planned doses as randomized and actual treatment was the same as randomized, [2] had a urogenital specimen collected at the TOC Visit, with available culture results, [3] had not taken any other systemic antibiotic prior to the TOC Visit, unless it was taken for the current infection, and [4] had no major deviation that prevented evaluation of efficacy).
- Safety Population: All participants who received at least 1 dose of study treatment.

The micro-ITT Population was the primary analysis population.

The primary efficacy endpoint was culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., microbiological success) at the TOC (Analysis Day 4 to 10) Visit. The non-inferiority of gepotidacin to ceftriaxone/azithromycin was evaluated using two-side 95% Miettinen and Nurminen confidence interval stratified by sex and sexual orientation combination (i.e., men who have sex with men, men who have sex with women, or female), with a non-inferiority margin of 10%. The 10% margin was consistent with recommendations in the FDA Guidance for Industry, *Uncomplicated Gonorrhea: Developing Drugs for Treatment*.

Secondary efficacy endpoints included the following:

- Culture-confirmed bacterial eradication of NG from the rectal body site at the TOC Visit
- Culture-confirmed bacterial eradication of NG from the pharyngeal body site at the TOC Visit

Secondary efficacy endpoints were summarized descriptively.

6.2.2.4. Results of Analyses, Study EAGLE-1

A total of 660 participants were screened in the study. Among them, 627 participants were randomized, with one participant randomized twice (22 months apart).

Table 6. Participant Disposition, EAGLE-1

Disposition Outcome	Gepotidacin N=314	Ceftriaxone-Azithromycin N=314
Participants Randomized[a]	314 (100.0)	314 (100.0)
ITT population	314 (100.0)	314 (100.0)
Micro-ITT population	202 (64.3)	204 (65.0)
Micro-ITT rectal population	26 (8.3)	15 (4.8)
Micro-ITT pharyngeal population	18 (5.7)	17 (5.4)
ME population	187 (59.6)	186 (59.2)
Safety population[c]	309	313
Study treatment not completed[b]	13 (4.1)	2 (0.6)
Not dosed	5 (1.6)	2 (0.6)
Prematurely Discontinued	8 (2.5)	0
Adverse event	3 (1.0)	0
Lost to follow-up	4 (1.3)	0
Withdrawal by participant	1 (0.3)	0
Discontinued study[b]	20 (6.4)	19 (6.1)
Adverse event	3 (1.0)	0
Lost to follow-up	10 (3.2)	14 (4.5)
Withdrawal by participant	4 (1.3)	1 (0.3)
Physician decision	0	2 (0.6)
Protocol deviation	0	1 (0.3)
Other	3 (1.0)	1 (0.3)

Source: Statistical Reviewer Analysis; adsl.xpt, adds.xpt;
[a] One participant was randomized twice (22 months apart) and entered both arms. This participant was counted twice in ITT and safety populations. This participant was not in the Micro-ITT population.
[b] Percentages are based on number of randomized participants.
[c] The safety population was presented by actual treatment received. Four participants randomized to gepotidacin, and two participants randomized to ceftriaxone/azithromycin were not dosed. Another participant randomized to gepotidacin received ceftriaxone/azithromycin.
Abbreviations: ITT, Intention-to-treat population; micro-ITT, microbiological intent-to-treat; ME, microbiologically evaluable; N, number of participants in treatment group; n, number of participants in specified population or group;

Gepotidacin was administered as two oral doses in a day. Note that 8 participants did not complete the second dose due to adverse event, lost to follow-up, or withdrawal by participant.

Demographic characteristics are listed in the table below. Patient demographic and baseline characteristics were generally balanced between treatment groups. The majority of participants were male at birth (89%), non-Hispanic (82%), and White (75%).

Table 7. Baseline Demographics and Clinical Characteristics, ITT Population, EAGLE-1

Characteristic	Gepotidacin N=314	Ceftriaxone-Azithromycin N=314
Sex and sexual orientation, n (%)		
Female	35 (11.1)	34 (10.8)
Male	279 (88.9)	280 (89.2)
MSM	218 (69.4)	221 (70.4)
MSW	58 (18.5)	59 (18.8)
Missing	3 (1.0)	0
Age, years		
Mean (SD)	33.9 (10.42)	33.7 (10.70)
Median	33.0	32.0
Min, Max	16.0, 64.0	17.0, 71.0

Characteristic	Gepotidacin N=314	Ceftriaxone-Azithromycin N=314
Age group (years), n (%)		
<18	1 (<1)	1 (<1)
≥18 to 65	313 (99.7)	311 (99.0)
>65	0	2 (<1)
Race, n (%)		
White	231 (73.6)	241 (76.8)
Black or African American	49 (15.6)	39 (12.4)
Asian	12 (3.8)	17 (5.4)
American Indian or Alaska Native	9 (2.9)	10 (3.2)
Native Hawaiian or Other Pacific Islander	7 (2.2)	2 (<1)
Multiple	6 (1.9)	5 (1.6)
Ethnicity, n (%)		
Hispanic	52 (16.6)	62 (19.7)
Non-Hispanic	262 (83.4)	250 (79.6)
Missing	0	2 (<1)
Baseline height (cm)		
Mean (SD)	176.3 (8.58)	176.3 (8.42)
Median	176.0	176.5
Min, Max	147.6, 199.0	150.0, 210.0
Missing	3	3
Baseline weight (kg)		
Mean (SD)	76.1 (13.58)	75.8 (12.26)
Median	74.9	75.4
Min, Max	47.7, 118.2	49.0, 119.8
Missing	3	3
BMI (kg/m^2)		
Mean (SD)	24.5 (4.02)	24.4 (3.65)
Median	24.2	24.0
Min, Max	14.2, 38.6	17.4, 41.3
Missing	3	3
Region, n (%)		
Americas	59 (18.8)	41 (13.1)
Asia-Pacific	51 (16.2)	54 (17.2)
Europe	204 (65.0)	219 (69.7)
Country of participation, n (%)		
Australia	51 (16.2)	54 (17.2)
Germany	70 (22.3)	69 (22.0)
Spain	90 (28.7)	96 (30.6)
United Kingdom	44 (14.0)	54 (17.2)
Mexico	8 (2.5)	7 (2.2)
United States	51 (16.2)	34 (10.8)
History of sexually transmitted infection(s), n (%)		
Yes	173 (55.1)	178 (56.7)
No	134 (42.7)	131 (41.7)
Unknown or Missing	7 (2.2)	5 (1.6)
HIV status, n (%)		
Negative	233 (74.2)	233 (74.2)
Positive	68 (21.7)	68 (21.7)
Missing	13 (4.1)	13 (4.1)

Source: FDA Analysis; adsl.xpt;
Abbreviations: ITT, intent-to-treat; MSM, men who have sex with men; MSW, men who have sex with women; N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

Microbiological Success at the Urogenital Body Site

The table below displays analysis results for the primary efficacy endpoint of microbiological success at TOC evaluated in the micro-ITT population. Treatment with gepotidacin demonstrated non-inferiority to the active control of ceftriaxone/azithromycin with a non-inferiority margin of 10% in the primary analysis. All treatment failures in the primary analysis were due to "unable to determine" outcomes. To evaluate the impact of unable to determine outcomes, the reviewer conducted the following additional sensitivity analyses, with details summarized in the table.

Firstly, the primary analysis was conducted including out-of-window TOC culture results (out-of-window TOC results were collected from Day 11 to Day 17). Results were similar to the original primary analysis, demonstrating non-inferiority of gepotidacin to the active control.

Secondly, the primary analysis was conducted including out-of-window TOC culture results, results processed beyond 24 hours, and actual culture results regardless of additional use of systematic antimicrobials. Results were similar to the original primary analysis, demonstrating non-inferiority of gepotidacin to the active control.

Thirdly, a worst-case scenario analysis was conducted. All unable to determine outcomes in the gepotidacin arm were considered as failures, while all unable to determine outcomes in the ceftriaxone-azithromycin arm were considered as successes. This analysis can rule out a treatment difference of -12.7% between gepotidacin and the active control. According to the FDA Guidance for Industry, *Uncomplicated Gonorrhea: Developing Drugs for Treatment*, 11.9% is a conservative estimate of the effect of an antibacterial drug in the treatment of uncomplicated gonorrhea. If spontaneous resolution rates for uncomplicated gonorrhea were used as a comparison to effective treatment, the estimated treatment difference would be much larger than 11.9%. This worst-case scenario analysis supports the conclusion that gepotidacin treatment is better than spontaneous resolution.

Table 8. NG Culture from the Urogenital Body Site, Micro-ITT Population, Study EAGLE-1

Primary Analysis	Gepotidacin N=202	Ceftriaxone-Azithromycin N=204	Difference % (95% CI[a])
Microbiological Success (Negative for NG), n (%)	187 (92.6)	186 (91.2)	-0.1% (-5.6%, 5.5%)
Non-presumptive NG	3 (1.5)	11 (5.4)	
Failure, n (%)	15 (7.4)	18 (8.8)	
Positive for NG	0	0	
Unable to Determine	15 (7.4)	18 (8.8)	
No TOC Culture Data	6 (3.0)	8 (3.9)	
Negative for NG, culture processed beyond 24 hours[b]	6 (3.0)	1 (0.5)	
Negative for NG, TOC occurred out of window[c]	3 (1.5)	7 (3.4)	
Negative for NG, Use of other systematic antimicrobials before TOC	0	2 (1.0)	
Include Out of Window Results	**Gepotidacin N=202**	**Ceftriaxone-Azithromycin N=204**	**Difference % (95% CI[a])**
Cure, n (%)	190 (94.1)	193 (94.6)	-2.0% (-6.8%, 2.8%)
Include All Available Culture Outcomes	**Gepotidacin N=202**	**Ceftriaxone-Azithromycin N=204**	**Difference % (95% CI[a])**
Cure, n (%)	196 (97.0)	196 (96.1)	0.4% (-3.4%, 4.3%)
Worst Case Scenario	**Gepotidacin N=202**	**Ceftriaxone-Azithromycin N=204**	**Difference % (95% CI[a])**
Cure, n (%)	187 (92.6)	204 (100)	-8.7% (-12.7%, -4.7%)

Source: FDA Analysis; admic.xpt.
[a] 95% CI was calculated with Miettinen and Nurminen confidence interval stratified by sex and sexual orientation combination (i.e., men who have sex with men, men who have sex with women, or female)
[b] One culture from the Ceftriaxone/Azithromycin was processed beyond 4 days. All cultures from the Gepotidacin arm processed beyond 24 hours were processed on the following day of collection.
[c] Including one participant from the Ceftriaxone/Azithromycin whose Day 11 culture result was non-presumptive NG.
Abbreviations: Micro-ITT, microbiological intent-to-treat; TOC, test-of-cure; CI, confidence interval; NG, *Neisseria gonorrhoeae*

The table below summarizes the primary endpoint by subgroup. The treatment effect with gepotidacin based on microbiological success rate was generally consistent in subgroup analyses except certain categories with small sample sizes. As there were no failures of the primary endpoint in either arm of the micro-ITT population due to being positive for NG, this was also true in all subgroups.

Table 9. NG Culture Microbiological Success Rate from the Urogenital Body Site by Subgroup, Micro-ITT Population, Study EAGLE-1

Characteristic	Gepotidacin N=202	Ceftriaxone-Azithromycin N=204	Difference % (95% CI[a])
Overall	187/202 (92.6%)	186/204 (91.2%)	1.4% (-4.1%, 6.9%)
Sex and sexual orientation, n (%)			
Female	16/17 (94.1%)	16/17 (94.1%)	0 (-22.6%, 22.6%)
MSM	133/144 (92.4%)	138/146 (94.5%)	-2.2% (-8.4%, 3.8%)
MSW	38/41 (92.7%)	32/41 (78.0%)	14.6% (-0.8%, 30.7%)

Characteristic	Gepotidacin N=202	Ceftriaxone-Azithromycin N=204	Difference % (95% CI[a])
Age group (years), n (%)			
<18	0	1/1 (100.0%)	
≥18 to <65	187/202 (92.6%)	185/203 (91.1)	1.4% (-4.1%, 7.0%)
Race, n (%)			
White	138/146 (94.5%)	143/153 (93.5%)	1.1% (-4.7%, 6.9%)
Black or African American	31/36 (86.1%)	19/25 (76.0%)	10.1% (-9.6%, 31.9%)
Asian	6/7 (85.7%)	14/16 (87.5%)	-1.8% (-42.0%, 26.7%)
American Indian or Alaska Native	5/5 (100.0%)	6/6 (100.0)	0 (-45.8%, 41.3%)
Native Hawaiian or Other Pacific Islander	4/5 (80.0%)	0	
Multiple	3/3 (100.0%)	4/4 (100.0%)	0 (-59.9%, 52.8%)
Ethnicity, n (%)			
Hispanic	30/32 (93.8%)	36/38 (94.7%)	-1.0% (-15.7%, 12.2%)
Non-Hispanic	157/170 (92.4%)	148/164 (90.2%)	2.1% (-4.1%, 8.5%)
Missing	0	2/2 (100.0%)	
Region, n (%)			
Americas	28/33 (84.8%)	18/22 (81.8%)	3.0% (-16.8%, 25.8%)
Asia-Pacific	30/35 (85.7%)	33/37 (89.2%)	-3.5% (-20.4%, 12.9%)
Europe	129/134 (96.3%)	135/145 (93.1%)	3.2% (-2.4%, 9.0%)
History of sexually transmitted infection(s), n (%)			
Yes	104/110 (94.5%)	107/115 (93.0%)	1.5% (-5.4%, 8.4%)
No	80/89 (89.9%)	76/85 (89.4%)	0.5% (-9.0%, 10.2%)
Unknown or Missing	3/3 (100.0%)	3/4 (75.0%)	25.0% (-43.8%, 72.3%)
HIV status, n (%)			
Negative	147/155 (94.8%)	149/163 (91.4%)	3.4% (-2.3%, 9.4%)
Positive	38/43 (88.4%)	31/35 (88.6%)	-0.2% (-15.2%, 16.1%)
Missing	2/4 (50.0%)	6/6 (100.0%)	-50.0% (-85.9%, 4.3%)

Source: FDA Analysis; adsl.xpt; admic.xpt.
[a] 95% CI was calculated with unstratified Miettinen and Nurminen confidence interval
Abbreviations: Micro-ITT, microbiological intent-to-treat; N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

Microbiological Success at the Rectal Body Site

The microbiological success rate at the rectal body site was higher in the gepotidacin arm, but the failures were due to unable to determine outcomes, and the total sample size was small (N=41). See the table below for details.

Table 10. NG Culture from the Rectal Body Site, Micro-ITT Rectal Population, Study EAGLE-1

Primary Analysis	Gepotidacin N=26	Ceftriaxone-Azithromycin N=15	Difference % (95% CI[a])
Microbiological Success (Negative for NG), n (%)	26 (100.0)	12 (80.0)	20.0% (5.2%, 45.5%)
Non-presumptive NG	0	1 (6.7)	
Failure, n (%)	0	3 (20.0)	
Positive for NG	0	0	
Unable to Determine	0	3 (20.0)	
No TOC Culture Data	0	2 (13.3)	
Negative for NG, TOC occurred out of window	0	1 (6.7)	

Source: FDA Analysis; admic.xpt.
[a] 95% CI was calculated with unstratified Miettinen and Nurminen confidence interval.
Abbreviations: Micro-ITT, microbiological intent-to-treat; TOC, test-of-cure; CI, confidence interval; NG, *Neisseria gonorrhoeae*

Microbiological Success at the Pharyngeal Body Site

The microbiological success rate at the pharyngeal body site was numerically higher in the ceftriaxone/azithromycin arm, but the total sample size was small (N=35). See the table below for details.

Table 11. NG Culture from the Pharyngeal Body Site, Micro-ITT Pharyngeal Population, Study EAGLE-1

Primary Analysis	Gepotidacin N=18	Ceftriaxone-Azithromycin N=17	Difference % (95% CI[a])
Microbiological Success (Negative for NG), n (%)	14 (77.8)	16 (94.1)	-16.3% (-41.1%, 8.8%)
Non-presumptive NG	0	1 (5.9)	
Failure, n (%)	4 (22.2)	1 (5.9)	
Positive for NG	2 (11.1)	0	
Unable to Determine	2 (11.1)	1 (5.9)	
No TOC Culture Data	0	1 (5.9)	
Negative for NG, culture processed beyond 24 hours	1 (5.6)	0	
Negative for NG, TOC occurred out of window	1 (5.6)	0	

Source: FDA Analysis; admic.xpt.
[a] 95% CI was calculated with unstratified Miettinen and Nurminen confidence interval.
Abbreviations: Micro-ITT, microbiological intent-to-treat; TOC, test-of-cure; CI, confidence interval; NG, *Neisseria gonorrhoeae*

NG NAAT Results AT TOC

The NG NAAT positive rates were similar between the gepotidacin arm and the ceftriaxone/azithromycin arm at TOC at the urogenital site and at the rectal site. The NG NAAT positive rate was numerically higher in the gepotidacin arm at the pharyngeal site, but the sample size was small (N=31). See the table below for details.

Table 12. NG NAAT Result at TOC, Micro-ITT Population NG NAAT Baseline Central Lab Positive Participants, Study EAGLE-1

NG NAAT Result at Urogenital Site, Micro-ITT Population	Gepotidacin N=183	Ceftriaxone-Azithromycin N=176
Negative, n (%)	151 (82.5)	133[c] (75.6)
Positive, n (%)	20 (10.9)	21 (11.9)
Missing, n (%)	12 (6.6)	22 (12.5)
Difference in negative rate between two arms % (95% CI[a])	6.9% (-1.5%, 15.4%)	
NG NAAT Result at the Rectal Site, Micro-ITT Rectal Population	**Gepotidacin N=25**	**Ceftriaxone-Azithromycin N=14**
Negative, n (%)	24 (96.0)	9 (64.3)
Positive, n (%)	0	0
Missing, n (%)	1 (4.0)	5 (35.7)
NG NAAT Result at the Pharyngeal Site, Micro-ITT Pharyngeal Population	**Gepotidacin N=15**	**Ceftriaxone-Azithromycin N=16**
Negative, n (%)	8 (53.3)	13 (81.3)
Positive, n (%)	6 (40.0)	2 (12.5)
Missing, n (%)	1 (6.7)	1 (6.3)

Source: FDA Analysis; admic.xpt.
[a] 95% CI was calculated with unstratified Miettinen and Nurminen confidence interval.
[b] Participants who had missing results or tested negative for NG NAAT at baseline were excluded from this analysis.
[c] One participant from the ceftriaxone-azithromycin arm who tested negative at TOC received other systemic antimicrobial before TOC.
Abbreviations: Micro-ITT, microbiological intent-to-treat; TOC, test-of-cure; NAAT: nucleic acid amplification test; NG, *Neisseria gonorrhoeae*; CI, confidence interval; N, number of participants in treatment group; n, number of participants in specified population or group

6.2.3. Study BTZ116576

6.2.3.1. Design, Study BTZ116576

Study BTZ116576 was a phase 2, multicenter, randomized, dose-ranging study that enrolled adult participants with uncomplicated urogenital gonorrhea in the US and UK. Eligible patients were randomized 1:1 to receive a single oral dose of gepotidacin 1.5 g or 3 g. The randomization was stratified by [redacted]. Study visits occurred at the Baseline (Day 1) and Test-of-Cure (TOC, Day 4 to 8). The study enrolled 106 participants between April 15, 2015, and July 22, 2016.

6.2.3.2. Eligibility Criteria, Study BTZ116576

A participant was eligible for inclusion in this study only if all of the following criteria applied:

1. The participant was an adult male or female at least 18 years of age at the time of signing informed consent who met one of the following criteria:
   a. A nonpregnant, nonlactating female of childbearing potential who 1) was sexually inactive by abstinence, 2) had a sole male partner who had been sterilized, or 3) used a contraceptive method with a failure rate of <1% through the Test-of-Cure Visit. Females of childbearing potential must not become pregnant during the study.
   b. A female of non-childbearing potential, which included the following:

i. Females who were surgically sterile with a documented hysterectomy and/or bilateral oophorectomy.
ii. Females with documented tubal ligation. If the procedure was done hysteroscopically, the effectiveness of tubal occlusion must have been documented by hysterosalpingogram after the procedure (typically 3 months after the procedure).
iii. Females who were postmenopausal, defined as amenorrhoeic for greater than 1 year. For women whose menopausal status was in doubt, documented previous confirmatory blood samples with follicle-stimulating hormone >40 mIU/mL and estradiol <40 pg/mL (<140 pmol/L) would need to be confirmed, or they would be required to use one of the contraception methods

2. There was clinical suspicion that the participant had a urogenital gonococcal infection as confirmed by the presence of purulent discharge upon physical examination and by one or more of the following:
   - A prior culture or nucleic acid amplification test (NAAT) positive for *N. gonorrhoeae*
   - A Gram stain positive or presumptive for Gram-negative diplococci
   - Participant-reported sexual contact with a partner diagnosed with gonorrhea within the past 14 days
3. The participant had provided written, dated, informed consent and was willing and able to comply with the study protocol.

A participant was not eligible for inclusion in this study if any of the following criteria applied:

1. The participant was pregnant or nursing.
2. The participant was a hysterectomized female without a cervix.
3. The participant was a male with a current diagnosis of epididymitis or orchitis at the time of the Baseline Visit.
4. The participant had a body mass index ≥40.0 kg/m^2.
5. The participant had a serious underlying disease that could be imminently life threatening, or the participant was unlikely to survive for the duration of the study period.
6. The participant had a medical condition or required medication that might be aggravated by inhibition of acetylcholinesterase, such as:
   - Poorly controlled asthma or chronic obstructive pulmonary disease at baseline and, in the opinion of the investigator, was not stable on current therapy
   - Acute severe pain, uncontrolled with conventional medical management
   - Active peptic ulcer disease
   - Parkinson's disease
   - Myasthenia gravis
   - A history of seizure disorder requiring medications for control. This did not include a history of childhood febrile seizures
   - Any evidence of mechanical obstruction of the urinary or digestive tracks
7. The participant had any past history or current diagnosis of *Clostridium difficile* infection at the time of the Baseline Visit.
8. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up.

9. The participant had a history of sensitivity to the study medication, or components thereof, or a history of a drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicated their participation.
10. The participant had a PR interval <120 or >220 msec.
11. The participant had a corrected QT (QTc) >450 msec or a QTc >480 msec for participants with bundle-branch block.
12. The participant had QRS duration <70 or >120 msec.
13. The participant had the following cardiovascular medical conditions or family history:
    - Pre-existing Grade II atrioventricular block or higher or a history of significant vasovagal and/or syncopal episodes or episodes of symptomatic bradycardia
    - Pre-existing or known moderate to severe heart failure
    - Family history of QT prolongation or sudden death Hepatic
14. The participant had a current or chronic history of liver disease (with the exception of Gilbert's syndrome), including symptomatic viral hepatitis and moderate to severe liver insufficiency (Child-Pugh class B or C).
15. The participant had been previously enrolled in this study or had previously been treated with gepotidacin.
16. The participant had participated in a clinical trial and had received an investigational product within 30 days or 5 half-lives, whichever was longer.
17. The participant had the following gonococcal infections:
    - Suspected or confirmed pelvic inflammatory disease
    - Suspected or confirmed gonococcal arthritis
    - Other evidence of disseminated gonococcal infection
18. The participant had received treatment with a systemic or intravaginal antibacterial within 14 days of study entry.
19. Participant was taking a medication that had a known risk of torsades de pointes (TdP) per the Crediblemeds.org "Known Risk of TdP" category at the time of their Baseline (Day 1) Visit or consumed grapefruit or other juice containing flavonoids (e.g., cranberry juice) within 24 hours before study drug administration.

6.2.3.3. Statistical Analysis Plan, Study BTZ116576

The following analysis populations were included in the study:

- All Randomized Population: All participants who were randomized.
- Microbiological Evaluable (ME) Population: All randomized participants who have *N. gonorrhoeae* isolated from baseline cultures of urogenital swab specimens, received any dose of gepotidacin, and returned for their Test-of-Cure Visit.
- Safety Population: All randomized participants who received any dose of gepotidacin.
- PK Population: All randomized participants with a valid PK sample taken.

The Microbiological Evaluable Population was the primary analysis population. The primary efficacy endpoint was culture-confirmed bacterial eradication of urogenital *N. gonorrhoeae* at the Test-of-Cure (TOC) Visit.

6.2.3.4. Results of Analyses, Study BTZ116576

A total of 106 participants were randomized in this study. One participant in the gepotidacin 1500 mg arm was unable to swallow the capsules and did not complete the study.

Table 13. Participant Disposition, BTZ116576

Disposition Outcome	Gepotidacin 1500 mg N=53	Gepotidacin 3000 mg N=53
Participants Randomized	53 (100.0)	53 (100.0)
Safety population[a]	52 (98.1)	53 (100.0)
ME population	30 (56.6)	39 (73.6)
PK population	34 (64.2)	36 (67.9)

Source: Statistical Reviewer Analysis; adsl.xpt, adds.xpt;
[a] One participant was unable to swallow the capsules and withdraw from the study. All other randomized participants completed the study.
Abbreviations: ME, microbiologically evaluable; N, number of participants in treatment group; n, number of participants in specified population or group;

Demographic characteristics are listed in the table below. The majority of participants were male (95%) and non-Hispanic (82%). The most common reported race was Black or African American (44%).

Table 14. Baseline Demographics and Clinical Characteristics, All Randomized Population, BTZ116576

Characteristic	Gepotidacin 1500 mg N=53	Gepotidacin 3000 mg N=53
Sex, n (%)		
Female	3 (5.7)	2 (3.8)
Male	50 (94.3)	51 (96.2)
Age, years		
Mean (SD)	34.1 (11.45)	32.4 (11.33)
Median	31.0	28.0
Min, Max	18.0, 63.0	18.0, 69.0

Characteristic	Gepotidacin 1500 mg N=53	Gepotidacin 3000 mg N=53
Age group (years), n (%)		
18 to 64	53 (100.0)	52 (98.1)
65 to 74	0	1 (1.9)
Race, n (%)		
Black or African American	22 (41.5)	25 (47.2)
White	24 (45.3)	21 (39.6)
Asian	1 (1.9)	1 (1.9)
American Indian or Alaska Native	1 (1.9)	1 (1.9)
Native Hawaiian or Other Pacific Islander	0	1 (1.9)
Multiple	0	1 (1.9)
Missing	5 (9.4)	3 (5.7)
Ethnicity, n (%)		
Hispanic	12 (22.6)	7 (13.2)
Non-Hispanic	41 (77.4)	46 (86.8)
Baseline height (cm)		
Mean (SD)	175.6 (11.06)	175.6 (9.45)
Median	175.3	175.3
Min, Max	136.4, 193.0	152.4, 198.0
Baseline weight (kg)		
Mean (SD)	76.1 (13.58)	75.8 (12.26)
Median	74.9	75.4
Min, Max	47.7, 118.2	49.0, 119.8
BMI (kg/m^2)		
Mean (SD)	24.5 (4.02)	24.4 (3.65)
Median	24.2	24.0
Min, Max	14.2, 38.6	17.4, 41.3
Country of participation, n (%)		
United States	51 (96.2)	53 (100.0)
United Kingdom	2 (3.8)	0

Source: FDA Analysis; adsl.xpt;
Abbreviations: N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

NG Culture Result at TOC

The table below displays NG culture results at TOC in the microbiological evaluable population. Both arms had negative culture rates above 90% at the urogenital site. The number of participants with available TOC cultures at the rectal site and pharyngeal site was small.

Table 15. NG Culture Result at TOC, ME Population, Study BTZ116576

NG Culture Result at the Urogenital Site	Gepotidacin 1500 mg N=30	Gepotidacin 3000 mg N=39
Negative, n (%)	29 (96.7)	37 (94.9)
Positive, n (%)	1 (3.3)	2 (5.1)
NG Culture Result at the Rectal Site	**Gepotidacin 1500 mg N=1**	**Gepotidacin 3000 mg N=2**
Negative, n (%)	1 (100.0)	2 (100.0)
Positive, n (%)	0	0
NG Culture Result at the Pharyngeal Site	**Gepotidacin 1500 mg N=0**	**Gepotidacin 3000 mg N=2**
Negative, n (%)	0	1 (50.0)
Positive, n (%)	0	1 (50.0)

Source: FDA Analysis; admb.xpt.
Abbreviations: ME, microbiological evaluable; TOC, test-of-cure; NG, *Neisseria gonorrhoeae*; N, number of participants in treatment group; n, number of participants in specified population or group

6.3. Key Efficacy Review Issues

There are no key efficacy review issues.

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. These studies were reviewed under the original NDA submission.

Exposure Multiples

Exposure multiples based on the new maximum recommended human dose (6 g in a single day, administered as 3 g, 12 hours apart) were calculated based on the clinical pharmacokinetic data as shown in the two tables below.

Table 16: Safety Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (µg*hr/mL)	Safety Margin multiples based on exposures[a]
28-day Rat	150	12.7	0.2
28-day Dog	125	143.5	2
13-week Rat	750	197	3
13-week dog	60	82.3	1
28-day Rat (Impurity qualification study)	750	167	2

Source: Reviewer constructed table.
[a] Exposure multiples were based on population pharmacokinetics analysis from phase 3 trials, where the maximum clinical dosage resulted in systemic geometric mean exposures of AUC0-12hr of 75.9 µg•hr/mL. Exposures in nonclinical studies were based on mean combined sex calculations.

Table 17: Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (µg*hr/mL)	Safety Margin multiples based on exposures [a]
Rat FEED	750	114[b]	2
Rat EFD	150	14.2[b]	0.2
Mouse EFD	200	15.8[b]	0.2
Mouse PPND	1000	118[b]	1.5
Juvenile Rat	300/1250	252, 128, and 107 for postpartum days 13, 22, and 32.[c]	3, 2, 1

Source: Reviewer constructed table.
[a] Exposure multiples were based on population pharmacokinetics analysis, where the maximum clinical dosage resulted in systemic geometric mean exposures of $AUC_{0\text{-}24hr}$ of 75.9 µg•hr/mL.
[b] Safety margin was calculated using TK data from other studies in that species using the noted dose when available. Rat FEED was read-across from the rat 13-week repeat dose study, rat EFD was read-across from the rat 28-day study, mouse EFD and mouse PPND were read-across from the mouse 10-day dose-range finding study.
[c] Dose range finding study. Animals were administered 300 mg/kg from postpartum day 4 to 21 and 1250 from postpartum day 22 to 32 or 35. Value for day 13 was from different group administered 300/1000 mg/kg/day.
Abbreviations: $AUC_{0\text{-}24hr}$, area under the concentration curve from time 0 to 24 hours; hr, hour; NOAEL, no observed adverse effect level; FEED, fertility and early embryonic development study; EFD, embryo-fetal development study; PPND, pre- and post-natal development study

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

Gepotidacin is a triazaacenaphthylene antibacterial that inhibits Type II topoisomerases including bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, thereby inhibiting DNA replication. 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 7.6.1.5.1. and 7.7.2.

7.2.1. Dose Packaging and Risk of Drug Resistance

Drug-resistant gonorrhea in the United States and internationally is a high priority urgent threat. Emergent and worldwide spread of antibacterial resistance to many drugs previously used as first-line treatment (i.e., penicillins, narrow-spectrum cephalosporins, tetracyclines, macrolides, and fluoroquinolones) has led to limited treatment options for gonorrhea. Current United States guidelines recommend a single intramuscular injection of ceftriaxone for treatment of urogenital *N. gonorrhoeae*[12]. Single dose therapy is the preferred treatment recommendation for *N. gonorrhoeae* as it assures adequate treatment adherence.

Additional factors potentiating drug-resistant gonorrhea include inappropriate selection and overuse of antibacterial drugs, genetic mutations within the organisms, and infections outside the genital area where *N. gonorrhoeae* may exchange genetic material with other organisms in these parts of the body (namely, the throat and rectum)[13]. Errors in antibacterial dosing such as incomplete treatment courses, empiric treatment, and treatment based on diagnostic testing without susceptibility testing in well-resourced countries can also contribute to a risk of drug resistance.

Gepotidacin provides an oral antibacterial option for the treatment of uncomplicated urogenital gonorrhea. However, it is delivered as a two-dose series -- 4 (750 mg each) pills taken once and then again 12 hours later. The FDA Guidance for Industry, *Safety Considerations for Product Design to Minimize Medication Errors,* recommends against multiple units to achieve a usual single dose to reduce dosing errors[14].

Amid the urgent high-priority threat of drug-resistant gonorrhea, we recommend the Applicant consider uGC dose-pack packaging that clearly instructs the proper dose and product administration interval to reduce dosing error risks and two dose adherence concerns.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Gepotidacin was approved in the United States on March 25, 2025, but has not yet become commercially available.

7.4. FDA Approach to the Safety Review

The clinical development program for gepotidacin includes 22 clinical studies, including 4 phase 3, randomized, active-controlled efficacy studies and 3 open-label phase 2 studies assessing

[12] CDC. "Gonococcal Infections Among Adolescents and Adults." 21 September 2022. https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm

[13] WHO. "Multi-drug resistant gonorrhoea." 22 October 2025. https://www.who.int/news-room/fact-sheets/detail/multi-drug-resistant-gonorrhoea

[14] FDA. "Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry." April 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-product-design-minimize-medication-errors-guidance-industry

safety, tolerability, and PK. The safety review for this sNDA was primarily focused on the data from the single phase 3 uGC efficacy study (EAGLE-1).

Additional safety data were reviewed from an additional phase 3 uUTI efficacy study (EAGLE-J) which was submitted with this sNDA. That study investigated the efficacy and safety of gepotidacin 1500 mg BID for 5 days in Japanese females with uUTI.

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). These studies were previously reviewed in the original NDA review.

No major data quality or integrity issues were identified that would preclude performing a safety review for this sNDA. 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 phase 3 study, EAGLE-1, 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 consisted of 302 participants in EAGLE-1 who received two 3000 mg doses of oral gepotidacin and 7 participants who received a single 3000 mg dose of gepotidacin. Fifty-four healthy participants from two phase 1 studies were exposed to 2 oral doses of 3000 mg gepotidacin. An additional six healthy phase 1 participants were exposed to 1500 mg 3-hour intravenous doses of gepotidacin thrice daily for at least eight days. Their total daily dosing of 4500 mg IV was equivalent to 10,000 mg orally. Overall, 362 participants were exposed to at least two doses equivalent to 3000 mg oral gepotidacin. A cross-comparison of all safety signals in these smaller phase 1 studies will not be performed in this review as these studies were previously evaluated in the original NDA review.

The primary safety population for this review included all participants in the EAGLE-1 study who received at least one 3000 mg dose of gepotidacin (n=309).

The table below presents demographic characteristics of the safety population in the EAGLE-1 study. The study included mainly male participants (88.7%) with a mean age of 33.9 years. Most participants were white (73.5%), not Hispanic (83.2%), and from Europe (65%). One (0.3%) adolescent participant was exposed to gepotidacin.

Table 18. Demographic and Baseline Clinical Characteristics, Safety Population, Study EAGLE-1

Characteristic	Gepotidacin 2x3000 mg N=309	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313
Sex, n (%)		
Female	35 (11.3)	33 (10.5)
Male	274 (88.7)	280 (89.5)
Age, years		
Mean (SD)	33.9 (10.4)	33.7 (10.7)
Median (min, max)	33 (16, 64)	32 (17, 71)
Age group, years, n (%)		
Adolescents (12 to 17)	1 (0.3)	1 (0.3)
Adult (18 to 64)	308 (99.7)	309 (98.7)
≥65 to 84	0	3 (1.0)
Race, n (%)		
American Indian or Alaska Native	9 (2.9)	10 (3.2)
Asian	12 (3.9)	17 (5.4)
Black or African American	48 (15.5)	39 (12.5)
Multiple	6 (1.9)	5 (1.6)
Native Hawaiian or other Pacific Islander	7 (2.3)	2 (0.6)
White	227 (73.5)	240 (76.7)
Ethnicity, n (%)		
Hispanic or Latino	52 (16.8)	62 (19.8)
Not Hispanic or Latino	257 (83.2)	249 (79.6)
Missing	0	2 (0.6)
Country of participation, n (%)		
Australia	51 (16.5)	53 (16.9)
Germany	69 (22.3)	69 (22.0)
Spain	88 (28.5)	96 (30.7)
Great Britain	44 (14.2)	53 (16.9)
United States	49 (15.9)	35 (11.2)
Mexico	8 (2.6)	7 (2.2)
Is in United States, n (%)		
United States	49 (15.9)	35 (11.2)
Non-United States	260 (84.1)	278 (88.8)

Source: FDA analysis; adsl.xpt; Software: R
Abbreviations: N, number of participants in treatment arm; n, number of participants with given characteristic; SD, standard deviation

Study EAGLE-1 was a two-dose study of gepotidacin 3000 mg with 302 (98%) participants receiving both doses of study drug. 313 participants received the comparator treatment of single dose IM ceftriaxone and oral azithromycin.

See Section 7.7.1 for additional discussion of the safety database.

7.6. Safety Results

7.6.1. Safety Results, Study EAGLE-1

7.6.1.1. Overview of Treatment-Emergent Adverse Events, Study EAGLE-1

As shown in the table below, the overall incidence of TEAEs in study EAGLE-1 was 74.4% in the gepotidacin arm and 33.2% in the ceftriaxone and azithromycin arm. Most TEAEs were mild or moderate in severity.

TEAE rates in the gepotidacin arm were higher in study EAGLE-1 than in studies EAGLE-2 and EAGLE-3 in uUTI (74.4% in EAGLE-1 compared to 35.1% EAGLE-2 and EAGLE-3 pooled). Studies EAGLE-2 and EAGLE-3 used gepotidacin 1500 mg BID dosing for five days and enrolled solely female participants.

One serious adverse event (SAE) was observed in study EAGLE-1. No grade 4 or 5 TEAEs were observed, and no deaths were observed. TEAEs leading to discontinuation of study drug occurred in 3 (1%) participants in the gepotidacin arm.

Table 19. Overview of Treatment Emergent Adverse Events, Safety Population

Adverse Event Category	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n (%)
Any SAE	1 (0.3)	0
Death	0	0
Life-threatening	0	0
Initial or prolonged hospitalization	1 (0.3)	0
AE leading to permanent discontinuation of treatment	3 (1.0)	0
Any AE	230 (74.4)	104 (33.2)
Severe and worse	1 (0.3)	1 (0.3)
Moderate	91 (29.4)	32 (10.2)
Mild	138 (44.7)	71 (22.7)

Source: FDA analysis; adae.xpt; Software: R
Note: Treatment-emergent AE defined as any AE with an onset date on or after treatment start date/time.
MedDRA version 26.1.
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
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.
Participants may be counted more than once in the AE leading to action taken of treatment analysis.
Severity scale as defined by the protocol.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Study EAGLE-1

No deaths were reported in study EAGLE-1.

7.6.1.3. Serious Treatment-Emergent Adverse Event, Study EAGLE-1

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 hospitalization, resulted in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or was a congenital anomaly or birth defect. Pertinent details for the one SAE are noted below.

A 34-year-old male who reported six units of ethanol use per week developed a Grade 2 SAE of lower limb fracture on Day 3, one day after the last dose of gepotidacin. On Day 3 the participant sustained multiple fractures of the right lower leg due to falling downstairs. On Day 9, during a hospital stay, surgeons used screws and an angle plate to repair the fractures. On Day 12, the hospital discharged the participant, and, at study completion, the SAE was considered ongoing. The study investigator and Applicant considered this event unrelated to gepotidacin. Given the available information, the clinical reviewer concurs that the episode of lower limb fracture is likely unrelated to gepotidacin.

Additionally, this participant developed a drug related Grade 2 AE of diarrhea on Day 1 which resolved by Day 2 without treatment. The clinical reviewer concurs that diarrhea was likely related to gepotidacin.

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study EAGLE-1

Three (1%) participants who received gepotidacin reported at least one TEAE that led to treatment discontinuation (table below). Two participants reported both GI and other organ system TEAEs as the reasons for study drug discontinuation (visual impairment, dizziness, nausea, and diarrhea in one participant; general discomfort, dizziness, pyrexia, and vomiting in the other participant). One participant reported syncope as the reason for discontinuing gepotidacin. TEAEs leading to treatment discontinuation occurred quickly after the first gepotidacin dose (mean time elapsed after first exposure was 66 minutes with a range of 30 minutes to 135 minutes).

The ceftriaxone and azithromycin arm had no treatment discontinuations as it was single dose therapy.

Table 20. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study EAGLE-1

System Organ Class Preferred Term	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n (%)
Participants with at least one AE leading to treatment discontinuation	3 (1.0)	0
Eye disorders (SOC)	1 (0.3)	0
Visual impairment	1 (0.3)	0
Gastrointestinal disorders (SOC)	2 (0.6)	0
Diarrhea	1 (0.3)	0
Nausea	1 (0.3)	0
Vomiting	1 (0.3)	0
General disorders and administration site conditions (SOC)	1 (0.3)	0
Discomfort	1 (0.3)	0
Pyrexia	1 (0.3)	0
Nervous system disorders (SOC)	3 (1.0)	0
Dizziness	2 (0.6)	0
Syncope	1 (0.3)	0

Source: FDA analysis; adae.xpt; Software: R
Treatment-emergent AE defined as any AE with an onset date on or after treatment start date/time.
MedDRA version 26.1.
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with at least one event; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Study EAGLE-1

TEAEs occurred in 74.4% of participants who received gepotidacin and 33.2% of participants who received ceftriaxone and azithromycin (table below). Risk differences were defined as differences in incidence rates of TEAEs between the gepotidacin arm compared to the ceftriaxone and azithromycin arm. The TEAEs with risk differences of $\geq$1% in the gepotidacin arm included blurred vision, diarrhea, nausea, flatulence, vomiting, soft feces, abdominal pain, abdominal distension, hemorrhoids, fatigue, discomfort, chlamydial infection, myoclonus, dizziness, and hyperhidrosis.

The role of acetylcholinesterase inhibition in gastrointestinal (GI) TEAEs and non-GI TEAEs is discussed in Section 7.7.2. Diarrhea was the most common TEAE reported, and it was observed more commonly after gepotidacin administration compared to ceftriaxone and azithromycin. GI TEAEs were designated as AESI; please refer to Section 7.6.1.5.1 for additional information.

Blurred vision, fatigue, myoclonus, dizziness, and hyperhidrosis occurred in gepotidacin participants at 1% or more and may be related to gepotidacin exposure as a cholinergic adverse effect. Headache and discomfort also occurred in gepotidacin participants at >1%, but it is unclear if these are related to gepotidacin exposure or not as they can be nonspecific symptoms.

Chlamydial infection occurred in 8.7% of gepotidacin exposed participants and 4.2% in the comparator arm. The comparator arm included azithromycin which would treat chlamydial infections. As gepotidacin does not have activity against chlamydia, these infections are not related to gepotidacin exposure.

Table 21. Participants With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.5% of Participants in Any Arm, Safety Population, Study EAGLE-1

System Organ Class Preferred Term	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n (%)
Any TEAE	230 (74.4)	104 (33.2)
Eye disorders (SOC)	12 (3.9)	0
Vision blurred	6 (1.9)	0
Gastrointestinal disorders (SOC)	206 (66.7)	49 (15.7)
Diarrhea[a]	161 (52.1)	31 (9.9)
Nausea	73 (23.6)	9 (2.9)
Abdominal pain[b]	25 (8.1)	6 (1.9)
Flatulence	20 (6.5)	1 (0.3)
Vomiting	20 (6.5)	2 (0.6)
Abdominal distension	5 (1.6)	2 (0.6)
Hemorrhoids	3 (1.0)	0
Abnormal feces	2 (0.6)	0
General disorders and administration site conditions (SOC)	13 (4.2)	9 (2.9)
Fatigue[c]	10 (3.2)	0
Discomfort	3 (1.0)	0
Pyrexia	2 (0.6)	1 (0.3)
Injection site pain	0	5 (1.6)
Infections and infestations (SOC)	43 (13.9)	33 (10.5)
Chlamydial infection[d]	27 (8.7)	13 (4.2)
Haemophilus infection	0	2 (0.6)
Urethritis mycoplasmal	0	3 (1.0)
Nasopharyngitis	0	4 (1.3)
Musculoskeletal and connective tissue disorders (SOC)	6 (1.9)	4 (1.3)
Myoclonus[e]	3 (1)	0
Arthralgia	2 (0.6)	0
Myalgia	2 (0.6)	0
Musculoskeletal pain	0	2 (0.6)
Nervous system disorders (SOC)	28 (9.1)	10 (3.2)
Dizziness	16 (5.2)	2 (0.6)
Headache	10 (3.2)	8 (2.6)
Renal and urinary disorders (SOC)	5 (1.6)	5 (1.6)
Dysuria	2 (0.6)	2 (0.6)
Urethral discharge	0	3 (1.0)
Reproductive system and breast disorders (SOC)	7 (2.3)	1 (0.3)
Pruritus genital	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders (SOC)	4 (1.3)	2 (0.6)
Rhinorrhea	2 (0.6)	0

System Organ Class Preferred Term	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n (%)
Skin and subcutaneous tissue disorders (SOC)	10 (3.2)	2 (0.6)
Hyperhidrosis	7 (2.3)	0
Flushing[f]	2 (0.6)	0

Source: FDA analysis; adae.xpt; Software: R
[a] In the gepotidacin arm, diarrhea includes diarrhea (n=151) and soft feces (n=16); 6 participants reported both diarrhea and soft feces. In the ceftriaxone and azithromycin arm, diarrhea includes diarrhea (n=30) and soft feces (n=1).
[b] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort
[c] Fatigue includes fatigue and lethargy
[d] Chlamydial infection includes chlamydial infection, genitourinary chlamydia infection, pharyngeal chlamydia infection, proctitis chlamydial, urethritis chlamydial, vaginitis chlamydial
[e] Myoclonus includes muscle spasms, muscle twitching, myoclonus
[f] Flushing includes flushing and hot flush
Treatment-emergent AE defined as any AE with an onset date on or after treatment start date/time.
MedDRA version 26.1.
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with at least one event; SOC, system organ class

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.

Cardiovascular Events

Cardiac AESIs reported during the clinical studies included one (0.3%) Grade 1 case of tachycardia in each arm. The narrative for the gepotidacin recipient is noted below.

A 21-year-old male who reported no past medical history developed Grade 1 TEAE of tachycardia (no vital sign measurement performed), Grade 1 diarrhea, and Grade 1 blurred vision immediately after the second dose of gepotidacin. All TEAEs resolved on Day 1 without treatment. The study investigator considered the tachycardia and blurred vision unrelated to gepotidacin. The clinical reviewer suspects all three TEAEs were likely gepotidacin related and potentially AChE-I related.

Non-clinical studies indicate gepotidacin causes dose dependent QTc prolongation likely due to hERG current inhibition. QTc prolongation was not observed in the EAGLE-1 clinical trial, but post-baseline ECGs were not routinely performed, and this risk may be under recognized due to the design of the clinical trial. See Section 7.7.3 (Key Safety Review Issues, QTc Prolongation) for further discussion.

Gepotidacin labeling includes a warning for QTc prolongation. Additional language in the warning will be included for the uGC indication as the dose is double the uUTI dose.

Gastrointestinal Events

Gastrointestinal events were the most common TEAEs reported with gepotidacin (66.7%) and occurred at a higher rate than with ceftriaxone and azithromycin (15.7%). Diarrhea (52.1% gepotidacin; 9.9% ceftriaxone and azithromycin), nausea (23.6% gepotidacin; 2.9% ceftriaxone and azithromycin), vomiting (6.5% gepotidacin; 0.6% ceftriaxone and azithromycin), and

abdominal pain (8.1% gepotidacin; 1.9% ceftriaxone and azithromycin) were the most frequently reported GI TEAEs. All diarrhea TEAEs were designated as mild to moderate severity, and most were considered related to study drug (table below).

Table 22. Participants With Diarrhea, Safety Population, Study EAGLE-1

Adverse Event Category	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg plus azithromycin 1 g N=313 n (%)
Diarrhea[a]	161 (52.1)	31 (9.9)
Maximum severity		
Moderate	37 (12)	3 (1.0)
Mild	124 (40.1)	28 (8.9)
Diarrhea onset after drug exposure		
Within first day	137 (44.3)	23 (7.3)
After first day	24 (7.8)	8 (2.6)

Source: FDA Analysis
a: Diarrhea includes diarrhea and soft feces

Of study participants who developed diarrhea, most participants' diarrhea was graded as mild severity. Diarrhea developed within the first day of drug exposure in both arms. The overall incidence of diarrhea was much higher in the gepotidacin arm.

Table 23. Participants With Nausea, Safety Population, Study EAGLE-1

Adverse Event Category	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg plus azithromycin 1 g N=313 n (%)
Nausea	73 (23.6)	9 (2.9)
Maximum severity		
Moderate	12 (3.9)	0
Mild	61 (19.7)	9 (2.9)
Nausea onset after drug exposure		
Within first day	69 (22.3)	7 (2.2)
After first day	4 (1.3)	2 (0.6)

Source: FDA Analysis

Of study participants who developed nausea, most participants' nausea was graded as mild severity and most events developed within the first day of drug exposure in both arms. The overall incidence of nausea was much higher in the gepotidacin arm.

C. difficile Infection

No cases of CDI were identified during the study EAGLE-1.

AEs Related to Acetylcholinesterase Inhibition

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

7.6.1.6. Laboratory Findings, Study EAGLE-1

Chemistry and Hematology

Chemistry and hematology laboratory values between the two arms were similar. There were no significant differences between treatment arms in baseline mean 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

At baseline, very few participants had elevated creatinine levels or reduced eGFR in either study arm. One percent of participants in each arm had Level 1 creatinine elevation from baseline and one participant (0.3%) in the gepotidacin arm had a Level 2 creatinine elevation from baseline (table below).

Table 24. Participants With Kidney Function Analyte Values Exceeding Specified Levels from Baseline, Safety Population, Study EAGLE-1

Laboratory Parameter	Gepotidacin 2x3000 mg N=309 n/N_w (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n/N_w (%)
Creatinine, high (mg/dL)		
Level 1 (≥1.5X baseline)	3/291 (1.0)	3/290 (1.0)
Level 2 (≥2X baseline)	1/291 (0.3)	0/290 (0)
Level 3 (≥3X baseline)	0/291 (0)	0/290 (0)
eGFR, low (mL/min/1.73 m^2)		
Level 1 (≥25% decrease)	4/286 (1.4)	3/285 (1.1)
Level 2 (≥50% decrease)	1/286 (0.3)	0/285 (0)
Level 3 (≥75% decrease)	0/286 (0)	0/285 (0)

Source: adlb.xpt; Software: R
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria).
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
Participant counts are cumulative for each abnormality threshold.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of participants in treatment arm; n, number of participants meeting the specified laboratory criteria; N_w, total number of participants with data available for the laboratory test of interest

7.6.1.7. Assessment of Drug-Induced Liver Injury, Study EAGLE-1

There were no significant differences between the two treatment arms in the proportions of participants with abnormal liver chemistry values (ALT, AST, alkaline phosphatase [AP], total bilirubin). At baseline more participants in the gepotidacin arm had elevated bilirubin levels.

The table below shows peak post-baseline elevations of ALT, AST, AP, and bilirubin among all participants. Six (2.0%) participants in the gepotidacin arm had post-baseline elevated bilirubin levels compared to one (0.3%) in the comparator arm. However, only 2 participants in the gepotidacin arm had levels >2X ULN. In general, the incidence of elevation in liver enzymes and bilirubin values was low and balanced between arms.

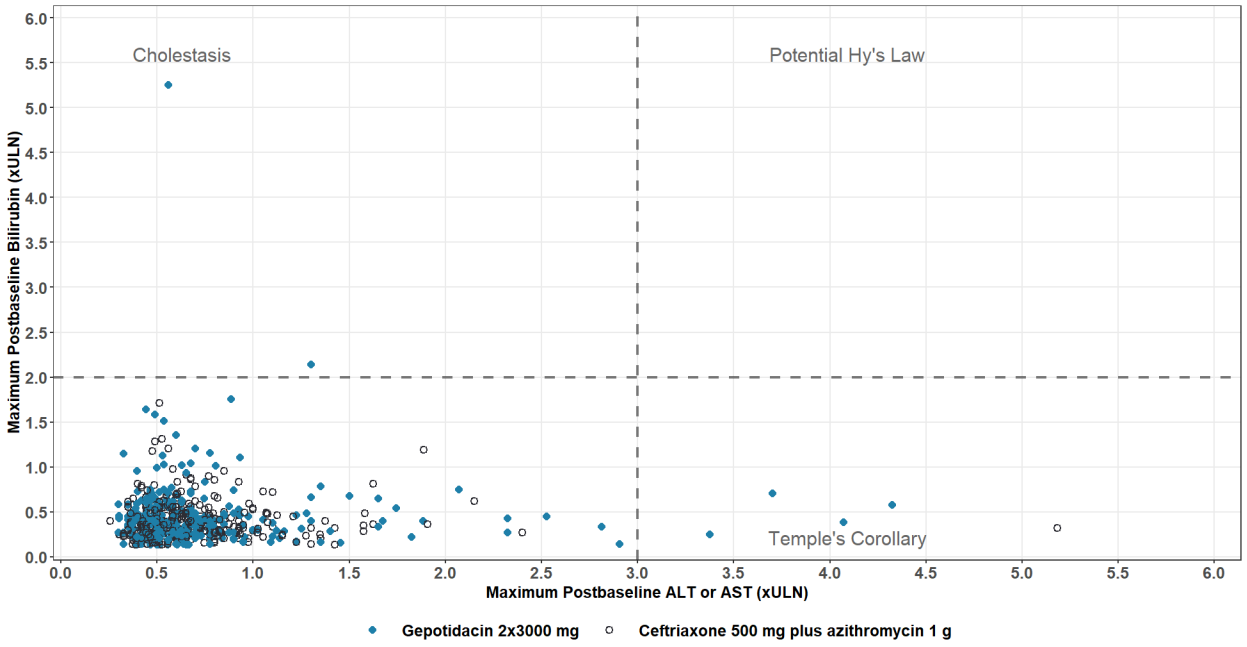
Figure 2 shows a screening assessment for potential cases of serious drug-induced liver injury. Overall, the number of participants in the four screening quadrants for drug-induced liver injury were balanced between the two treatment arms (Table 26). There were no identified cases of Hy's law.

Table 25. Participants With Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study EAGLE-1

Laboratory Parameter	Gepotidacin 2x3000 mg N=309 n/N_w (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n/N_w (%)
Alkaline phosphatase, high (U/L)		
Level 1 (>1.5X ULN)	0/296 (0)	2/297 (0.7)
Level 2 (>2X ULN)	0/296 (0)	2/297 (0.7)
Level 3 (>3X ULN)	0/296 (0)	0/297 (0)
Alanine aminotransferase, high (U/L)		
Level 1 (>3X ULN)	2/294 (0.7)	1/296 (0.3)
Level 2 (>5X ULN)	0/294 (0)	1/296 (0.3)
Level 3 (>10X ULN)	0/294 (0)	0/296 (0)
Aspartate aminotransferase, high (U/L)		
Level 1 (>3X ULN)	2/293 (0.7)	0/296 (0)
Level 2 (>5X ULN)	0/293 (0)	0/296 (0)
Level 3 (>10X ULN)	0/293 (0)	0/296 (0)
Bilirubin, total, high (mg/dL)		
Level 1 (>1.5X ULN)	6/295 (2.0)	1/296 (0.3)
Level 2 (>2X ULN)	2/295 (0.7)	0/296 (0)
Level 3 (>3X ULN)	1/295 (0.3)	0/296 (0)

Source: FDA analysis; adlb.xpt; Software: R
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria).
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
Participant counts are cumulative for each abnormality threshold.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Participants in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot..." and "Participants in Each Quadrant for Cholestatic DILI Screening Plot…"
Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants meeting the specified laboratory criteria; N_w, total number of participants with data available for the laboratory test of interest; ULN, upper limit of normal

Figure 2. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial BTZ116577



Source: FDA analysis; adlb.xpt; Software: R
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
Each data point represents a participant 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. Those participants who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary quadrants.
All participants 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 participants in each quadrant, see the table "Participants in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot …" and the listing "Listing of Participants in Hepatocellular Drug-Induced Liver Injury Screening…".
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 26. Participants in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot, Safety Population, Study EAGLE-1

Quadrant	Gepotidacin 2x3000 mg N=309 n/N_w (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n/N_w (%)
Potential Hy's Law (right upper quadrant)	0/294 (0)	0/296 (0)
Cholestasis (left upper quadrant)	2/294 (0.7)	0/296 (0)
Temple's corollary (right lower quadrant)	4/294 (1.4)	1/296 (0.3)
Total	6/294 (2)	1/296 (0.3)

Source: FDA analysis; adlb.xpt; Software: R
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
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; DILI, drug-induced liver injury; N, number of participants in treatment arm; n, number of participants meeting the specified laboratory criteria; N_w, total number of participants with laboratory data available; ULN, upper limit of normal

7.6.1.8. Vital Signs, Study EAGLE-1

Review of mean values and mean changes in vital signs from baseline to Test of Cure (Day 4-8) did not reveal significant differences between the two study arms.

7.6.1.9. Subgroups, Study EAGLE-1

The proportion of participants with at least one TEAE in demographic subgroups is shown in the table below. As observed in the overall safety analysis, rates of TEAEs were higher in study participants who received gepotidacin across all demographic subgroups for which there were data. However, the small number of participants in some subgroups (e.g., adolescents, age ≥65 years, non-White/non-Black race) precluded interpretation of the observed imbalances in TEAEs. Of note, TEAEs occurred at the same rate in male and female participants.

Table 27. Overview of Adverse Events by Demographic Subgroups, Safety Population, Study EAGLE-1

Characteristic	Gepotidacin 2x3000 mg N=309 n/N_s (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n/N_s (%)
Any AE	230/309 (74.4)	104/313 (33.2)
Sex		
Female	26/35 (74.3)	11/33 (33.3)
Male	204/274 (74.5)	93/280 (33.2)
Age group, years		
Adolescents (12 to 17)	1/1 (100)	0/1 (0)
Adult (18 to 64)	229/308 (74.4)	102/309 (33.0)
≥65 to 84	0/0 (NA)	2/3 (66.7)
Age group ≥65, years		
<65	230/309 (74.4)	102/310 (32.9)
≥65	0/0 (NA)	2/3 (66.7)
Age group ≥75, years		
<75	230/309 (74.4)	104/313 (33.2)
Race		
American Indian or Alaska Native	4/9 (44.4)	3/10 (30.0)
Asian	8/12 (66.7)	7/17 (41.2)
Black or African American	24/48 (50.0)	10/39 (25.6)
Multiple	5/6 (83.3)	2/5 (40.0)
Native Hawaiian or other Pacific Islander	5/7 (71.4)	1/2 (50.0)
White	184/227 (81.1)	81/240 (33.8)
Ethnicity		
Hispanic or Latino	35/52 (67.3)	17/62 (27.4)
Not Hispanic or Latino	195/257 (75.9)	87/249 (34.9)
Missing	0/0 (NA)	0/2 (0)
Is in United States		
United States	21/49 (42.9)	5/35 (14.3)
Non-United States	209/260 (80.4)	99/278 (35.6)

Source: FDA analysis; adae.xpt; Software: R
Duration is two doses over one to two days for the gepotidacin arm and a single dose for the ceftriaxone/azithromycin arm.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of participants in treatment arm; n, number of participants with at least one event; NA, not applicable; N_s, total number of participants for each specific subgroup

7.6.1.10. Exposure-Adjusted Analyses, Study EAGLE-1

Not applicable.

7.6.2. Safety Results, Study EAGLE-J

The original NDA review included summarized safety results from a phase 3 uUTI study in Japanese females 12 years of age and older weighing at least 40 kilograms. Please see the original NDA review for further information regarding this study, including rates of TEAEs, potential AChE-I TEAEs, and pharmacologic exploratory analyses of plasma drug exposures and AChE-I events.

As part of this sNDA submission, a safety review was performed on the complete datasets from the EAGLE-J study. Information pertinent to the safety profile of gepotidacin are detailed below.

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

As shown in the table below, the overall incidence of TEAEs in study EAGLE-1 was 71.5% in the gepotidacin arm and 19.4% in the nitrofurantoin arm. Most TEAEs were mild or moderate in severity.

TEAE rates in the EAGLE- J gepotidacin arm were similar to the TEAE rates in study EAGLE-1 and much higher than in the EAGLE-2 and EAGLE-3 uUTI studies (71.5% in the EAGLE-J study compared to 74.4% in EAGLE-1 and 35.1% pooled rate in the EAGLE-2 and EAGLE-3 studies). The EAGLE-1 study used a 3000 mg dose of gepotidacin administered twelve hours apart assessed in a mostly male population while the uUTI studies (EAGLE-2, 3, and J) used gepotidacin 1500 mg BID for five days and assessed solely female participants.

An analysis of AChE-I events and plasma exposure was conducted using data from studies EAGLE-2 and EAGLE-J (see original NDA review, 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.

Two gepotidacin participants reported three serious adverse events (SAE) in the study EAGLE-J. One grade 4 TEAE occurred. No grade 5 TEAEs or deaths occurred. TEAEs leading to discontinuation of study drug occurred in 40 (14.2%) participants in the gepotidacin arm.

Table 28. Overview of Adverse Events, Safety Population, Study EAGLE-J

Adverse Event Category	Gepotidacin 1500 mg BID N=281 n (%)	Nitrofurantoin 100 mg BID N=93 n (%)
Any SAE	2 (0.7)	0
Death	0	0
Life-threatening	1 (0.4)	0
Initial or prolonged hospitalization	2 (0.7)	0
AE leading to permanent discontinuation of treatment	40 (14.2)	1 (1.1)
AE leading to action taken with treatment	1 (0.4)	1 (1.1)
AE leading to interruption of treatment	1 (0.4)	1 (1.1)
Not applicable	43 (15.3)	5 (5.4)
Any AE	201 (71.5)	18 (19.4)
Severe and worse	9 (3.2)	0
Moderate	78 (27.8)	5 (5.4)
Mild	114 (40.6)	13 (14.0)

Source: FDA Analysis; adae.xpt; Software: R
Treatment-emergent AE defined as any AE with an onset date on or after treatment start date/time.
MedDRA version 26.1.
Duration is a median of 5 days.
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.
Participants may be counted more than once in the AE leading to action taken of treatment analysis.
Severity scale as defined by the protocol.
Abbreviations: AE, adverse event; BID, twice daily; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, Study EAGLE-J

No deaths occurred in study EAGLE-J.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Study EAGLE-J

The table below summarizes the SAEs in study EAGLE-J. 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 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 SAEs was low. The clinical reviewer assessed all narratives for participants who experienced SAEs and found three SAEs in two participants with details below.

Table 29. Participants With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study EAGLE-J

System Organ Class Preferred Term	Gepotidacin 1500 mg BID N=281 n (%)	Nitrofurantoin 100 mg BID N=93 n (%)
Any SAE	2 (0.7)	0
Gastrointestinal disorders (SOC)	1 (0.4)	0
Diarrhea	1 (0.4)	0
Vomiting	1 (0.4)	0
Infections and infestations (SOC)	1 (0.4)	0
Clostridium difficile infection	1 (0.4)	0

Source: FDA Analysis; adae.xpt; Software: R
Treatment-emergent AE defined as any AE with an onset date on or after treatment start date/time.
MedDRA version 26.1.
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 a median of 5 days.
Abbreviations: AE, adverse event; BID, twice daily; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SOC, system organ class

- A 68-year-old Japanese female who reported no past medical history developed Grade 4 SAEs of diarrhea and vomiting and Grade 1 tremor one hour after the first dose of gepotidacin. The participant was hospitalized for observation of her symptoms. Additionally, a Grade 1 AE of increased blood pressure developed 1 hour and 44 minutes after the first dose of gepotidacin. The participant received calcium chloride dihydrate, glucose, potassium chloride, sodium chloride, sodium lactate, metoclopramide hydrochloride, and famotidine. Gepotidacin was discontinued. The SAE of vomiting resolved on Day 2 and the SAE of diarrhea resolved on Day 7. The study investigator considered these events related to gepotidacin. The clinical reviewer concurs that the SAEs were likely related to gepotidacin and were potentially cholinergic in nature.
- A 53-year-old Japanese woman who reported a medical history of post-menopausal state took ten doses of gepotidacin. On day 2, ten hours after the first dose and three hours after the most recent dose, she developed Grade 2 diarrhea which resolved on Day 10.
- On day 24, 24 days after the first dose and 20 days after the most recent dose of gepotidacin, the participant developed a grade 3 SAE of *C. difficile* infection (CDI). She underwent emergency hospitalization on day 26 for acute enteritis. The *C. difficile* antigen test was positive, but the toxin test was negative which did not meet the Applicant's prespecified diagnostic criteria for CDI. She received IV fluids and *Clostridium butyricum* as treatment for CDI. After six days, the participant stopped taking *Clostridium butyricum* on her own prior to the prescribed treatment duration. On Day 42, CDI resolved.

The study investigators considered the SAE of CDI related to gepotidacin. The clinical reviewer concurs that the diarrhea experienced on Day 2 was likely gepotidacin related. However, the SAE of CDI did not meet the prespecified definition (both *C. difficile* antigen and toxin presence) and the symptoms are not specific to CDI.

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study EAGLE-J

Forty (14.2%) participants who received gepotidacin reported at least one TEAE that led to treatment discontinuation compared to 1 (1.1%) participant who received nitrofurantoin (table below). Gastrointestinal TEAEs were the most common events that resulted in discontinuation, with a greater proportion of participants who received gepotidacin reporting occurrences of diarrhea, nausea, and vomiting that led to treatment discontinuation. Nervous system disorders TEAEs, including episodes of dizziness, dysarthria, tremor, headache, and blepharospasm occurred more frequently in the gepotidacin arm. Other gepotidacin participants discontinued treatment due to cold sweats (n=2) and orthostatic hypotension (n=1). Many of these gastrointestinal and nervous system events in the gepotidacin arm were potentially related to AChE-I, were discussed in the original NDA review, and are discussed in Section 7.7.2.

One case of tongue paralysis was considered by the clinical reviewer to be a case of dysarthria based on participant narrative, which is as follows:

- A 28-year-old Japanese female on the concomitant medication of desogestrel ethinylestradiol received two doses of gepotidacin. On day 1, two and a half hours after dose 1, she experienced grade 2 tongue paralysis and tremor. These events resolved one hour after their onset. Additionally, 20 minutes after dose 2 of gepotidacin, she developed grade 2 back pain for which she received apronalide, caffeine, and ibuprofen. The study drug was discontinued after these adverse events. The investigator felt the tongue paralysis and tremor were drug related. However, the back pain which was still ongoing at the 29-day visit was felt to be unrelated to study drug by the investigator.

The FDA clinical reviewer believes the tongue paralysis may represent a case of dysarthria. Taken together, this adverse event and the muscle tremors likely represent acetylcholinesterase inhibition related to gepotidacin. Insufficient details preclude further assessment of the back pain's relatedness to gepotidacin.

Cardiac adverse events leading to treatment discontinuation occurred in the gepotidacin arm. Investigators determined some cardiac TEAEs, such as electrocardiogram (ECG) ST segment elevation (n=1), and palpitations (n=1), were related to the study drug. However, one TEAE of ECG QT prolongation was determined not to have met QTc prolongation criteria by the Applicant's cardiac safety panel.

Table 30. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study EAGLE-J

System Organ Class Preferred Term	Gepotidacin 1500 mg BID N=281 n (%)	Nitrofurantoin 100 mg BID N=93 n (%)
Participants with at least one AE leading to treatment discontinuation	40 (14.2)	1 (1.1)
Cardiac disorders (SOC)	1 (0.4)	0
Palpitations	1 (0.4)	0
Eye disorders (SOC)	1 (0.4)	0
Blepharospasm	1 (0.4)	0

System Organ Class Preferred Term	Gepotidacin 1500 mg BID N=281 n (%)	Nitrofurantoin 100 mg BID N=93 n (%)
Gastrointestinal disorders (SOC)	33 (11.7)	0
Diarrhea	27 (9.6)	0
Nausea	14 (5.0)	0
Vomiting	11 (3.9)	0
Abdominal pain	2 (0.7)	0
Abdominal discomfort	1 (0.4)	0
Abdominal distension	1 (0.4)	0
Abdominal pain upper	1 (0.4)	0
General disorders and administration site conditions (SOC)	1 (0.4)	0
Malaise	1 (0.4)	0
Infections and infestations (SOC)	2 (0.7)	0
Gastroenteritis	1 (0.4)	0
Pyelonephritis acute	1 (0.4)	0
Investigations (SOC)	3 (1.1)	0
Alanine aminotransferase increased	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.4)	0
Electrocardiogram QT prolonged	1 (0.4)	0
Electrocardiogram ST segment elevation	1 (0.4)	0
Gamma-glutamyltransferase increased	1 (0.4)	0
Musculoskeletal and connective tissue disorders (SOC)	2 (0.7)	0
Back pain	1 (0.4)	0
Muscular weakness	1 (0.4)	0
Myalgia	1 (0.4)	0
Nervous system disorders (SOC)	8 (2.8)	0
Dizziness	3 (1.1)	0
Dysarthria	3 (1.1)	0
Headache	3 (1.1)	0
Tremor	2 (0.7)	0
Psychiatric disorders (SOC)	0	1 (1.1)
Vomiting psychogenic	0	1 (1.1)
Renal and urinary disorders (SOC)	1 (0.4)	0
Neurogenic bladder	1 (0.4)	0
Ureterolithiasis	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.4)	0
Laryngeal discomfort	1 (0.4)	0
Skin and subcutaneous tissue disorders (SOC)	2 (0.7)	0
Cold sweat	2 (0.7)	0
Vascular disorders (SOC)	1 (0.4)	0
Orthostatic hypotension	1 (0.4)	0

Source: FDA analysis; adae.xpt; Software: R
Treatment-emergent AE defined as any AE with an onset date on or after treatment start date/time.
MedDRA version 26.1.
Duration is a median of 5 days.
Abbreviations: AE, adverse event; BID, twice daily; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with at least one event; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Study EAGLE-J

TEAEs occurred in 71.5% of participants who received gepotidacin and 19.4% of participants who received nitrofurantoin (table below). 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% in gepotidacin arm included diarrhea, nausea, vomiting, soft feces, headache, nasopharyngitis, cystitis, abdominal discomfort, cold sweat, dizziness, malaise, COVID-19, dysarthria, eczema, and abnormal hepatic function.

The role of acetylcholinesterase inhibition in gastrointestinal (GI) TEAEs and non-GI TEAEs is discussed in Section 7.7.2. Diarrhea was the most common TEAE reported, and it occurred 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.

Cold sweat, dizziness, malaise, and dysarthria occurred in gepotidacin participants at >1% and may be related to gepotidacin exposure as a cholinergic adverse effect. Headache, nasopharyngitis, and pyrexia also occurred in gepotidacin participants at >1%, but it is unclear if these are related to gepotidacin exposure as they are nonspecific symptoms.

Cystitis (2.8%) and COVID-19 (1.1%) occurred in gepotidacin exposed participants but are not related to gepotidacin exposure.

Table 31. Participants With Common Adverse Events Occurring at ≥1% Frequency by Preferred Term, Safety Population, Study EAGLE-J

Preferred Term	Gepotidacin 1500 mg BID N=281 n (%)	Nitrofurantoin 100 mg BID N=93 n (%)
Any AE	201 (71.5)	18 (19.4)
Diarrhea	168 (59.8)	7 (7.5)
Nausea	35 (12.5)	2 (2.2)
Vomiting	15 (5.3)	0
Feces soft	13 (4.6)	1 (1.1)
Headache	13 (4.6)	2 (2.2)
Nasopharyngitis	9 (3.2)	1 (1.1)
Cystitis	8 (2.8)	1 (1.1)
Abdominal discomfort	4 (1.4)	0
Cold sweat	4 (1.4)	0
Dizziness	4 (1.4)	0
Malaise	4 (1.4)	0
COVID-19	3 (1.1)	0
Dysarthria	3 (1.1)	0
Eczema	3 (1.1)	0
Hepatic function abnormal	3 (1.1)	0
Abdominal distension	3 (1.1)	1 (1.1)
Pyrexia	3 (1.1)	1 (1.1)
Back pain	1 (0.4)	1 (1.1)
Coronavirus infection	1 (0.4)	1 (1.1)
Dyspepsia	1 (0.4)	1 (1.1)
White blood cell count decreased	1 (0.4)	1 (1.1)
Nasal congestion	0	1 (1.1)

Preferred Term	Gepotidacin 1500 mg BID N=281 n (%)	Nitrofurantoin 100 mg BID N=93 n (%)
Vomiting psychogenic	0	1 (1.1)

Source: FDA analysis; adae.xpt; Software: R
Treatment-emergent AE defined as any AE with an onset date on or after treatment start date/time.
MedDRA version 26.1.
Duration is a median of 5 days.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; BID, twice daily; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with adverse event

7.6.2.6. Laboratory Findings, Study EAGLE-J

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, treatment arms did not have differences in outlier laboratory values.

Renal Function

Eighteen (6.6%) participants who received gepotidacin and two (2.2%) participants who received nitrofurantoin had a ≥25% decrease in creatinine clearance from baseline (table below). Of these study participants, 16 participants who received gepotidacin and both participants who received nitrofurantoin had mild renal impairment (CrCl ≥60-89 mL/min) during the study period. No participants had 50% or more decrease in creatinine clearance from baseline. The proportion of participants and the degree of renal function decline were less than observed in the EAGLE-2/3 uUTI studies.

Table 32. Participants With Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Study EAGLE-J

Laboratory Parameter	Gepotidacin 1500 mg BID N=281 n/N_w (%)	Nitrofurantoin 100 mg BID N=93 n/N_w (%)
CrCl, low (mL/min)		
Level 1 (≥25% decrease)	18/274 (6.6)	2/93 (2.2)
Level 2 (≥50% decrease)	0/274 (0)	0/93 (0)
Level 3 (≥75% decrease)	0/274 (0)	0/93 (0)

Source: FDA Analysis; adlb.xpt; Software: R
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria).
Duration is a median of 5 days.
Participant counts are cumulative for each abnormality threshold.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: BID, twice daily; CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; N, number of participants in treatment arm; n, number of participants meeting the specified laboratory criteria; N_w, total number of participants with data available for the laboratory test of interest

7.6.2.7. Assessment of Drug-Induced Liver Injury, Study EAGLE-J

No study participants met criteria for Hy's law. Two gepotidacin study participants had increased bilirubin >2x the upper limit of normal. Four gepotidacin exposed participants had increased ALT and/or AST >3x the upper limit of normal without elevated bilirubin values. These participants' ALT and AST values declined or normalized during the study.

7.6.2.8. Vital-Sign Analyses, Study EAGLE-J

No gepotidacin exposed participants had clinically significant changes in vital signs during Study EAGLE-J.

7.7. Key Safety Review Issues

7.7.1. Limited Safety Database

Issue

The safety database for the proposed dose and duration is smaller than what is recommended in the guidance.

Background

The FDA guidance for industry, *Uncomplicated Gonorrhea: Developing Drugs for Treatment,* recommends a "preapproval safety database of approximately 500 patients." In September 2019, the FDA reviewed a phase 3 uGC protocol which planned to enroll 250 to 300 participants in the gepotidacin arm. FDA did not comment on the proposed enrollment at that time. Of note, it was not clear how development of gepotidacin for this indication would proceed or whether any safety signals identified during clinical development would require further characterization. However, on June 29, 2021, as part of a Type C meeting where the Applicant reported significant recruitment issues for the uGC study due to operational challenges related to COVID-19 pandemic restrictions, FDA recommended including a minimum of 400 gepotidacin exposed participants in the safety database.

In late August 2021, the Applicant requested FDA consider a safety database of 360 total participants with only 302 exposed to the study drug at both doses in the phase 3 study and the remainder from several phase 1 studies. FDA noted this was likely sufficient for the safety database pending further characterization of any safety signals identified during clinical development.

During review of the original NDA for the uUTI indication, the team noted high rates of AEs including high rates of potential AChE-I AEs. The dose in the uGC study (3,000 mg) is double that of the approved dose for uUTI (1,500 mg), but for a shorter duration (1 day vs. 5 days). The top line safety results from the uGC study reported a much higher rate of AEs (74%) compared to the uUTI studies (35%). The FDA cautioned that the safety database size for the uGC indication would be a review issue and recommended conducting an additional clinical trial to assess safety and efficacy of gepotidacin in adults and adolescents with uGC. Alternatively, the

FDA proposed a limited indication for the treatment of uGC in patients with limited or no alternative treatment options if the Applicant refused to conduct an additional safety trial.

Assessment

The Applicant submitted their sNDA for the treatment of uGC with a proposed restricted indication. In lieu of an additional phase 3 safety study, the Applicant proposed (b) (4)

As noted in section 7.7.2, the review of the study results noted the finding that the rates of TEAEs and potential AChE-I AEs were much higher in the uGC study (EAGLE-1) and the Japanese uUTI study (EAGLE-J) compared to EAGLE-2/3. The cause(s) of these higher AE rates is(are) unclear. The higher C_{max} with the uGC dosing may be a contributing factor. Other possible factors include low body weight, specific races/ethnicities, and diet. A pharmacometric analysis of data from EAGLE-2 and EAGLE-J was not able to identify a clear cause for the different rates of AEs.

The current safety database of approximately 300 participants should identify adverse events occurring at a rate of 1% or higher. A safety database of approximately 600 participants (300 additional participants) should detect adverse events occurring at a rate of 0.5% or higher. Due to the current small safety population at the proposed dose and duration for the treatment of uGC, the unexplained higher rate of overall AEs and higher rate of potential cholinergic AEs in both EAGLE-J and EAGLE-1, and the possibility of other potential cholinergic AEs that have not been observed to date, an additional safety trial is warranted to examine the safety signals associated with gepotidacin.

Conclusion

The current safety database provides a reasonable understanding of the safety profile of gepotidacin at the proposed dose for uGC. As the proposed indication is for patients with limited or no alternative treatment options, the current safety database is considered adequate. However, given the potential for increased antibacterial drug resistance, gepotidacin use for uGC may increase in the future. As a result, the Division will issue a PMR for a safety trial to obtain controlled safety data to increase the safety database, better understand the AE profile at the higher uGC dose, and improve the ability to detect AEs occurring at a low rate. For the proposed PMR safety trial, the Division encouraged the Applicant to include clinical trial sites that will enrich the population with women and adolescents, as the original clinical trial underrepresented these populations. Of note, the rate and nature of the known adverse reactions were similar between males and females in the phase 3 uGC trial, despite low female representation.

7.7.2. Acetylcholinesterase Inhibition

Issue

Gepotidacin inhibits acetylcholinesterase and caused cholinergic adverse events in clinical studies. Potential AChE-I AE rates were much higher in the EAGLE-J and EAGLE-1 studies compared to the EAGLE-2/3 studies.

Background

The Applicant identified AChE-I TEAEs during phase 1 studies. Subsequent in vitro studies showed that gepotidacin is a reversible inhibitor of acetylcholinesterase.

Acute cholinergic symptoms secondary to acetylcholinesterase inhibition can present with several clinical features related to 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, and prolonged QTc. Stimulation of nicotinic receptors can cause tremor, fasciculations, proximal muscle weakness, paralysis, decreased tendon reflexes, tachycardia, and hypertension[15]. Muscle spasms, headaches, and seizures can also occur.

The currently approved gepotidacin PI notes the following adverse reactions which are potentially related to acetylcholinesterase inhibition: dysarthria, presyncope, muscle spasms, diarrhea, nausea, vomiting, abdominal pain, hypersalivation, and hyperhidrosis.

Study EAGLE-1 included a prespecified list of possible AChE-I TEAE preferred terms. During this review, FDA conducted exploratory analyses adjudicating TEAEs as potentially AChE-I associated to better understand this safety signal, compare the safety signal in the EAGLE-1 study to that of the uUTI phase 3 studies (EAGLE-2, 3, and J), and identify potential approaches to risk mitigation.

Assessment

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

In EAGLE-1, the Applicant identified 64% (n=197) and 11% (n=34) of participants experienced at least one potential AChE-I event in the gepotidacin and ceftriaxone and azithromycin arms, respectively. The Applicant categorized most potential AChE-I TEAEs as GI events, but 4% (n=11) of gepotidacin participants reported non-GI AChE-I TEAEs.

FDA Cholinergic TEAE Exploratory Analyses

As gepotidacin can remain in circulation for more than 12 hours, FDA performed exploratory analyses of potential AChE-I events that occurred within 60 hours (estimated 5 half-lives) of drug exposure. FDA imputed start times at midnight on the day of event for TEAEs with missing time of onset after study drug for FDA analysis of AChE-I TEAEs. The Applicant prespecified PTs for their analysis of potential AChE-I associated TEAEs. The FDA clinical team adjudicated these PTs to determine if the PTs met FDA's potential AChE-I definitions. FDA identified

[15] Attalla M, Alshamsi F, Perri D, Klimaszyk D. Cholinergic Syndrome (Cholinergic Toxicity). McMaster Textbook of Internal Medicine. Kraków: Medycyna Praktyczna. https://empendium.com/mcmtextbook/chapter/B31.II.20.12. Accessed October 28, 2025.

additional PTs from the TEAEs observed in the studies and classified them as potential AChE-I PTs based on scientific literature review and concurrence with FDA neurologists.

FDA review of EAGLE-1 identified 18 additional gepotidacin exposed participants and 19 more ceftriaxone and azithromycin exposed participants who met the FDA's potential AChE-I TEAE definition (table below). Overall rates of potential AChE-I TEAEs were much higher in the gepotidacin participants compared to the ceftriaxone and azithromycin arm. The majority of potential AChE-I TEAEs were gastrointestinal; however, a number were non-GI including neurologic TEAEs.

Gepotidacin participants in the EAGLE-1 study demonstrated a much higher overall rate of potential AChE-I TEAEs compared to the rate in EAGLE-2/3 studies (table below). Gepotidacin exposed participants in EAGLE-J demonstrated a higher potential AChE-I TEAE rate than the EAGLE-2/3 studies despite the two studies having the same study design with the same dose of gepotidacin for uUTI (see section 7.6.2). The rationale for the higher observed rates of potential AChE-I TEAEs in EAGLE-J and EAGLE-1 remains unclear. In addition, investigators categorized most events as gastrointestinal, but EAGLE-J and EAGLE-1 gepotidacin exposed participants also experienced more non-GI AChE-I events than EAGLE-2/3 participants.

Table 33 Participants With Potential AChE-I TEAEs by PT, Safety Population, All Phase 3 Trials

	EAGLE-1		EAGLE-J		EAGLE-2/3	
	Gepotidacin 3000 mg N=309 n (%)	Ceftriaxone azithromycin N=313 n (%)	Gepotidacin 1500 mg N= 281 n (%)	Nitrofurantoin N=93 n (%)	Gepotidacin 1500 mg N=1570 n (%)	Nitrofurantoin N=1558 n (%)
All AEs	230 (74.4)	104 (33.2)	201 (72)	18 (19)	551 (35.1)	365 (23.4)
Potential AChE-I AEs (Applicant)	197 (64)	34 (11)	178 (63)	11 (9)	347 (22.1)	124 (8.0)
Potential AChE-I AEs (FDA Analysis)	215 (69.6)	53 (16.9)	192 (68.3)	12 (12.9)	375 (23.9)	157 (10.1)
Potential GI AChE-I AEs*	205 (66.3)	44 (14.1)	189 (67.3)	11 (11.8)	347 (22.1)	126 (8.1)
Potential non-GI AChE-I AEs*	50 (16.2)	12 (3.8)	31 (11)	2 (2.2)	64 (4.1)	58 (3.7)

Source: FDA analysis
*Using FDA AChE-I definitions
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; N, number of participants in treatment arm; n, number of participants with adverse event; PT, preferred terms; TEAE, treatment-emergent adverse event

In EAGLE-1, all three participants who discontinued gepotidacin therapy due to TEAEs reported rapid onset of AChE-I TEAEs with one reporting syncope and the other two reporting both GI and non-GI TEAEs (Section 7.6.1.4).

Gastrointestinal disorders comprised most potential AChE-I TEAEs with diarrhea presenting as the most common TEAE (table below). More participants in the gepotidacin arm experienced occurrences of nausea, vomiting, abdominal pain, and flatulence compared to the comparator

arm. More participants in the gepotidacin arm experienced non-GI AChE-I TEAEs including dizziness, fatigue, hyperhidrosis, and blurred vision compared to the comparator arm. Although these TEAEs represent potential cholinergic effects, the nonspecific nature of the events precluded causality assessments.

Table 34. Participants With Potential AChE-I TEAEs by PT, Safety Population, Study EAGLE-1

Preferred Term	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n (%)
Diarrhea[a]	161 (52.1)	29 (9.3)
Nausea	73 (23.6)	9 (2.9)
Abdominal pain[b]	23 (7.4)	4 (1.3)
Flatulence	20 (6.5)	1 (0.3)
Vomiting	19 (6.1)	2 (0.6)
Dizziness	16 (5.2)	2 (0.6)
Fatigue[c]	10 (3.2)	0
Headache	10 (3.2)	4 (1.3)
Hyperhidrosis	7 (2.3)	0
Vision blurred	6 (1.9)	0
Myoclonus[d]	4 (1.3)	0
Abdominal distension	3 (1.0)	2 (0.6)
Abnormal feces	2 (0.6)	0
Flushing[e]	2 (0.6)	0
Myalgia	2 (0.6)	0
Rhinorrhea	2 (0.6)	0
Decreased appetite	1 (0.3)	0
Frequent bowel movements	1 (0.3)	0
Esophageal discomfort	1 (0.3)	0
Gastroenteritis	1 (0.3)	1 (0.3)
Blepharospasm	1 (0.3)	0
Dry mouth	1 (0.3)	0
Dysarthria	1 (0.3)	0
Dyspnea	1 (0.3)	0
Eye pain	1 (0.3)	0
Lacrimation increased	1 (0.3)	0
Photopsia	1 (0.3)	0
Pollakiuria	1 (0.3)	0
Poor quality sleep	1 (0.3)	0
Presyncope	1 (0.3)	0
Salivary hypersecretion	1 (0.3)	0
Syncope	1 (0.3)	0
Tachycardia	1 (0.3)	0
Vertigo	1 (0.3)	0
Visual impairment	1 (0.3)	0
Dyspepsia	0	1 (0.3)
Insomnia	0	1 (0.3)
Musculoskeletal pain	0	2 (0.6)
Nasopharyngitis	0	3 (1.0)

Preferred Term	Gepotidacin 2x3000 mg N=309 n (%)	Ceftriaxone 500 mg Plus Azithromycin 1 g N=313 n (%)
Rhinitis	0	1 (0.3)

Source: FDA analysis
[a] Diarrhea includes diarrhea and soft feces
[b] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort
[c] Fatigue includes fatigue and lethargy
[d] Myoclonus includes muscle contraction involuntary, muscle spasms, muscle twitching, myoclonus
[e] Flushing includes flushing and hot flush
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; N, number of participants in treatment arm; n, number of participants with adverse event; PT, preferred terms; TEAE, treatment-emergent adverse event

Most participants with potential cholinergic TEAEs reported mild or moderate severity events. One hundred and three (33.3%) gepotidacin participants reported two or more potential AChE-I AEs compared to seven (2.2%) ceftriaxone and azithromycin participants (table below). The majority of potential cholinergic TEAEs in both arms resolved by study completion in EAGLE-1. Male and female EAGLE-1 participants experienced potential cholinergic TEAEs at the same frequency in the gepotidacin arm.

Potential AChE-I TEAEs occurred quickly after gepotidacin suggesting a likely relationship to gepotidacin (table below). Currently, no specific test exists to differentiate TEAEs due to cholinergic effects. However, rapid resolution of TEAEs after discontinuation of gepotidacin lends credence to cholinergic adverse drug effects as the Applicant considers the cholinergic events to be rapidly reversible.

Table 35. Characteristics of Participants with Potential AChE-I TEAEs*, Safety Population, Study EAGLE-1

	Gepotidacin 3000 mg N=309 n (%)	Ceftriaxone and Azithromycin N=313 n (%)
Potential AChE-I TEAEs	215 (69.6)	53 (16.9)
Maximum severity		
Mild	154 (49.8)	49 (15.7)
Moderate	61 (19.7)	4 (1.3)
Experienced >2 AChE-I TEAEs	103 (33.3)	7 (2.2)
Adverse Event Onset after Drug Exposure		
Within first day	193 (90)	39 (73.6)
Resolution of AChE-I TEAE by Study End	212 (98.6)	50 (94.3)
Sex+		
Male	190/274 (69.3)	49/280 (17.5)
Female	25/35 (71.4)	4/33 (12.1)

Source: FDA analysis
*Using FDA AChE-I definitions
+Rate of potential AChE-I TEAEs by sex
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; N, number of participants in treatment arm; n, number of participants with adverse event; PT, preferred terms; TEAE, treatment-emergent adverse event

The Applicant previously included dysarthria as a likely cholinergic adverse reaction in the prescribing information and medication guide due to several cases that investigators observed in

the development program. Investigators also observed dysarthria in one EAGLE-1 gepotidacin participant and three EAGLE-J gepotidacin participants.

The cause of the higher rate of AChE-I TEAEs in gepotidacin participants in studies EAGLE-1 and EAGLE-J remains unclear, but gepotidacin exposure, cultural, dietary, or genetic factors may have contributed to the higher rates of these adverse events. FDA conducted an analysis of AChE-I events and plasma exposure using data from studies EAGLE-2 and EAGLE-J. The analysis found that the difference in the incidence of potentially AChE-I associated TEAEs between the two studies was not due to a difference in gepotidacin exposure (see original NDA review). EAGLE-1 did not include pharmacokinetic sampling which precludes further analyses of gepotidacin exposure and adverse events.

Conclusion

Participants who received gepotidacin in the uGC EAGLE-1 study commonly experienced potential cholinergic TEAEs (215, 69.6%) and most events were gastrointestinal in nature (diarrhea [52.1%], nausea [23.6%], vomiting [6.1%], and abdominal pain [7.4%]). The majority of cholinergic TEAEs occurred within the first day after study drug initiation. Investigators considered the majority of cholinergic TEAEs resolved by study completion.

Investigators identified neurologic TEAEs potentially related to AChE-I including dysarthria, syncope, presyncope, dizziness, muscle spasms, blurred vision, headache, and fatigue. Gepotidacin administration uncommonly caused dysarthria. However, strokes and transient ischemic attacks can also present similarly, leading to potentially extensive neurologic evaluations when patients develop dysarthria (see original NDA review). To mitigate the potential risks of AChE-I associated adverse reactions, the product labeling contains a warning describing AChE-I and a medication guide will be provided to patients.

A postmarketing requirement for an additional safety trial of gepotidacin for uGC treatment will enhance the current safety database.

7.7.3. QTc Prolongation

Issue

While gepotidacin's QTc prolongation risk was assessed for the uUTI indication, the proposed uGC dosing regimen of 3000 mg twice daily (versus 1500 mg twice daily for uUTI) results in significantly higher exposure and Cmax, creating an elevated risk of QT prolongation that requires re-evaluation.

Background

Gepotidacin prolongs the QTc interval in a dose- and concentration-dependent manner as demonstrated in a thorough QT (TQT) study of gepotidacin 1000 mg (mean ΔΔQTc = 12 msec) and 1800 mg (mean ΔΔQTc = 22 msec) administered by IV infusion over 2 hours. This QTc prolongation risk has been assessed for the uUTI indication in the original submission.

Although the proposed uGC dosing regimen (2 oral doses of 3000 mg taken approximately 12 hours apart) has a shorter treatment duration of one day compared to the approved uUTI indication (1500 mg BID for 5 days), the higher 3000 mg dose results in increased gepotidacin

exposure and Cmax, consequently leading to a heightened risk of QT prolongation that requires re-evaluation for the uGC indication.

Assessment

Patients with uGC without Specific Risk Factors for Increased Gepotidacin Concentrations

For the general population with no risk factors for increased gepotidacin concentrations (i.e., patients without predisposing factors to QT prolongation who have body weight ≥60 kg with no moderate or severe organ impairment, or are not taking strong or moderate CYP3A4 inhibitors), no reassessment of QT prolongation risk is needed for the treatment of uGC based on the previous findings from uUTI. This conclusion is based on the following two key facts. First, the population PK model observed Cmax,ss of gepotidacin (11.6 μg/mL) does not exceed the exposure from a single IV dose of 1800 mg (13.6 μg/mL) evaluated in the QT assessment study (BTZ115775). Second, results from the pivotal study (EAGLE-1) demonstrated no disproportionate increase in cardiovascular adverse events of special interest in uGC patients treated with the recommended gepotidacin dose compared to those receiving standard of care (ceftriaxone plus azithromycin), with only one event of grade 1 tachycardia observed among 302 patients receiving gepotidacin (<1%).

Specific Populations and Drug Interactions

However, there are concerns regarding QTc prolongation in clinical scenarios with increased gepotidacin exposure. The Applicant used a previously developed population PK model to predict gepotidacin Cmax following the second dose of the proposed dosage in patients with uGC and the associated QTcF prolongation under various intrinsic and extrinsic factors.

The Applicant's PK model-predicted Cmax was found to be underestimated by a factor of 1.5-fold compared to the observed Cmax, and consequently the associated predicted QTcF prolongation was underestimated. Thus, the review team reassessed the expected QTcF prolongation after correcting the predicted Cmax by multiplying by a factor of 1.5.

Based on the corrected modeling results, gepotidacin dosing recommendations are primarily driven by QTc prolongation risk, with a 20 msec ΔΔQTcF safety threshold serving as the key clinical decision-making criterion.

Single Risk Factor

The risk factors listed below were identified as concerns for the uUTI indication (1500 mg BID for 5 days) and also apply to uGC (3000 BID for one day). Patients with any of the following conditions have a high risk of increased gepotidacin Cmax and associated QTc prolongation of at least 20 msec:

- Severe renal impairment
- Severe hepatic impairment
- Concomitant use of strong CYP3A4 inhibitors

See Section 8 and Section 14.5 for a more details.

Multiple Risk Factors

Patients receiving the dosing regimen of 3000 mg 12 hours apart for 2 doses over one day with a single risk factor below require no dosage adjustment, which is consistent with the

recommendations for uUTI (1500 mg BID for 5 days) with a single risk factor. However, different from recommendations for uUTI, due to the increased dose, uGC patients with two or more of the following risk factors have a higher risk of increased gepotidacin Cmax and an associated QTc prolongation of at least 20 msec:

- Concomitant use of moderate CYP3A4 inhibitors
- Body weight between 45 kilograms and 60 kilograms
- Moderate renal impairment (eGFR 30-59 mL/min)
- Moderate hepatic impairment (Child- Pugh Class B)

See Section 8 and Section 14.5 for a more details.

Conclusion

Gepotidacin should be avoided in patients described in the Single Risk Factor and Multiple Risk Factor sections above, because gepotidacin concentrations may reach levels associated with QTc prolongation above 20 msec. Enhanced warnings regarding QTc prolongation will be included in the prescribing information for the uGC indication.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Hepatic Impairment

The recommended dosing strategy for gepotidacin in patients with hepatic impairment varies by severity. No dosage adjustment is required for patients with mild hepatic impairment or moderate hepatic impairment alone. However, gepotidacin should be avoided when moderate hepatic impairment is combined with additional risk factors that increase drug exposure. Gepotidacin should be avoided in patients with severe hepatic impairment.

Gepotidacin undergoes ~30% metabolism in blood, with biliary excretion representing a major route of elimination (approximately 30% of unchanged gepotidacin eliminated in feces). A dedicated hepatic impairment study (Study BTZ117352) using a single 1500 mg oral dose demonstrated:

- Mild hepatic impairment: No clinically significant effect on gepotidacin pharmacokinetics
- Moderate hepatic impairment (Child-Pugh Class B): ~1.2-fold increase in both Cmax and AUC
- Severe hepatic impairment (Child-Pugh Class C): ~1.9-fold increase in Cmax, ~1.7-fold increase in AUC

Due to gepotidacin's linear pharmacokinetics, similar fold-increases are expected at the 3000 mg dose used for uGC treatment.

In patients with severe hepatic impairment, the nearly 2-fold increase in Cmax significantly increases the risk of QT prolongation. Additionally, patients with severe hepatic impairment were excluded from the phase 3 efficacy and safety studies, limiting the available safety data in this population. Thus, use of gepotidacin should be avoided in this population.

Population pharmacokinetic modeling and simulation analyses for the uGC dosing regimen (2 oral doses of 3000 mg taken 12 hours apart) were conducted to inform dosing recommendations and mitigation strategies for patients with hepatic impairment. Patients with mild hepatic impairment showed no meaningful QTc prolongation risk. Moderate hepatic impairment alone did not increase risk; however, when combined with additional factors that increase gepotidacin concentrations (moderate CYP3A4 inhibitors, body weight <60 kg, or moderate renal impairment), predicted median ΔΔQTcF values exceeded the established 20 msec safety threshold. (see Section 14.5).

8.1.2 Renal Impairment

No dose adjustment is required for patients with mild to moderate renal impairment, in the absence of other factors that increase drug exposure. However, gepotidacin should be avoided in patients with moderate renal impairment when combined with additional risk factors that increase drug exposure. Gepotidacin should be avoided in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2).

Gepotidacin undergoes significant renal elimination with 31% of the administered oral dose recovered in urine as drug-related material, of which 67% represents unchanged parent drug. The population PK model estimates a renal clearance of 12.5 L/hour or over 200 mL/min, which exceeds the normal glomerular filtration rate (~120 mL/min), indicating that gepotidacin elimination occurs primarily through active tubular secretion rather than passive filtration alone.

A dedicated renal impairment study using a single oral dose of 1500 mg gepotidacin (Study BTZ116849) demonstrated progressive increases in gepotidacin exposure with declining renal function:

- Mild renal impairment (eGFR 60-89 mL/min): No clinically significant changes
- Moderate renal impairment (eGFR 30-59 mL/min): ~1.2-fold increase in Cmax, ~1.5-fold increase in AUC
- Severe renal impairment/ESRD not on hemodialysis (eGFR <30 mL/min): ~1.7-fold increase in Cmax, ~2.1-fold increase in AUC
- ESRD on hemodialysis:
  - Administered before hemodialysis: ~2.3-fold increase in Cmax, ~2.4-fold increase in AUC
  - Administered after hemodialysis: ~6.0-fold increase in Cmax, ~4.1-fold increase in AUC
  - Only ~6% of gepotidacin dose removed during 4-hour hemodialysis session

Due to gepotidacin's linear pharmacokinetics, similar fold-increases in exposure are expected at the 3000 mg dose used for uGC treatment.

In patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) the approximately 2-fold increase in Cmax significantly increases the risk of QTc prolongation. Additionally, patients with severe renal impairment were excluded from pivotal phase 3 studies limiting safety data and this population often has comorbid conditions and electrolyte imbalances that predispose to cardiac arrhythmias potentially compounding gepotidacin-related cardiac effects. Thus, gepotidacin should be avoided in patients with severe renal impairment.

Population pharmacokinetic modeling and simulation analyses for the uGC dosing regimen demonstrated concentrations associated with progressively increasing QTc prolongation risk with declining renal function. Patients with severe renal impairment showed the highest risk with predicted mean ΔΔQTcF of 28.9 msec, further supporting the avoid use recommendation in this population. While the predicted ΔΔQTcF was approximately 17.7 msec for moderate renal impairment as a single factor, the combination of moderate renal impairment with moderate CYP3A4 inhibitor, body weight less than 60 kg, or moderate hepatic impairment results in predicted median ΔΔQTcF values all above 20 msec. Thus, patients with moderate renal impairment with these additional risk factors should avoid gepotidacin. Patients with mild renal impairment can receive the 3000 mg dose without additional risk of QTc prolongation (see Section 14.5).

8.1.3 Other Intrinsic Factors

Population PK analysis indicated that age, sex, and race have no clinically relevant effect on gepotidacin exposure.

Body Weight

While body weight alone does not produce clinically significant effects, population pharmacokinetic modeling and simulation analyses for the uGC dosing regimen revealed that QTc prolongation risk increases progressively as body weight decreases, when other factors that increase gepotidacin concentrations are present. Patients weighing less than 60 kg who also have moderate hepatic impairment, moderate renal impairment, or concomitant use of moderate CYP3A4 inhibitors showed predicted median ΔΔQTcF values exceeding 20 msec. Therefore, the labeling will recommend avoiding use in patients weighing less than 60 kg who have additional risk factors that increase gepotidacin exposure (e.g., moderate hepatic impairment, moderate renal impairment, or concomitant use with moderate CYP3A4 inhibitors). (see Section 14.5)

8.2. Extrinsic Factors

8.2.1 Food Effect

Gepotidacin is recommended to be administered with food to improve gastrointestinal tolerability. However, the effect of coadministration of a high-fat meal with gepotidacin has not been directly studied in clinical trials. A clinical study with a moderate fat meal (Study 213678) demonstrated that food slightly delays time to maximum concentration (Tmax) but has no meaningful effect on gepotidacin plasma exposure.

8.2.2 The Effect of Drug-Drug Interactions

Gepotidacin is a CYP3A4 substrate. The recommended risk mitigation strategy for gepotidacin is to avoid use with strong CYP3A4 inhibitors, avoid use with moderate CYP3A4 inhibitors in patients with one or more risk factors for increased gepotidacin exposure, and avoid concomitant use with strong and moderate CYP3A4 inducers.

CYP3A4 Inhibitors

Strong CYP3A4 Inhibitor

A DDI study (Study BTZ117349) demonstrated that co-administration of the strong CYP3A4 inhibitor itraconazole significantly increased gepotidacin plasma AUC and Cmax by approximately 48% and 42%, respectively. Model-predicted ΔΔQTcF when co-administered with a strong CYP3A4 inhibitor is >21 msec, which exceeds the predefined safety threshold of 20 msec for the treatment of uGC. Therefore, concomitant use with strong CYP3A4 inhibitors should be avoided.

Moderate CYP3A4 Inhibitor

The PBPK model simulation results indicated that gepotidacin AUC and Cmax increase approximately 1.4- and 1.2-fold, respectively, with co-administration of a moderate CYP3A4 inhibitor (such as fluconazole). Given that the AUC increase is within 2-fold and the Cmax increase is not clinically significant, no dose adjustment is needed when patients take gepotidacin concomitantly with moderate CYP3A4 inhibitors

However, population PK simulation results demonstrate that combinations of a moderate CYP3A4 inhibitor with moderate renal impairment, body weight less than 60 kg, or moderate hepatic impairment result in predicted median ΔΔQTcF values above 20 msec. (See Section 14.5 Pharmacometrics Assessment for details.) Therefore, concomitant use with moderate CYP3A4 inhibitors should be avoided when additional risk factors for increased gepotidacin exposure are present.

The Applicant proposed a more conservative approach to avoid use of moderate CYP3A4 inhibitors with gepotidacin, which the review team found to be acceptable.

Strong and Moderate CYP3A4 Inducer

A DDI study demonstrated that co-administration of gepotidacin with the strong CYP3A4 inducer rifampicin decreased gepotidacin plasma exposure by >50%. PBPK modeling and simulation indicated that the moderate CYP3A4 inducer efavirenz decreased Cmax and AUC by 34% and 49%, respectively. These reductions in gepotidacin exposure may compromise treatment efficacy and bacterial resistance suppression. Since uGC requires prompt treatment and CYP3A4 induction effects can persist after discontinuation, temporary avoidance of inducers is not clinically feasible. Therefore, concomitant use with strong and moderate CYP3A4 inducers should be avoided, and alternative antibacterial therapy should be considered for patients taking these medications.

8.3. Plans for Pediatric Drug Development

Urogenital gonorrhea does not commonly occur prior to sexual maturity. As a result, the PREA requirement for pediatric patients less than 12 years of age will be waived for this indication.

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

See the review for the original NDA for information on these topics.

9. Product Quality

Approval

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 218230 with respect to chemistry, manufacturing and controls (CMC), including the updated CMC information submitted as part of this supplement, and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this sNDA from a quality perspective (refer to the OPQ review of this supplement dated October 24, 2025, in Panorama).

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 3 clinical study sites that participated in Study EAGLE-1. The Office of Scientific Investigations' assessment was that the trial appears to have been conducted in observance of good clinical practice principles and in compliance with FDA regulations. The data generated by the clinical investigators appear to be acceptable in support of this sNDA. Please refer to the review by John Lee dated October 31, 2025, 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

On June 29, 2016, GlaxoSmithKline, LLC (Applicant for current sNDA) requested Qualified Infectious Disease Product (QIDP) designation for the use of gepotidacin capsules in the treatment of uncomplicated urogenital infections caused by *N. gonorrhoeae* under IND 111885. Upon review of the submission, the Division concluded that gepotidacin qualified as a QIDP based on the determination that uncomplicated urogenital GC are serious infections and may lead to more serious sequelae. The Division granted gepotidacin capsules QIDP on August 26, 2016, for uncomplicated urogenital infections caused by *N. gonorrhoeae*.

Subsequent to garnering QIDP designation for uGC, GSK elected to change the formulation of gepotidacin from (b) (4) a capsule configuration to a mesylate salt in a tablet. As the GAIN Act requires QIDP designations to be company, product and indication specific, the Applicant was required to submit a subsequent QIDP designation request, which was received by the Division on November 9, 2018. Upon the review of the second QIDP designation request, the Division made similar findings and designated the tablet (mesylate salt) formulation of gepotidacin for treatment of uncomplicated urogenital infections caused by *N. gonorrhoeae* as QIDP on January 8, 2019.

On March 25, 2025, the Applicant received marketing approval of their new drug application (NDA) 218230 for Blujepa (gepotidacin) tablets 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 (uUTI) caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, *Staphylococcus saprophyticus*, and *Enterococcus faecalis*. Prior to this original NDA approval, the Applicant informed the Division of Anti-Infectives (Division) of their intent to immediately submit an sNDA, pending the approval of their original application, for the additional indication of uncomplicated gonorrhea (uGC). Pursuant to this, the Applicant requested, and was granted a pre-sNDA meeting on April 7, 2025, for a May 15, 2025, meeting.

On May 2, 2025, the Division provided Meeting Preliminary Responses for the pre-sNDA meeting. For purposes of the meeting, the Applicant sought the Division's agreement that an sNDA comprised of data from one phase 3 study would be sufficient to support the proposed restricted indication of uGC, (b) (4) . In particular, the Applicant wished to confirm that the restricted indication being sought (uGC) would provide an alternative treatment option for those patients with the greatest unmet need. In addition, the Applicant wished to reach an agreement with the Division that an additional clinical trial would not be needed to support the proposed restricted indication.

In the Meeting Preliminary Responses, the Division conveyed that they concurred that the proposed approach would support the submission of an sNDA for Blujepa for a limited uGC indication. The Applicant was informed that the adequacy of the provided data would be a review issue. The Division added that additional dialogue during the sNDA review cycle could be held, related to product labeling and postmarketing requirements or commitments

(PMR/PMC). Following review of the Meeting Preliminary Responses, the Applicant elected to cancel the pre-sNDA meeting scheduled for May 15, 2025.

On June 11, 2025, the Applicant submitted an efficacy supplement sNDA 218230/S-001 for the use of Blujepa (gepotidacin) for the treatment of uGC in adult and pediatric patients 12 years of age and older weighing more than 45 kg, (b) (4)

On August 7, 2025, the Applicant was informed that the Division had not identified any potential review issues, and that the application would be considered filed. The Applicant was additionally informed that their review classification for the application would be Priority, with a Prescription Drug User Fee Act (PDUFA) action goal date of December 11, 2025. sNDA 218230/S-001 is the subject of this review.

13. Pharmacology Toxicology

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

Studies were reviewed or summarized under the original application; reviews and summaries can be found there.

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

13.2.1. Safety of Impurities

- The Applicant did not submit any additional studies for impurity qualification.
- Specified impurities (b) (4) are qualified as described in the original NDA review and with comparison shown below for the current 6 gram/day dose.
- Specified impurity (b) (4) was evaluated for use of gepotidacin as a surrogate for read across to qualify the impurity. This approach was found acceptable as described below.
- (Q)SAR positive potential genotoxic impurities were evaluated in the original NDA review, and it was determined that their final concentrations would be below the threshold of toxicological concern by manufacturing processes.
- The identified nitrosamine drug substance related impurity (NDSRI) was reviewed in the original NDA submission and is acceptable based on that analysis at the current maximum recommended human dose (3 g/day).
- There are no new inactive ingredients, elemental impurities, or solvents of concern.
- Impurities as described for the new dose and duration for the indication in this sNDA do not present a safety concern.

Specified impurities

The Applicant reported eight impurities in this drug product requiring qualification for the proposed specification limit including a nitrosamine. The review of the nitrosamine drug substance related impurities (NDSRI) is in the review for the original NDA and updated here for the new clinical dose. Because the maximum daily exposures to impurities at the desired qualification limit are (b) (4), the Applicant provided (Q)SAR analysis for any structural alerts for mutagenicity (see review for the original NDA submission).

Table 36: Impurities With Specified Limits

Impurity identifier	Structure	Desired Limit to be qualified (%w/w)
(b) (4)		

Impurity identifier	Structure	Desired Limit to be qualified (%w/w)
	(b) (4)	

A summary review of the repeat dose rat study provided to qualify impurities is included in the original NDA review. The NOAEL in this study was (b) (4) mg/kg/day, the highest dose tested. The levels of impurities qualified by this study based on the impurity levels in the test-article for that study are shown in the table below. Maximum daily clinical intakes of the impurities are calculated based on the provided specifications and the labeled daily intake of 3,000 mg/day and are also shown in the table below. Exposures in the nonclinical studies were compared to clinical

exposures at the specified limit after scaling animal NOAELs to human equivalent doses based on body surface area. As noted in FDA guidance, this is the most appropriate comparison unless specific justification for another scaling method would be provided.[16] Based on these calculations, (b) (4) is qualified at this clinical dose (6 g/day gepotidacin).

Table 37: Drug Substance Impurities and Dose Multiples

Impurity	Specification Limits	Impurity Level % in Nonclinical Qualification Study	(Nonclinical Species) Total Daily Intake of Impurity (mg/m^2)	Human Total Daily Intake of Impurity (mg/m^2)	Dose Multiple
(b) (4)					

Source: Reviewer generated table
Human: Drug total daily dose = 6000 mg (60 kg patient)
NOAEL for the pivotal nonclinical rat study = (b) (4) mg/kg/day

The Applicant used gepotidacin as a surrogate for read-across to qualify the impurities (b) (4) at the specified limits. The impurities are also negative in the provided (Q)SAR analyses and mutagenicity assays, where available. We agree that use of gepotidacin is an appropriate surrogate to use for read-across to these impurities based on structural similarity. The more sensitive species for gepotidacin in repeat-dose toxicology studies was the dog and for the longest duration study available in dog (13-weeks) the NOAEL was (b) (4) mg/kg/day (See the review of the original NDA, Section 13.1.4.1 General Toxicology). Uncertainty factors of 2 for interspecies, 10 for intraspecies variation, 1 for toxicity severity, 1 for availability of NOAEL, 1 for the duration of the study, and 5 for use of gepotidacin as surrogate were used to derive a permitted daily exposure of (b) (4) mg/day as shown in Equation 1 below. With exposures at the specified limits of (b) (4) % for each (b) (4) the respective worse case exposures at the maximum daily dose would be (b) (4) mg respectively. Based on this comparison, these impurities are qualified at the proposed specified limits.

[16] FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005).

Equation 1. Calculation of PDE for Impurities Using Gepotidacin as a Surrogate and Dog 13-Week Study.

$$PDE = \text{(b) (4)}$$

UF1= 2 to account for interspecies extrapolation from dog to humans

UF2=10 to account for difference between individuals

UF3=1 as the duration of the study is appropriate for the expected duration of exposures

UF4=1 because no severe toxicity was encountered

UF5=1 because a NOAEL was available

UF6=5 because gepotidacin was used as a surrogate molecule for read-across

Source: Reviewer-generated equation
Abbreviations: PDE, permitted daily exposure, UF, Uncertainty factor; NOAEL, no adverse effect level

(Q)SAR positive potential genotoxic impurities

(Q)SAR positive potential genotoxic impurities were reviewed under the original NDA submission. No concerns were identified.

Nitrosamine Impurities

(b) (4)

Inactive Ingredients, Elemental Impurities, and Solvent Impurities

Inactive ingredients, elemental impurities, and solvent impurities were reviewed and found to be at acceptable use levels.

14. Clinical Pharmacology

14.1. In Vitro Studies

Previously conducted in vitro studies encompassed protein binding, blood-to-plasma distribution ratio, and comprehensive in vitro drug-drug interaction assessments involving both cytochrome P450 enzyme-mediated interactions and transporter-mediated pathways. These studies were evaluated in the original submission for the uncomplicated urinary tract infection indication. For more details on the methodologies and results see the integrated review for NDA 218230 approved on 03/25/2025.

Well-characterized PK/PD animal models for *N. gonorrhoeae* were not available during the initial clinical development of gepotidacin. Consequently, traditional in vivo PK/PD studies to establish efficacy targets were not conducted for gepotidacin against *N. gonorrhoeae*. The PK/PD index and magnitude predictive of gepotidacin efficacy against *N. gonorrhoeae* remain undefined through conventional preclinical methods. However, subsequent in vitro hollow-fiber infection model studies were conducted to determine resistance suppression targets.

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

The Applicant examined the nonclinical pharmacokinetic-pharmacodynamic (PK-PD) properties of gepotidacin using a dynamic in vitro hollow fiber infection model (HFIM) with *Neisseria gonorrhoeae* to support dose selection for the pivotal phase 3 clinical trial treating uncomplicated urogenital gonorrhea.

To determine the gepotidacin exposure required to suppress resistance amplification observed in phase 2 study BTZ116576, duplicate 7-day HFIM studies were conducted using a clinical isolate (GSK#8) harboring GyrA S91F:D95A and ParC D86N mutations with an MIC of 1 μg/mL. The study design included inactive controls (no treatment and ciprofloxacin 0.5 g oral), an active control (ceftriaxone 0.25 g intramuscular), and gepotidacin regimens ranging from single or divided oral doses of 0.75 g to 12 g.

The HFIM demonstrated an inverted-U relationship between gepotidacin dose and change in $\log_{10}$ CFU/mL of resistant subpopulations:

- Low gepotidacin doses (0.75-3 g) resulted in treatment failure with resistance amplification
- Intermediate doses showed maximum resistance amplification
- Gepotidacin regimens totaling ≥4.5 g (corresponding to $fAUC_{0–24}$/MIC values ≥46) as a single dose successfully prevented resistance amplification and sterilized the model system by day 7
- Divided doses of two 3 g administrations given 8-12 hours apart also achieved sterilization and prevented resistance development (See Section 5.1, Figure 1)

Analysis of gepotidacin-resistant isolates revealed specific resistance mechanisms involving additional GyrA mutations: V36I substitutions (4-fold MIC increases) and A75S or A92T/V substitutions (16-fold MIC increases). These mutations were consistent with those identified in clinical isolates from gepotidacin-treated patients in a phase 2 study. The variable efficacy observed with the 3 g dose in the HFIM also aligned with clinical study results.

Despite limitations including evaluation of only one isolate and simulation of plasma rather than tissue-specific exposures, the concordance between in vitro and clinical findings demonstrates that these data provide support for selecting gepotidacin dosing regimens of ≥4.5 g total dose for treating uncomplicated urogenital gonorrhea while minimizing on-therapy resistance amplification risk.

Because *N. gonorrhoeae* is human-specific and grows poorly in animals, the Applicant did not submit any PK-PD information from *N. gonorrhoeae* in vivo infection model studies.

14.2. In Vivo Studies

14.2.1. Healthy Participants

Comprehensive in vivo studies evaluating the impact of both intrinsic and extrinsic factors on gepotidacin pharmacokinetics were conducted as part of the original uUTI NDA submission. Intrinsic factor investigations included dedicated phase 1 studies in specific populations with renal impairment (Study BTZ116849), hepatic impairment (Study BTZ117352), elderly participants (Study BTZ117349), and adolescents (Study 209611), along with a thorough QT study (Study BTZ115775) that established the concentration-QT relationship critical for safety assessments in the uGC indication.

Extrinsic factor evaluations encompassed food effect studies across multiple trials (Studies BTZ117349, BTZ114595, BTZ117351, and 213678) demonstrating no clinically meaningful impact on gepotidacin absorption, comprehensive drug-drug interaction studies including itraconazole (40-50% exposure increases), rifampicin (>50% exposure decreases), and cimetidine (no significant interactions), and transporter interaction investigations identifying gepotidacin as a substrate of P-glycoprotein, BCRP, MATE1, and MATE2-K. Physiologically-based pharmacokinetic modeling (reports 2022N524769 and 2020N458711) predicted that moderate CYP3A4 inhibitors like fluconazole would increase gepotidacin exposures by 40% and 20% for AUC and Cmax, respectively, while moderate inducers like efavirenz would decrease these parameters by 49% and 34%, respectively.

Detailed study designs, methodologies, and results are documented in the uUTI NDA review.

14.2.2. Infected Participants

14.2.2.1. Phase 2 Dose Ranging Study

Study BTZ116576

BTZ116576 was a phase 2, randomized, multicenter, dose-ranging study evaluating the efficacy, safety, and tolerability of single doses of gepotidacin (1500 mg or 3000 mg) in 106 adult participants with uncomplicated urogenital gonorrhea caused by *Neisseria gonorrhoeae*. The study was conducted across 12 centers with participants randomized into two dosing cohorts. The PK population consisted of 70 participants, presenting 66% of the randomized population. A summary of the study populations is shown in the table below. Gepotidacin plasma concentrations were determined using a validated UHPLC-MS/MS method, which met precision and accuracy criteria (±15%, ±20% at LLOQ) and incurred sample re-analysis criteria (≥66.7%) per ICH M10 guidance (see Section 14.3 for details).

Table 38. Summary of Study Populations (All Randomized Population)

Population	Gepotidacin 1500 mg N (%)	Gepotidacin 3000 mg N (%)	Total N (%)
All Randomized	53 (100)	53 (100)	106 (100)
Safety	52 (98)	53 (100)	105 (>99)
Microbiologically Evaluable	30 (57)	39 (74)	65 (56)
Pharmacokinetics	34 (64)	36 (68)	70 (66)

Source: Table 6 in the clinical study report BTZ116577

In the microbiologically evaluable (ME) population, participants were predominantly male (n=67 participants, 97%), with only 2 female participants (3%). The mean age was 33.4 years (range: 18 to 69 years) and the mean body mass index was 25.31 kg/m^2 (range: 17.6 to 39.3 kg/m^2).

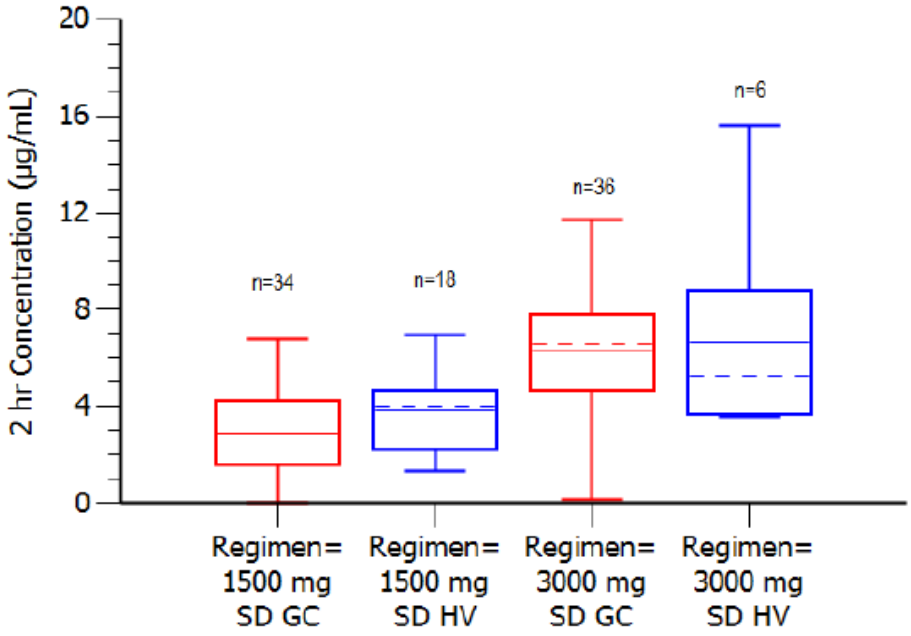
Mean gepotidacin plasma concentrations at approximately 2 hours post dose were 2893.0 ng/mL and 6348.4 ng/mL for the 1500 mg and 3000 mg doses, respectively (see table below). These plasma concentrations in gonorrhea patients were comparable to those observed in healthy participants from phase 1 studies (See figure below). However, exposure-response analyses could not be performed due to insufficient pharmacokinetic data, as only 59% of the microbiologically evaluable population had available PK measurements.

Table 39. Summary of Plasma Gepotidacin Pharmacokinetic Concentrations (Pharmacokinetic Population)

Treatment	Planned Relative Time	n	Number Imputed	Mean (ng/mL)	CV	Median (ng/mL)	Min, Max (ng/mL)
Gepotidacin 1500 mg (N=34)	2 hours postdose	34	2	2893.0	62.2	2865.0	0, 6780
Gepotidacin 3000 mg (N=36)	2 hours postdose	36	0	6348.4	42.9	6615.0	110, 11700

Source: Table 3 in the clinical study report BTZ116577
Abbreviations: CV, coefficient of variation; max, maximum; min, minimum

Figure 3. Comparison of Gepotidacin Plasma Concentrations at 2 hours Postdose Between Participants with Gonorrhea (Phase 2) and Healthy Volunteers (Phase 1)



Source: Figure 5 in the clinical study report BTZ116577
Note: The solid midline is the mean, and the broken midline is the median. The 1500 mg HV data from study BTZ116778 (1500 mg single oral dose; fed condition). The 3000 mg HV data is from study BTZ116576 (3000 mg single oral dose; fasted conditions). The 1500 mg and 3000 mg GC data is from BTZ116576 (single oral dose; administered with food).
Abbreviations: GC, participants with gonorrhea; hr, hour; HV, healthy volunteers; SD, single dose

Both doses demonstrated ≥95% efficacy against urogenital *N. gonorrhoeae* infection with no unexpected safety signals. However, resistance analysis revealed that among 5 participants with baseline gepotidacin MIC of 1 µg/mL, 3 experienced microbiological failure. (Section 6.2.3). To address resistance concerns identified in this study, a 7-day hollow fiber infection model was conducted to establish a resistance suppression target and confirm the total daily dose needed to prevented resistance amplification to be used in the Phase 3 study (Section 14.1.1).

Reviewer comments:

- *The dosage form utilized in this study is a 500 mg oral capsule, which differs from the 750 mg oral tablet formulation used in the phase 3 study and intended for commercial marketing.*

14.3. Bioanalytical Method Validation and Performance

Gepotidacin plasma concentrations in Study BTZ116576 were determined using a validated UHPLC-MS/MS method (P1184). The method demonstrated acceptable performance characteristics, meeting precision and accuracy criteria (±15% for most concentrations, ±20% at the lower limit of quantification) and the incurred sample re-analysis criteria (≥66.7%), consistent with ICH M10 Bioanalytical Method Validation Guidance and Study Sample Analysis- Guidance for Industry (2022) (FDA 2022b). Comprehensive details regarding method

validation parameters, analytical performance, and regulatory assessment are documented in the integrated review for the uUTI indication approved on 03/25/2025.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable

14.5. Pharmacometrics Assessment

The Applicant used a previously developed population PK model (in healthy volunteers, patients with uncomplicated urinary tract infection or uncomplicated urogenital gonorrhea) to predict gepotidacin maximum concentration (Cmax) from the 2nd dose of the proposed dosage in patients with uncomplicated urogenital gonorrhea (uGC) and the associated QTcF prolongation, under different intrinsic and extrinsic factors linked to increased gepotidacin exposure.

However, the Applicant PK model-predicted Cmax was found to be underestimated by a factor of 1.5-fold compared to the observed Cmax, and consequently the associated predicted QTcF prolongation was underestimated.

The review team reassessed the expected QTcF prolongation after correcting the predicted Cmax under different levels of organ impairment, body weight or drug interaction with strong or moderate CYP3A4 inhibitors. As the Applicant was not able to improve the PK model and the review team was not able to adjust the PK absorption model to capture the Cmax, the corrected Cmax used to estimate QTcF prolongation was obtained by multiplying the model-predicted Cmax by a factor of 1.5.

The review team evaluation found that patients with any combination of the following risk factors have a higher risk of increased gepotidacin Cmax (≥ 13.3 ng/mL) and an associated QTc prolongation of at least 20 msec:

- Body weight <60 kg.
- Any level of moderate organ impairment (renal or hepatic).
- Concomitant use of moderate CYP3A4 inhibitors.

14.5.1. Applicant's Analysis

In the previous NDA submission (NDA 218230) for the indication in patients with uncomplicated urinary tract infection (uUTI), the Applicant developed a population PK model for gepotidacin to characterize the PK properties of gepotidacin administered orally (PO) or intravenously (IV). The data for PK modeling were collected from 14 clinical studies, with eleven phase 1 studies in healthy participants (BTZ116778, BTZ117349, BTZ117351, 209611, 213678, BTZ115198, BTZ115774, BTZ115775, BTZ116849, BTZ116666 and BTZ117352), two phase 2 study (BTZ116576, 206899) in patients with uncomplicated urogenital gonorrhea (uGC) and uUTI, and one phase 3 study 204989 in patients with uUTI. The studies covered dose levels ranging from 200 mg to 3000 mg.

The Applicant did not collect PK data from the phase 3 trial (BTZ116577) in patients with uGC. Therefore, in the current supplement, the Applicant used the previously developed PK model to perform PK simulations, predict gepotidacin Cmax from the 2nd dose of the proposed dosage in patients with uGC (2 separate doses of 3000 mg, taken 12h apart), and the associated QTcF prolongation under different organ impairment, body weight or drug interaction with strong or moderate CYP3A4 inhibitors (Table 40).

Table 40. Model-Predicted C_{max} and Associated QTcF Prolongation after Second Oral Doses of 3000 mg, Stratified by Factors for Increased Gepotidacin Exposure

	No CYP3A4 Inhibitor		Strong CYP3A4 Inhibitor		Moderate CYP3A4 Inhibitor, High-fat Meal	
Subpopulation Category	Day 1 Cmax (µg/mL) GM (90% PI)[a]	Predicted ΔΔQTcF (msec) Mean (90% PI)[b]	Day 1 Cmax (µg/mL) GM (90% PI)[c]	Predicted ΔΔQTcF (msec) Mean (90% PI)[b]	Day 1 Cmax (µg/mL) GM (90% PI)[d]	Predicted ΔΔQTcF (msec) Mean (90% PI)[b]
Renal Function (eGFR; mL/min/1.73 m²)						
≥90	6.97 (3.76, 12.9)	10.7 (6.02, 19.3)	9.89 (5.34, 18.3)	14.9 (8.31, 27.2)	8.92 (4.81, 16.5)	13.5 (7.55, 24.6)
60 to <90	7.36 (4.09, 13.2)	11.3 (6.50, 19.7)	10.4 (5.80, 18.7)	15.7 (8.99, 27.8)	9.42 (5.24, 16.9)	14.3 (8.17, 25.1)
45 to <60	7.83 (4.34, 14.1)	11.9 (6.86, 21.1)	11.1 (6.16, 20.0)	16.7 (9.51, 29.7)	10.0 (5.56, 18.0)	15.1 (8.63, 26.8)
30 to <45	8.31 (4.52, 15.3)	12.6 (7.12, 22.8)	11.8 (6.41, 21.7)	17.7 (9.88, 32.1)	10.6 (5.79, 19.6)	16.0 (8.97, 29.0)
15 to <30	8.49 (4.60, 15.7)	12.9 (7.24, 23.4)	12.0 (6.53, 22.3)	18.1 (10.0, 33.0)	10.9 (5.89, 20.1)	16.4 (9.11, 29.8)
Hepatic Impairment						
Moderate	8.28 (4.48, 15.3)	12.6 (7.07, 22.8)	11.7 (6.36, 21.7)	17.6 (9.80, 32.1)	10.6 (5.73, 19.6)	16.0 (8.89, 29.0)
Severe	12.9 (6.98, 23.8)	19.3 (10.7, 35.2)	18.3 (9.90, 33.8)	27.2 (15.0, 49.7)	16.5 (8.93, 30.5)	24.6 (13.5, 44.9)
Age Groups (Years)						
Adolescents (12 to <18)	8.22 (4.38, 15.4)	12.5 (6.92, 22.9)	11.7 (6.22, 21.9)	17.5 (9.59, 32.3)	10.5 (5.61, 19.7)	15.9 (8.71, 29.2)
Adolescents (12 to <18) + moderate impairment	9.86 (5.26, 18.5)[e]	14.9 (8.20, 27.4)	14.0 (7.46, 26.2)[e]	20.9 (11.4, 38.7)	12.6 (6.73, 23.7)[e]	18.9 (10.3, 35.0)
Elderly (>65)	7.30 (4.11, 13.0)	11.2 (6.53, 19.5)	10.4 (5.83, 18.4)	15.6 (9.03, 27.4)	9.34 (5.26, 16.6)	14.1 (8.20, 24.8)
Elderly (>65) + moderate impairment	8.76 (4.93, 15.6)[e]	13.3 (7.72, 23.2)	12.4 (7.00, 22.1)[e]	18.6 (10.7, 32.7)	11.2 (6.31, 20.0)[e]	16.9 (9.73, 29.6)
Weight >45 to <60 kg	9.16 (5.38, 15.6)	13.9 (8.38, 23.2)	13.0 (7.63, 22.1)	19.5 (11.7, 32.7)	11.7 (6.89, 20.0)	17.6 (10.6, 29.6)
Weight >45 to <60 kg + moderate impairment	11.0 (6.46, 18.7)[e]	16.5 (9.94, 27.8)	15.6 (9.16, 26.6)[e]	23.2 (13.9, 39.2)	14.1 (8.26, 24.0)[e]	21.0 (12.6, 35.4)

Source: m5.3.5.3, Simulation Report RPS-CLIN-108011, Table 9.
a. The 2-sided 90% PI from simulated steady-state Cmax in each subpopulation category (N=500 females and N=500 males).
b. The ΔΔQTcF predicted using the linear mixed-effect PK-QT model identified in Phase 1 TQT Study BTZ115775; mean ΔΔQTcF predicted using GM Cmax for each subpopulation category; 90% PI ΔΔQTcF predicted using the 90% PI Cmax for each subpopulation.
c. Calculated by multiplying the GM (90% PI) from simulated steady-state Cmax in the subpopulation category (N=500 females and N=500 males) with 1.4, the Cmax GMR for strong CYP3A4 inhibition in Phase 1 DDI Study BTZ117349.
d. Calculated by multiplying the GM (90% PI) from simulated steady-state Cmax in the subpopulation category (N=500 females and N=500 males) with 1.28, the Cmax GMR with concomitant moderate CYP3A4 inhibitor and high-fat meal predicted from PBPK simulations
e. Calculated by multiplying the GM (90% PI) from simulated steady-state Cmax in the subpopulation category (N=500 females and N=500 males) with 1.2, the Cmax GMR for moderate renal impairment in the Phase 1 renal impairment Study BTZ116849 and for moderate hepatic impairment in the Phase 1 hepatic impairment Study BTZ117352 .

Source: Applicant's Pharmacometric Study Report (tmf16148607-report), Table 6, page 49.

Reviewer's Comments:

- The review team noticed a discrepancy between the observed Cmax from the phase 1 studies with gepotidacin 3000 mg and the PK model-predicted Cmax, with the population PK model prediction underestimating the observed Cmax (Table 41). In a response to the FDA review team observation, the Applicant acknowledged that the observed Cmax was approximately 1.5-fold the model-predicted Cmax, but the difference was within 2-fold. Additional evaluation of differences between the median observed Cmax and the median of individual predicted Cmax from the phase 1 studies with 1500 mg single or twice daily dosing determined that the observed Cmax was approximately 1.4 to 1.67-fold the observed Cmax for most studies.

  The PK model visual predictive checks of the phase 1 and phase 2 studies, stratified by dose, show systematic underprediction of median Cmax (Figure 4).

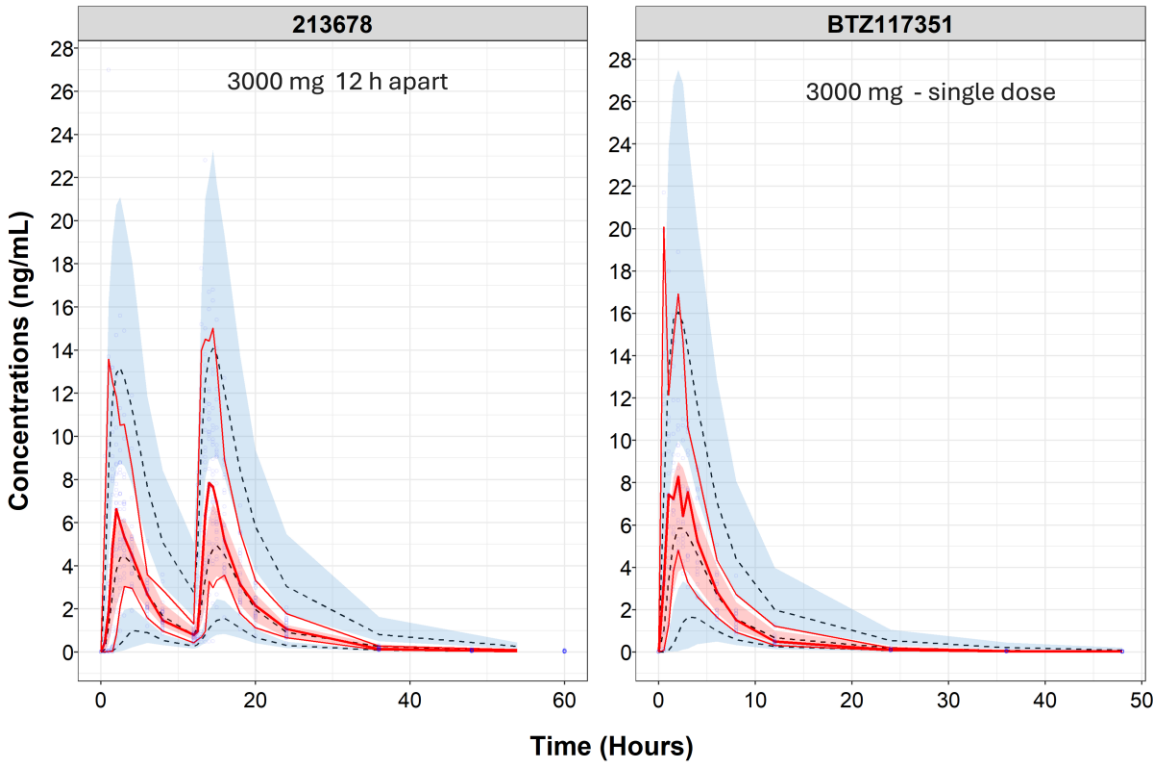
Table 41. Observed and Modeled-Predicted Cmax in Two Phase 1 Studies

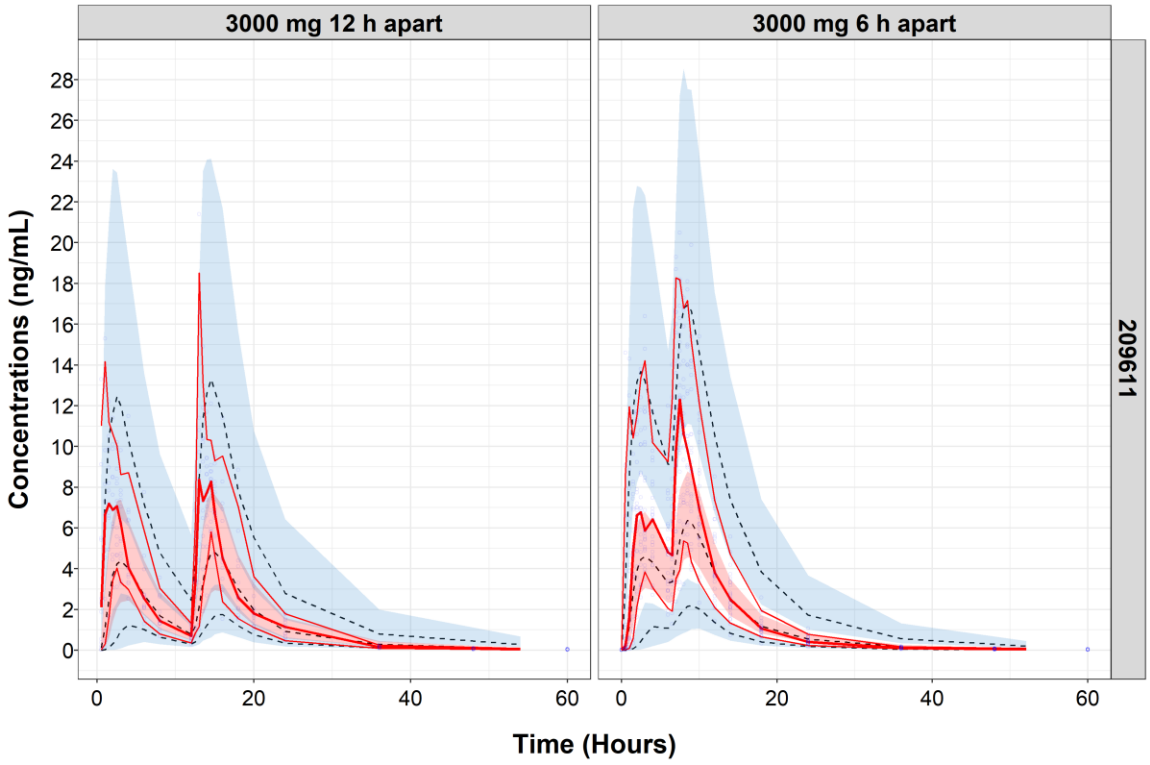
	Geometric mean Cmax (%CV) After Second 3000 mg Dose	
Study	**Observed (NCA)**	**Predicted (PK model)**
Study 209611		
Adults (12-h interval)	11.0 (28.1)	7.10 (29.1)
Adults (6-h interval)	13.0 (28.6)	8.04 (26.5)
Adolescents (6-h interval)	14.3 (29.5)	9.63 (29.2)
Study 213678		
Cohort 3 (Western, 12-h interval)	10.1 (47.7)	6.24 (35.4)
Cohort 4 (Japanese, 12-h interval)	12.4 (21.3)	7.56 (22.5)

Source: Excerpt from Applicant's Response to Information Request (of September 12, 2025), Table 2, page 2 to 3.

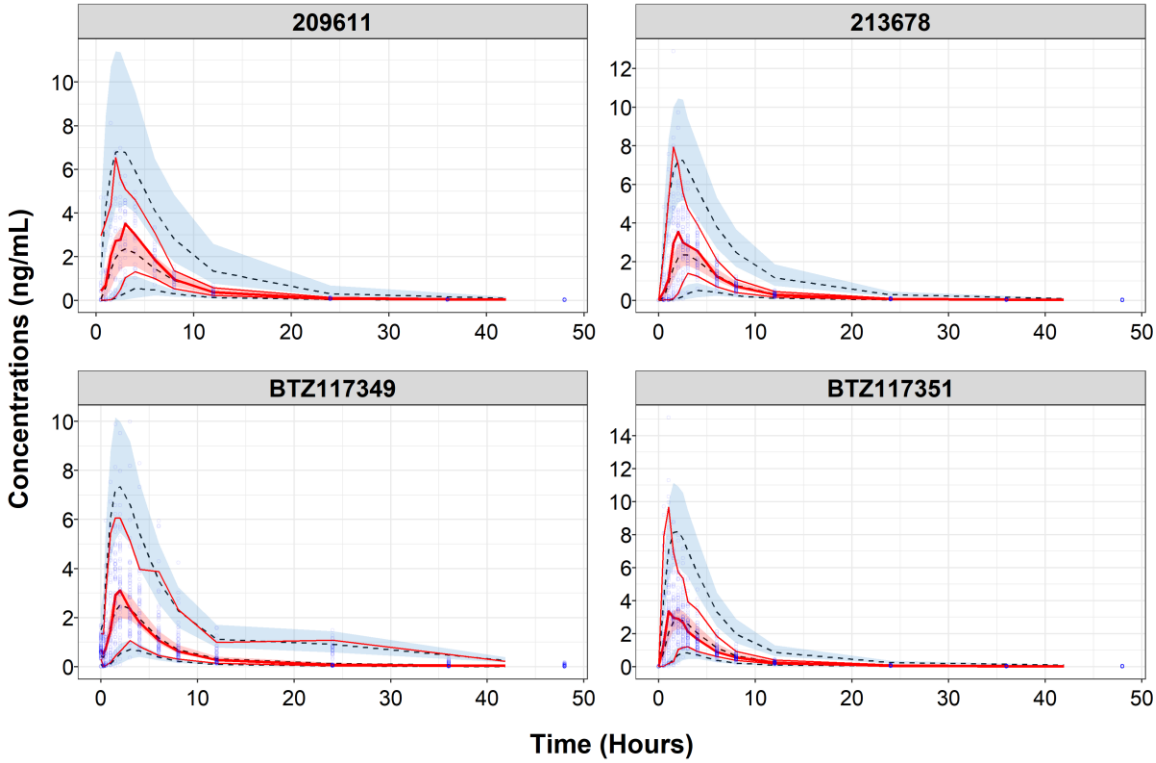
Figure 4. Visual Predictive Check From Final PK Model for Studies With Intensive PK Sampling, Stratified by Study, Dosing Regimen or Hepatic Impairment

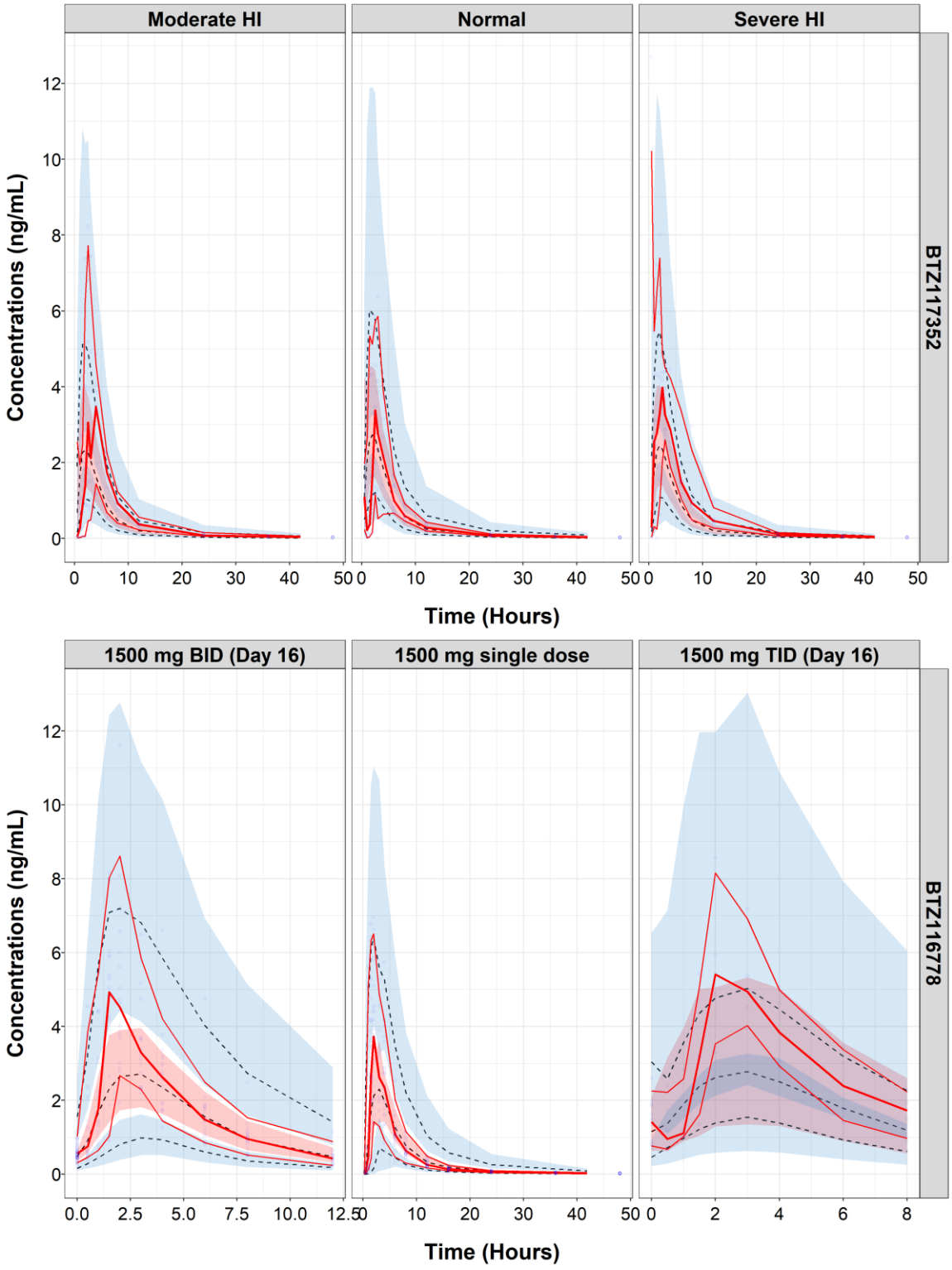
A. 3000 mg dose:

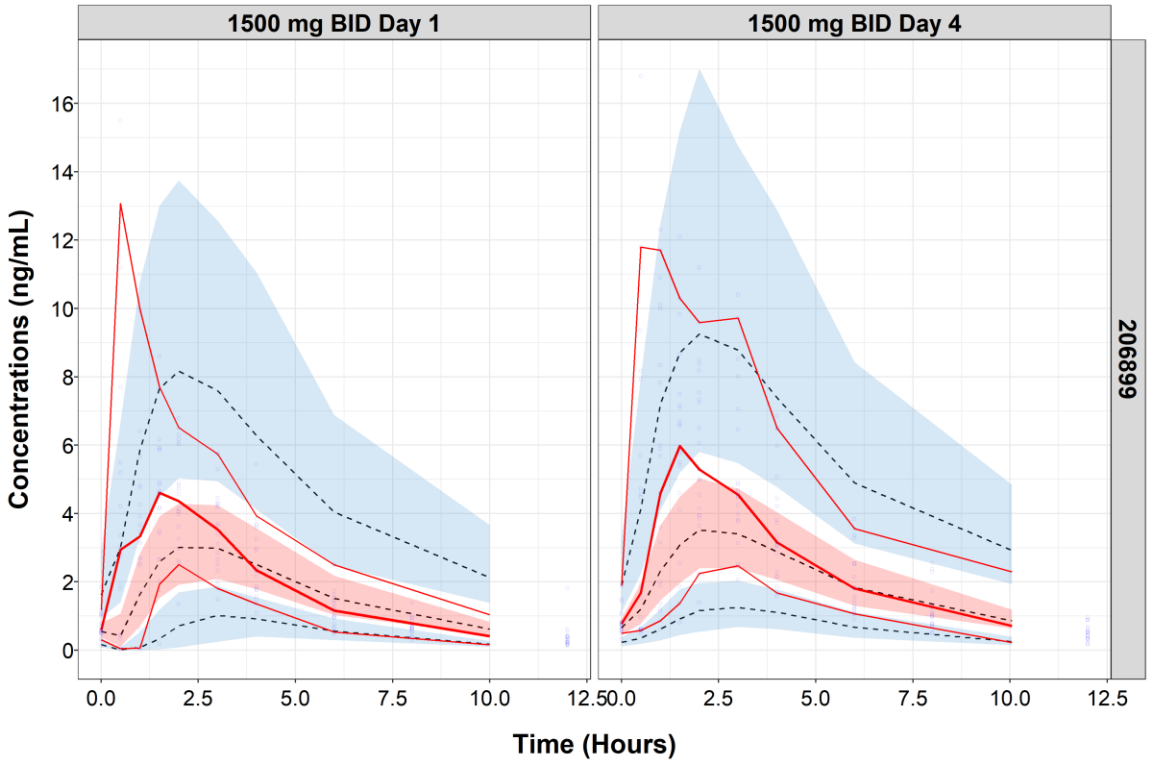




B. 1500 mg dose:




Moderate HI
Normal
Severe HI
BTZ117352
Concentrations (ng/mL)
Time (Hours)
1500 mg BID (Day 16)
1500 mg single dose
1500 mg TID (Day 16)
BTZ116778
Concentrations (ng/mL)
Time (Hours)



Source: FDA reviewer.
Note: Red solid lines represent the 5th, 50th and 95th percentiles of the observed concentrations. Black dashed lines represent the 5th, 50th and 95th percentiles of the simulated concentrations. Shaded areas represent the 95% confidence intervals for the 50th percentile (area in red), and for the 5th and 95th percentiles (areas in blue) of the simulated concentration (from 1000 dataset replicates). Open circles represent the observed concentrations.
Abbreviation: HI: Hepatic impairment.

As a consequence of the underprediction of Cmax by the PK model, the QTcF prolongation estimated by the Applicant (in Table 41) is underpredicted.

In addition, the Applicant used the PK model to predict Cmax and the associated QTcF prolongation in participants with various degrees of renal impairment. However, the previous review of NDA 218230 showed that the PK model underestimated the effect of moderate and severe renal impairment on steady-state Cmax and AUC.

Although the Applicant's PK model did not assess hepatic impairment as a covariate, the reviewer's evaluation found that the PK model underestimates the effect of hepatic impairment on gepotidacin clearance (from study BTZ117352), when including the covariate in the PK model. Of note, the previous reviewer's comment in the original review for NDA 218230 incorrectly mentioned that the PK model appropriately described the effect of hepatic impairment on total clearance.

The review team reassessed the expected QTcF prolongation after correcting for the predicted Cmax under different organ impairment status, body weight, or drug interaction with strong or moderate CYP3A4 inhibitors. As the Applicant was not able to improve the PK model and the review team was not able to adjust the PK absorption model to capture the Cmax, the corrected Cmax used to estimate QTcF prolongation was obtained by multiplying the model-predicted Cmax by a factor of 1.5.

The PK simulations used the same virtual adolescent and adult population as the Applicant (derived from NHANES 1999 to 2000), but with body weight ranging from 45 kg to 130 kg. As the PK model underpredicted the effect of renal function (with eGFR calculated using MDRD formula), PK simulations were performed as if all participants had normal renal function (median eGFR of 110 mL/min/1.73m^2, range: 90 to 130 mL/min/1.73m^2). To account for the various degrees of organ impairment or drug interaction, the corrected model-predicted Cmax from participants with normal renal function was further multiplied by the effects (geometric mean ratios) observed from the dedicated phase 1 studies (i.e., 1.2, and 1.7-fold for moderate and severe renal impairment; 1.2 and 1.9-fold for moderate and severe hepatic impairment; 1.17 and 1.4-fold for moderate and strong CYP3A4 inhibitor). For mild renal impairment, a geometric mean ratio of 1.13 was used based on the PK model-predicted effect for an eGFR of 60 mL/min/1.73m^2, which is likely overestimating the average effect of mild renal impairment and is more representative of patients with mild to moderate (stage 3a) chronic kidney disease.

Table 42 and Table 43 summarizes, respectively, the adjusted model-predicted Cmax and associated QTcF prolongation from the proposed dosage in patients with uGC (two doses 3000 mg taken 12 hours apart), stratified by different intrinsic and extrinsic factors for increased gepotidacin exposure.

Table 42 and Table 43 show that patients with any combination of the following risk factors have a higher risk of increased gepotidacin Cmax (≥ 13.3 ng/mL) and an associated QTc prolongation of at least 20 msec:

- Body weight <60 kg.
- Any level of moderate organ (hepatic or renal) impairment.
- Concomitant use of moderate CYP3A4 inhibitors.

Although, patients with mild renal impairment were predicted to have comparable QTc prolongation as patients with moderate renal impairment, the predictions are likely overestimating the effect of mild renal impairment on gepotidacin exposure, as it is representing the average effect in patient with an eGFR of 60 mL/min/1.73m^2 (upper bound of eGFR for moderate renal impairment). Therefore, patients with mild renal impairment were considered less at risk of having higher exposure and therefore QTc prolongation compared to patients with moderate renal impairment.

Table 42. Model-Predicted C_{max} (Virtual Population) after Second Oral Doses of 3000 mg, Stratified by Factors for Increased Gepotidacin Exposure

	=45 kg (N=39)	>45 to <50 kg (N=2562)	50 to <60 kg (N=9796)	60 to <80 kg (N=26465)	80 kg and above (N=25547)	Overall (N=64409)
Normal renal function						
Median [P5, P95]	12.8 [8.0, 21.6]	12.9 [6.9, 21.7]	11.5 [6.1, 19.1]	9.5 [5.0, 15.9]	7.5 [3.9, 12.8]	9.0 [4.5, 16.2]
Mild renal impairement						
Median [P5, P95]	14.5 [9.0, 24.4]	14.6 [7.7, 24.5]	13.0 [6.9, 21.6]	10.8 [5.7, 17.9]	8.5 [4.4, 14.4]	10.1 [5.1, 18.3]
Moderate renal impairement						
Median [P5, P95]	15.4 [9.6, 25.9]	15.5 [8.2, 26.1]	13.8 [7.3, 22.9]	11.4 [6.0, 19.0]	9.0 [4.7, 15.3]	10.8 [5.4, 19.5]
Severe renal impairement						
Median [P5, P95]	21.8 [13.6, 36.7]	22.0 [11.6, 36.9]	19.5 [10.4, 32.5]	16.2 [8.5, 27.0]	12.7 [6.6, 21.7]	15.3 [7.6, 27.6]
Moderate hepatic impairement						
Median [P5, P95]	15.4 [9.6, 25.9]	15.5 [8.2, 26.1]	13.8 [7.3, 22.9]	11.4 [6.0, 19.0]	9.0 [4.7, 15.3]	10.8 [5.4, 19.5]
Severe hepatic impairement						
Median [P5, P95]	24.4 [15.2, 41.0]	24.5 [13.0, 41.3]	21.8 [11.6, 36.3]	18.1 [9.6, 30.2]	14.2 [7.4, 24.2]	17.1 [8.5, 30.8]
Moderate CYP3A4 inhibitor						
Median [P5, P95]	15.0 [9.3, 25.2]	15.1 [8.0, 25.4]	13.4 [7.2, 22.4]	11.1 [5.9, 18.6]	8.8 [4.6, 14.9]	10.5 [5.3, 19.0]
Strong CYP3A4 inhibitor						
Median [P5, P95]	18.0 [11.2, 30.2]	18.1 [9.6, 30.4]	16.0 [8.6, 26.8]	13.3 [7.0, 22.2]	10.5 [5.5, 17.9]	12.6 [6.3, 22.7]

	=45 kg (N=39)	>45 to <50 kg (N=2562)	50 to <60 kg (N=9796)	60 to <70 kg (N=13182)	70 to <80 kg (N=13283)	80 kg and above (N=25547)	Overall (N=64409)
Moderate CYP3A4 inhibitor + mild RI							
Median [P5, P95]	17.0 [10.5, 28.5]	17.1 [9.1, 28.7]	15.2 [8.1, 25.3]	13.3 [7.1, 22.0]	11.9 [6.4, 19.6]	9.9 [5.2, 16.9]	11.9 [5.9, 21.5]
Moderate CYP3A4 inhibitor + moderate RI or HI							
Median [P5, P95]	18.0 [11.2, 30.3]	18.1 [9.6, 30.5]	16.1 [8.6, 26.8]	14.1 [7.5, 23.3]	12.6 [6.7, 20.8]	10.5 [5.5, 17.9]	12.6 [6.3, 22.8]

Source: FDA reviewer.
Cmax unit is in mg/L.
Abbreviations: RI, renal impairment; HI, hepatic impairment; P5, 5th percentile, P90, 90th percentile.

Table 43. Model-Predicted QTcF Prolongation (Virtual Population) after Second Oral Doses of 3000 mg, Stratified by Factors for Increased Gepotidacin Exposure

	=45 kg (N=39)	>45 to <50 kg (N=2562)	50 to <60 kg (N=9796)	60 to <80 kg (N=26465)	80 kg and above (N=25547)	Overall (N=64409)
Normal renal function						
Median [P5, P95]	19.2 [12.2, 31.9]	19.3 [10.5, 32.1]	17.2 [9.5, 28.4]	14.4 [7.9, 23.6]	11.4 [6.2, 19.1]	13.6 [7.1, 24.2]
Mild renal impairement						
Median [P5, P95]	21.6 [13.7, 36.0]	21.8 [11.8, 36.2]	19.4 [10.6, 32.0]	16.2 [8.8, 26.6]	12.8 [7.0, 21.5]	15.3 [7.9, 27.2]
Moderate renal impairement						
Median [P5, P95]	22.9 [14.5, 38.2]	23.1 [12.5, 38.5]	20.6 [11.2, 33.9]	17.2 [9.3, 28.3]	13.6 [7.4, 22.8]	16.2 [8.4, 28.9]
Severe renal impairement						
Median [P5, P95]	32.3 [20.3, 53.9]	32.5 [17.5, 54.2]	28.9 [15.7, 47.8]	24.1 [13.0, 39.8]	19.0 [10.2, 32.1]	22.7 [11.7, 40.7]
Moderate hepatic impairement						
Median [P5, P95]	22.9 [14.5, 38.2]	23.1 [12.5, 38.5]	20.6 [11.2, 33.9]	17.2 [9.3, 28.3]	13.6 [7.4, 22.8]	16.2 [8.4, 28.9]
Severe hepatic impairement						
Median [P5, P95]	36.0 [22.6, 60.2]	36.2 [19.5, 60.6]	32.2 [17.5, 53.4]	26.8 [14.4, 44.4]	21.2 [11.3, 35.8]	25.4 [13.0, 45.4]
Moderate CYP3A4 inhibitor						
Median [P5, P95]	22.4 [14.1, 37.3]	22.5 [12.2, 37.5]	20.1 [11.0, 33.1]	16.7 [9.1, 27.6]	13.3 [7.2, 22.2]	15.8 [8.2, 28.2]
Strong CYP3A4 inhibitor						
Median [P5, P95]	26.7 [16.8, 44.5]	26.9 [14.5, 44.8]	23.9 [13.0, 39.5]	19.9 [10.8, 32.9]	15.8 [8.5, 26.5]	18.8 [9.7, 33.6]

	=45 kg (N=39)	>45 to <50 kg (N=2562)	50 to <60 kg (N=9796)	60 to <70 kg (N=13182)	70 to <80 kg (N=13283)	80 kg and above (N=25547)	Overall (N=64409)
Moderate CYP3A4 inhibitor + mild RI							
Median [P5, P95]	25.2 [15.9, 42.0]	25.4 [13.7, 42.3]	22.6 [12.3, 37.3]	19.9 [10.8, 32.5]	17.9 [9.8, 29.1]	14.9 [8.1, 25.1]	17.8 [9.2, 31.8]
Moderate CYP3A4 inhibitor + moderate RI or HI							
Median [P5, P95]	26.8 [16.8, 44.6]	26.9 [14.5, 44.9]	24.0 [13.1, 39.6]	21.1 [11.5, 34.5]	18.9 [10.4, 30.8]	15.8 [8.5, 26.6]	18.9 [9.7, 33.7]

Source: FDA reviewer.
QTcF prolongation unit is in milliseconds. Abbreviation: RI = renal impairment; HI = hepatic impairment; P5 = 5th percentile, P90 = 90th percentile.
The QTcF prolongation relationship: mean ΔΔQTcF = (1.4545 x Cmax) + 0.5505.

Even after applying a correction factor of 1.5, the Monte-Carlo PK simulations from a virtual population tend to underestimate the median observed Cmax by about 20%. As a sensitivity analysis, the PK simulations were repeated using the individual PK parameters (i.e., Bayesian estimates or EBE) estimated from the study population used to develop the PK model (referred to thereafter as conditional simulations), followed by adjustment of the estimated Cmax by a factor of 1.5. Table 44 and Table 45 show the adjusted model-predicted Cmax and associated QTcF prolongation after the 2nd dose of 3000 mg from the conditional PK simulations.

Although the conditional simulations resulted in numerically higher predicted QTcF prolongation compared to the population PK simulation using a virtual population, similar categorization can be drawn regarding the groups of patients with higher risk of QTc prolongation, where patients with any combination of the following risk factors have a higher risk of increased gepotidacin Cmax (≥ 13.3 ng/mL) and an associated QTc prolongation of at least 20 msec:

- Body weight <60 kg
- Any level of mild to moderate organ impairment
- Concomitant use of moderate CYP3A4 inhibitors

Table 44. Model-Predicted C_{max} (Conditional Simulations) after Second Oral Doses of 3000 mg, Stratified by Factors for Increased Gepotidacin Exposure

	=45 kg (N=2)	>45 to <50 kg (N=13)	50 to <60 kg (N=96)	60 to <80 kg (N=407)	80 kg and above (N=317)	Overall (N=835)
Normal renal function						
Median [P5, P95]	16.2 [14.6, 17.9]	16.1 [10.7, 18.3]	14.6 [10.2, 17.0]	12.1 [7.7, 15.3]	9.8 [5.7, 12.3]	11.2 [6.8, 15.5]
Mild renal impairement						
Median [P5, P95]	18.4 [16.5, 20.3]	18.2 [12.1, 20.7]	16.5 [11.5, 19.2]	13.7 [8.7, 17.3]	11.1 [6.4, 13.8]	12.7 [7.7, 17.6]
Moderate renal impairement						
Median [P5, P95]	19.5 [17.5, 21.5]	19.4 [12.8, 22.0]	17.5 [12.2, 20.4]	14.5 [9.3, 18.4]	11.8 [6.8, 14.7]	13.5 [8.1, 18.7]
Severe renal impairement						
Median [P5, P95]	27.6 [24.8, 30.5]	27.4 [18.2, 31.1]	24.8 [17.3, 28.8]	20.5 [13.1, 26.1]	16.6 [9.6, 20.8]	19.1 [11.5, 26.4]
Moderate hepatic impairement						
Median [P5, P95]	19.5 [17.5, 21.5]	19.4 [12.8, 22.0]	17.5 [12.2, 20.4]	14.5 [9.3, 18.4]	11.8 [6.8, 14.7]	13.5 [8.1, 18.7]
Severe hepatic impairement						
Median [P5, P95]	30.9 [27.7, 34.1]	30.7 [20.3, 34.8]	27.7 [19.3, 32.2]	23.0 [14.7, 29.2]	18.6 [10.8, 23.3]	21.3 [12.9, 29.5]
Moderate CYP3A4 inhibitor						
Median [P5, P95]	19.0 [17.0, 21.0]	18.9 [12.5, 21.4]	17.1 [11.9, 19.8]	14.1 [9.0, 18.0]	11.5 [6.6, 14.3]	13.1 [7.9, 18.2]
Strong CYP3A4 inhibitor						
Median [P5, P95]	22.7 [20.4, 25.1]	22.6 [15.0, 25.7]	20.4 [14.2, 23.7]	16.9 [10.8, 21.5]	13.7 [7.9, 17.2]	15.7 [9.5, 21.8]

(Table 44 *continued*)

	=45 kg (N=2)	>45 to <50 kg (N=13)	50 to <60 kg (N=96)	60 to <70 kg (N=208)	70 to <80 kg (N=199)	80 kg and above (N=317)	Overall (N=835)
Moderate CYP3A4 inhibitor + mild RI							
Median [P5, P95]	21.5 [19.3, 23.7]	21.3 [14.1, 24.2]	19.3 [13.4, 22.4]	17.4 [11.0, 20.6]	14.9 [10.1, 18.2]	12.9 [7.5, 16.2]	14.9 [9.0, 20.6]
Moderate CYP3A4 inhibitor + moderate RI or HI							
Median [P5, P95]	22.8 [20.5, 25.2]	22.7 [15.0, 25.7]	20.5 [14.3, 23.8]	18.5 [11.7, 21.8]	15.8 [10.7, 19.4]	13.7 [8.0, 17.2]	15.8 [9.5, 21.8]

Source: FDA reviewer.
Cmax unit is in mg/L.
The conditional simulations used the study population with normal kidney and liver function. A correction factor for Cmax was included to predict Cmax under various degrees of organ impairment or drug interaction.
Abbreviation: RI, renal impairment; HI, hepatic impairment; P5, 5th percentile; P90, 90th percentile.

Table 45. Model-Predicted QTcF Prolongation (Conditional Simulations) after Second Oral Doses of 3000 mg, Stratified by Factors for Increased Gepotidacin Exposure

	=45 kg (N=2)	>45 to <50 kg (N=13)	50 to <60 kg (N=96)	60 to <80 kg (N=407)	80 kg and above (N=317)	Overall (N=835)
Normal renal function						
Median [P5, P95]	24.2 [21.7, 26.6]	24.0 [16.1, 27.2]	21.8 [15.3, 25.2]	18.1 [11.8, 22.9]	14.8 [8.8, 18.4]	16.9 [10.4, 23.2]
Mild renal impairement						
Median [P5, P95]	27.3 [24.5, 30.0]	27.1 [18.1, 30.7]	24.6 [17.2, 28.4]	20.4 [13.3, 25.8]	16.6 [9.9, 20.7]	19.0 [11.7, 26.1]
Moderate renal impairement						
Median [P5, P95]	28.9 [26.0, 31.8]	28.7 [19.2, 32.5]	26.0 [18.3, 30.2]	21.6 [14.0, 27.3]	17.6 [10.4, 21.9]	20.2 [12.4, 27.7]
Severe renal impairement						
Median [P5, P95]	40.7 [36.6, 44.9]	40.5 [27.0, 45.9]	36.7 [25.7, 42.5]	30.4 [19.7, 38.5]	24.8 [14.6, 30.8]	28.3 [17.3, 39.0]
Moderate hepatic impairement						
Median [P5, P95]	28.9 [26.0, 31.8]	28.7 [19.2, 32.5]	26.0 [18.3, 30.2]	21.6 [14.0, 27.3]	17.6 [10.4, 21.9]	20.2 [12.4, 27.7]
Severe hepatic impairement						
Median [P5, P95]	45.5 [40.8, 50.1]	45.2 [30.1, 51.2]	40.9 [28.6, 47.4]	33.9 [21.9, 43.0]	27.6 [16.2, 34.4]	31.6 [19.3, 43.5]
Moderate CYP3A4 inhibitor						
Median [P5, P95]	28.2 [25.3, 31.1]	28.0 [18.8, 31.7]	25.4 [17.8, 29.4]	21.1 [13.7, 26.7]	17.2 [10.2, 21.4]	19.7 [12.1, 27.0]
Strong CYP3A4 inhibitor						
Median [P5, P95]	33.6 [30.2, 37.1]	33.4 [22.3, 37.9]	30.3 [21.2, 35.1]	25.2 [16.3, 31.8]	20.5 [12.1, 25.5]	23.4 [14.4, 32.2]

	=45 kg (N=2)	>45 to <50 kg (N=13)	50 to <60 kg (N=96)	60 to <70 kg (N=208)	70 to <80 kg (N=199)	80 kg and above (N=317)	Overall (N=835)
Moderate CYP3A4 inhibitor + mild RI							
Median [P5, P95]	31.8 [28.6, 35.0]	31.6 [21.1, 35.8]	28.6 [20.1, 33.2]	25.8 [16.5, 30.5]	22.2 [15.2, 27.1]	19.4 [11.4, 24.1]	22.2 [13.6, 30.4]
Moderate CYP3A4 inhibitor + moderate RI or HI							
Median [P5, P95]	33.7 [30.3, 37.2]	33.5 [22.4, 38.0]	30.4 [21.3, 35.2]	27.4 [17.5, 32.3]	23.5 [16.1, 28.7]	20.5 [12.1, 25.6]	23.5 [14.4, 32.3]

Source: FDA reviewer.
QTcF prolongation unit is in milliseconds.
The QTcF prolongation relationship: mean ΔΔQTcF = (1.4545 x Cmax) + 0.5505.
Abbreviation: RI = renal impairment; HI = hepatic impairment; P5 = 5th percentile, P90 = 90th percentile.

In contrast to the predicted higher risk of QTc prolongation with the proposed dosing in patients with uGC, the approved dosing in patients with uUTI resulted in a lower predicted risk of

increased QTc prolongation, even after correcting for the underpredicted Cmax. Table 46 and Table 47 summarize model-predicted QTcF prolongation from the approved gepotidacin dosage in patients with uUTI (1500 mg twice daily for 5 days), from the Monte-Carlo simulations (Virtual Population) and the conditional simulations. Both simulations showing a lower risk of QTcF prolongation in patients with body weight 40 to < 60 kg and any combination of moderate renal or hepatic impairment or concomitant use of moderate CYP3A4 inhibitor.

Table 46. Model-Predicted Steady-State QTcF Prolongation (Virtual Population) After 1500 mg BID for 5 days, Stratified by Factors for Increased Gepotidacin Exposure

	=40 kg (N=15)	>40 to <50 kg (N=3840)	50 to <60 kg (N=9796)	60 to <80 kg (N=26465)	80 kg and above (N=25547)	Overall (N=65663)
Normal renal function						
Median [P5, P95]	13.3 [8.8, 17.5]	10.6 [5.8, 17.4]	9.1 [5.1, 14.8]	7.7 [4.3, 12.5]	6.2 [3.5, 10.3]	7.3 [3.9, 13.0]
Mild renal impairement						
Median [P5, P95]	14.9 [9.8, 19.7]	11.9 [6.5, 19.5]	10.2 [5.7, 16.7]	8.6 [4.8, 14.1]	6.9 [3.9, 11.5]	8.2 [4.4, 14.6]
Moderate renal impairement						
Median [P5, P95]	15.8 [10.4, 20.9]	12.6 [6.9, 20.7]	10.8 [6.1, 17.7]	9.1 [5.1, 14.9]	7.3 [4.1, 12.2]	8.7 [4.6, 15.5]
Severe renal impairement						
Median [P5, P95]	22.2 [14.5, 29.3]	17.6 [9.5, 29.1]	15.1 [8.3, 24.8]	12.6 [7.0, 20.9]	10.2 [5.6, 17.1]	12.1 [6.3, 21.7]
Moderate hepatic impairement						
Median [P5, P95]	15.8 [10.4, 20.9]	12.6 [6.9, 20.7]	10.8 [6.1, 17.7]	9.1 [5.1, 14.9]	7.3 [4.1, 12.2]	8.7 [4.6, 15.5]
Severe hepatic impairement						
Median [P5, P95]	24.7 [16.2, 32.7]	19.6 [10.6, 32.5]	16.8 [9.3, 27.7]	14.0 [7.7, 23.3]	11.3 [6.2, 19.0]	13.4 [7.0, 24.2]
Moderate CYP3A4 inhibitor						
Median [P5, P95]	15.4 [10.2, 20.3]	12.3 [6.7, 20.2]	10.6 [5.9, 17.3]	8.9 [5.0, 14.6]	7.2 [4.0, 11.9]	8.5 [4.5, 15.1]
Strong CYP3A4 inhibitor						
Median [P5, P95]	18.4 [12.0, 24.2]	14.6 [7.9, 24.1]	12.6 [7.0, 20.6]	10.5 [5.9, 17.3]	8.5 [4.7, 14.1]	10.1 [5.3, 18.0]

	=40 kg (N=15)	>40 to <50 kg (N=3840)	50 to <60 kg (N=9796)	60 to <70 kg (N=13182)	70 to <80 kg (N=13283)	80 kg and above (N=25547)	Overall (N=65663)
Moderate CYP3A4 inhibitor + mild RI							
Median [P5, P95]	17.4 [11.4, 22.9]	13.8 [7.5, 22.8]	11.9 [6.6, 19.4]	10.5 [5.9, 17.2]	9.4 [5.3, 15.5]	8.0 [4.5, 13.4]	9.5 [5.0, 17.0]
Moderate CYP3A4 inhibitor + moderate RI or HI							
Median [P5, P95]	18.4 [12.1, 24.3]	14.6 [8.0, 24.1]	12.6 [7.0, 20.6]	11.1 [6.2, 18.2]	10.0 [5.6, 16.5]	8.5 [4.7, 14.2]	10.1 [5.3, 18.1]

Source: FDA reviewer.
QTcF prolongation unit is in milliseconds.
The QTcF prolongation relationship: mean ΔΔQTcF = (1.4545 x Cmax) + 0.5505.
Abbreviation: RI = renal impairment; HI = hepatic impairment; P5 = 5th percentile, P90 = 90th percentile.

Table 47. Model-Predicted Steady-State QTcF Prolongation (Conditional Simulations) After 1500 mg BID for 5 days, Stratified by Factors for Increased Gepotidacin Exposure

	40 to <50 kg (N=19)	50 to <60 kg (N=96)	60 to <80 kg (N=407)	80 kg and above (N=317)	Overall (N=839)
Normal renal function					
Median [P5, P95]	12.5 [9.0, 15.0]	11.5 [8.2, 13.4]	9.7 [6.4, 12.1]	7.9 [4.9, 10.0]	9.1 [5.8, 12.3]
Mild renal impairement					
Median [P5, P95]	14.1 [10.1, 16.9]	13.0 [9.2, 15.0]	10.9 [7.2, 13.6]	8.9 [5.5, 11.2]	10.2 [6.4, 13.8]
Moderate renal impairement					
Median [P5, P95]	14.9 [10.6, 17.9]	13.7 [9.7, 15.9]	11.5 [7.6, 14.4]	9.4 [5.8, 11.8]	10.8 [6.8, 14.7]
Severe renal impairement					
Median [P5, P95]	20.9 [14.8, 25.1]	19.2 [13.5, 22.3]	16.0 [10.6, 20.2]	13.1 [8.0, 16.5]	15.0 [9.4, 20.5]
Moderate hepatic impairement					
Median [P5, P95]	14.9 [10.6, 17.9]	13.7 [9.7, 15.9]	11.5 [7.6, 14.4]	9.4 [5.8, 11.8]	10.8 [6.8, 14.7]
Severe hepatic impairement					
Median [P5, P95]	23.3 [16.5, 28.0]	21.4 [15.1, 24.9]	17.9 [11.8, 22.5]	14.6 [8.9, 18.4]	16.7 [10.4, 22.9]
Moderate CYP3A4 inhibitor					
Median [P5, P95]	14.6 [10.4, 17.4]	13.4 [9.5, 15.5]	11.2 [7.4, 14.1]	9.2 [5.7, 11.6]	10.5 [6.6, 14.3]
Strong CYP3A4 inhibitor					
Median [P5, P95]	17.3 [12.3, 20.8]	15.9 [11.2, 18.5]	13.3 [8.8, 16.8]	10.9 [6.7, 13.7]	12.5 [7.8, 17.0]

	40 to <50 kg (N=19)	50 to <60 kg (N=96)	60 to <70 kg (N=208)	70 to <80 kg (N=199)	80 kg and above (N=317)	Overall (N=839)
Moderate CYP3A4 inhibitor + mild RI						
Median [P5, P95]	16.4 [11.7, 19.6]	15.1 [10.6, 17.5]	13.6 [8.8, 16.1]	11.7 [8.1, 14.3]	10.3 [6.4, 13.0]	11.8 [7.4, 16.1]
Moderate CYP3A4 inhibitor + moderate RI or HI						
Median [P5, P95]	17.4 [12.4, 20.8]	16.0 [11.3, 18.5]	14.4 [9.3, 17.1]	12.4 [8.6, 15.1]	10.9 [6.7, 13.8]	12.5 [7.9, 17.1]

Source: FDA reviewer.
QTcF prolongation unit is in milliseconds.
The QTcF prolongation relationship: mean ΔΔQTcF = (1.4545 x Cmax) + 0.5505.
Abbreviation: RI, renal impairment; HI, hepatic impairment; P5, 5th percentile, P90, 90th percentile.

14.5.2. Physiologically-Based Pharmacokinetics

The evaluation of the adequacy of the Applicant's PBPK analyses to predict impact of weak or moderate CYP3A inhibitors or inducers on the PK of gepotidacin is documented in the original integrated review (dated 03/24/2025).

In the current supplement, the intended purpose of this PBPK analysis is to determine whether the combined effects of a high-fat meal and a CYP3A inhibitor would increase gepotidacin exposure to an extent that QT prolongation becomes a concern. Gepotidacin AUCinf and Cmax were dose-proportional from 1,500 mg to 3,000 mg. Therefore, the predicted effects of moderate or weak CYP3A inhibitors on a single 1,500 mg dose of gepotidacin could be applied to the 3,000 mg dose. Currently, the application of PBPK modeling to prospectively predict food effects is considered exploratory and cannot provide quantitative predictions. Given the narrow safety margins of gepotidacin, the PBPK approach is inappropriate for its intended purpose.

14.6. Pharmacogenetics

Not applicable

15. Study/Trial Design

Not applicable

16. Efficacy

EAGLE-1 Baseline Demographics and Clinical Characteristics in the Micro-ITT Population

A total of 406 participants were included in the micro-ITT population. The demographic and baseline characteristics in the micro-ITT population were comparable between treatment groups: 92% male; 74% White, 15% Black, 6% Asian, 17% Hispanic or Latino; the mean age was 33 years (range: 17 to 64); the mean weight was 76 kg (range: 48 to 120 kg).

Table 48. Baseline Demographics and Clinical Characteristics, Micro-ITT Population, EAGLE-1

Characteristic	Gepotidacin N=202	Ceftriaxone-Azithromycin N=204
Sex and sexual orientation, n (%)		
Female	17 (8.4)	17 (8.3)
Male	185 (91.6)	187 (91.7)
MSM	144 (71.3)	146 (71.6)
MSW	41 (20.3)	41 (20.1)
Age, years		
Mean (SD)	33.2 (10.29)	33.0 (10.18)
Median	31.5	32.0
Min, Max	18.0, 64.0	17.0, 61.0

Characteristic	Gepotidacin N=202	Ceftriaxone-Azithromycin N=204
Age group (years), n (%)		
<18	0	1 (<1)
≥18 to 65	202 (100.0)	203 (99.5)
Race, n (%)		
White	146 (72.3)	153 (75.0)
Black or African American	36 (17.8)	25 (12.3)
Asian	7 (3.5)	16 (7.8)
American Indian or Alaska Native	5 (2.5)	6 (2.9)
Native Hawaiian or Other Pacific Islander	5 (2.5)	0
Multiple	3 (1.5)	4 (2.0)
Ethnicity, n (%)		
Hispanic	32 (15.8)	38 (18.6)
Non-Hispanic	170 (84.2)	164 (80.4)
Missing	0	2 (1.0)
Baseline height (cm)		
Mean (SD)	176.9 (8.04)	176.4 (7.37)
Median	176.2	177.0
Min, Max	155.0, 198.0	156.0, 193.0
Missing	0	1
Baseline weight (kg)		
Mean (SD)	76.7 (13.81)	75.6 (12.38)
Median	75.0	76.0
Min, Max	47.7, 118.2	49.0, 119.8
Missing	0	1
BMI (kg/m^2)		
Mean (SD)	24.5 (4.03)	24.3 (3.80)
Median	23.9	24.0
Min, Max	14.2, 38.6	17.4, 41.3
Missing	0	1
Region, n (%)		
Americas	33 (16.3)	22 (10.8)
Asia-Pacific	35 (17.3)	37 (18.1)
Europe	134 (66.3)	145 (71.1)
Country of participation, n (%)		
Australia	35 (17.3)	37 (18.1)
Germany	41 (20.3)	36 (17.6)
Spain	58 (28.7)	68 (33.3)
United Kingdom	35 (17.3)	41 (20.1)
Mexico	1 (<1)	1 (<1)
United States	32 (15.8)	21 (10.3)
History of sexually transmitted infection(s), n (%)		
Yes	110 (54.5)	115 (56.4)
No	89 (44.1)	85 (41.7)
Unknown or Missing	3 (1.5)	4 (2.0)
HIV status, n (%)		
Negative	155 (76.7)	163 (79.9)
Positive	43 (21.3)	35 (17.2)
Missing	4 (2.0)	6 (2.9)

Source: FDA Analysis; adsl.xpt;
Abbreviations: Micro-ITT, microbiological intent-to-treat; MSM, men who have sex with men; MSW, men who have sex with women; N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

BTZ116576 Baseline Demographics and Clinical Characteristics in the Microbiological Evaluable Population

Table 49. Baseline Demographics and Clinical Characteristics, Microbiological Evaluable Population, BTZ116576

Characteristic	Gepotidacin 1500 mg N=30	Gepotidacin 3000 mg N=39
Sex, n (%)		
Female	1 (3.3)	1 (2.6)
Male	29 (96.7)	38 (97.4)
Age, years		
Mean (SD)	34.3 (11.26)	32.8 (11.71)
Median	32.0	28.0
Min, Max	18.0, 63.0	18.0, 69.0
Age group (years), n (%)		
18 to 64	30 (100.0)	38 (97.4)
65 to 74	0	1 (2.6)
Race, n (%)		
Black or African American	14 (46.7)	21 (53.8)
White	12 (40.0)	13 (33.3)
Asian	1 (3.3)	1 (2.6)
American Indian or Alaska Native	1 (3.3)	0
Multiple	0	1 (2.6)
Missing	2 (6.7)	3 (7.7)
Ethnicity, n (%)		
Hispanic	5 (16.7)	4 (10.3)
Non-Hispanic	25 (83.3)	35 (89.7)
Baseline height (cm)		
Mean (SD)	176.4 (10.95)	175.8 (9.76)
Median	178.9	175.3
Min, Max	136.4, 193.0	152.4, 198.0
Baseline weight (kg)		
Mean (SD)	79.6 (15.78)	77.7 (15.67)
Median	77.0	75.7
Min, Max	55.0, 115.9	49.3, 122.5
BMI (kg/m^2)		
Mean (SD)	25.6 (4.82)	25.1 (4.18)
Median	24.9	24.9
Min, Max	19.5, 39.3	17.6, 34.4
Country of participation, n (%)		
United States	30 (100.0)	39 (100.0)

Source: FDA Analysis; adsl.xpt;
Abbreviations: N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

BTZ116576 Primary Endpoint Subgroup Analysis

Table 50. Primary Endpoint Subgroup Analysis by Baseline Demographics, ME Population, BTZ116576

Characteristic	Gepotidacin 1500 mg N=30	Gepotidacin 3000 mg N=39
Sex, n (%)		
Female	1/1 (100.0)	1/1 (100.0)
Male	28/29 (96.6)	36/38 (94.7)
Age group (years), n (%)		
18 to 64	29/30 (96.7)	36/38 (94.7)
65 to 74	0	1/1 (100.0)
Race, n (%)		
Black or African American	14/14 (100.0)	20/21 (95.2)
White	11/12 (91.7)	13/13 (100.0)
Asian	1/1 (100.0)	1/1 (100.0)
American Indian or Alaska Native	1/1 (100.0)	0
Multiple	0	0/1 (0.0)
Missing	2/2 (100.0)	3/3 (100.0)
Ethnicity, n (%)		
Hispanic	5/5 (100.0)	4/4 (100.0)
Non-Hispanic	24/25 (96.0)	33/35 (94.3)

Source: FDA Analysis; adsl.xpt;
Abbreviations: N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

Study EAGLE-J (214144) Efficacy Results

EAGLE-J was a randomized, double-blind, double-dummy, active-controlled, multicenter study in Japanese female patients with uncomplicated urinary tract infection (uUTI). A total of 374 participants were randomized 3:1 to receive gepotidacin 1500 mg b.i.d. for 5 days or nitrofurantoin 100 mg b.i.d. for 5 days. Safety, clinical and microbiological assessments were conducted at the Baseline (Day 1) Visit and repeated at the On-therapy (Day 2 to 4), TOC (Day 10 to 13), and Follow-up (Day 28±3) Visits.

The following analysis sets were defined for participants enrolled in this study.

- Intent-to-Treat (ITT) Population: All participants randomly assigned to study treatment.
- Microbiological ITT (micro-ITT, mITT) Population: All participants 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 participants in the micro-ITT Population whose baseline qualifying bacterial uropathogens all were susceptible to nitrofurantoin (NTF-S). Participants with missing MIC susceptibility results for any qualifying uropathogens were not included in the NTF-S subpopulation.
- Micro-ITT MDR Population: All participants in the micro-ITT Population who had any qualifying baseline bacterial uropathogens that were resistant to two or more classes of antimicrobials.
- Pharmacokinetic (PK) Population: All randomized participants who received at least 1 dose of study treatment and had at least 1 nonmissing plasma or urine PK concentration.

- Safety Population: All randomized participants who received at least 1 dose of study treatment.

The primary efficacy endpoint was therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit in the Microbiological Intent-to-Treat Nitrofurantoin-Susceptible (micro-ITT NTF-S) Population, regardless of treatment discontinuation. Microbiological success was defined as reduction of all qualifying bacterial uropathogens at Baseline to $<10^3$ CFU/mL as observed on quantitative urine culture without the participant receiving other systemic antimicrobials. Clinical success was defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials.

A total of 374 participants were randomized in this study. Among them, 108 (28.9%) were included in the Micro-ITT NTF-S population for the primary efficacy endpoint.

Table 51. Participant Disposition, EAGLE-J

Disposition Outcome	Gepotidacin N=281 n (%)	Nitrofurantoin N=93 n (%)
Participants randomized	281 (100.0)	93 (100.0)
ITT population	281 (100.0)	93 (100.0)
mITT population	88 (31.3)	29 (31.2)
mITT NTF-S population	83 (29.5)	25 (26.9)
mITT MDR population	18 (6.4)	3 (3.2)
PK population	281 (100.0)	1 (1.1)
Safety population	281 (100.0)	93 (100.0)
Discontinued study drug[a]	43 (15.3)	2 (2.2)
Adverse event	40 (14.2)	1 (1.1)
Lost to follow-up	1 (0.4)	0
Participant reached protocol-defined stopping criteria	1 (0.4)	0
Withdrawal by participant	1 (0.4)	1 (1.1)
Discontinued study[a]	7 (2.5)	2 (2.2)
Adverse event	3 (1.1)	0
Lack of efficacy	0	1 (1.1)
Lost to follow-up	1 (0.4)	0
Withdrawal by participant	3 (1.1)	1 (1.1)

Source: Statistical Reviewer Analysis; adsl.xpt, adds.xpt;
[a] Percentages are based on number of randomized participants.
Abbreviations: ITT, Intention-to-treat population; mITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; MDR, multi-drug resistant; PK, Pharmacokinetic; N, number of participants in treatment group; n, number of participants in specified population or group;

Demographic characteristics are listed in next two tables below for the ITT population and Micro-ITT NTF-S population. Patient demographic and baseline characteristics were generally balanced between treatment groups in both populations.

Table 52. Baseline Demographics (ITT Population), EAGLE-J

Characteristic	Gepotidacin 1500 mg BID N=281 n (%)	Nitrofurantoin 100 mg BID N=93 n (%)
Sex, n (%)		
Female	281 (100.0)	93 (100.0)
Age, years		
Mean (SD)	45.2 (18.81)	46.7 (19.18)
Median	46.0	45.0
Min, Max	18.0, 85.0	19.0, 88.0
Age categories as randomized, n (%)		
≤50	165 (58.7)	53 (57.0)
>50	116 (41.3)	40 (43.0)
Race, n (%)		
Asian	280 (99.6)	92 (98.9)
Multiple	0	1 (1.1)
Missing	1 (<1)	0
Ethnicity, n (%)		
Not Hispanic or Latino	281 (100.0)	93 (100.0)
Baseline Height (cm)		
Mean (SD)	158.1 (5.99)	157.8 (6.57)
Median	158.3	158.0
Min, Max	136.5, 177.0	142.0, 172.0
Baseline Weight (kg)		
Mean (SD)	55.0 (10.16)	56.9 (10.37)
Median	52.8	56.0
Min, Max	40.0, 96.5	40.1, 90.8
BMI (kg/m^2)		
Mean (SD)	22.0 (3.87)	22.8 (3.72)
Median	21.2	22.2
Min, Max	15.2, 36.3	17.4, 34.0
Acute Cystitis Recurrence per CRF, n (%)		
Nonrecurrent Infection	213 (75.8)	73 (78.5)
Recurrent Infection	68 (24.2)	20 (21.5)
Baseline Symptom Score Category, n (%)		
2-5	127 (45.2)	42 (45.2)
6-8	137 (48.8)	43 (46.2)
9-12	17 (6.0)	8 (8.6)
Number of Uropathogens at Baseline, n (%)		
0	193 (68.7)	64 (68.8)
1 Qualifying + any number of Non-Qualifying	2 (<1)	0
1 Qualifying Only	86 (30.6)	29 (31.2)

Source: Statistical Reviewer Analysis; adsl.xpt;
Abbreviations: ITT, Intention-to-treat population, SD, standard deviation

Table 53. Baseline Demographics (Micro-ITT NTF-S Population), Study EAGLE-J

Characteristic	Gepotidacin 1500 mg BID N=83 n (%)	Nitrofurantoin 100 mg BID N=25 n (%)
Sex, n (%)		
Female	83 (100.0)	25 (100.0)
Age, years		
Mean (SD)	48.1 (18.99)	44.4 (19.97)
Median	48.0	42.0
Min, Max	19.0, 84.0	20.0, 82.0
Age categories as randomized, n (%)		
≤50	44 (53.0)	15 (60.0)
>50	39 (47.0)	10 (40.0)
Race, n (%)		
Asian	82 (98.8)	25 (100.0)
Missing	1 (1.2)	0
Ethnicity, n (%)		
Not Hispanic or Latino	83 (100.0)	25 (100.0)
Baseline Height (cm)		
Mean (SD)	158.2 (6.26)	159.6 (6.41)
Median	159.4	160.0
Min, Max	136.5, 177.0	148.5, 172.0
Baseline Weight (kg)		
Mean (SD)	55.5 (10.35)	58.1 (9.37)
Median	54.0	57.2
Min, Max	40.5, 91.8	41.1, 82.5
BMI (kg/m^2)		
Mean (SD)	22.2 (4.10)	22.8 (3.12)
Median	21.1	22.4
Min, Max	15.9, 35.2	17.7, 30.9
Acute Cystitis Recurrence per CRF, n (%)		
Nonrecurrent Infection	70 (84.3)	22 (88.0)
Recurrent Infection	13 (15.7)	3 (12.0)
Baseline Symptom Score Category, n (%)		
2-5	36 (43.4)	11 (44.0)
6-8	41 (49.4)	11 (44.0)
9-12	6 (7.2)	3 (12.0)
Number of Qualifying Uropathogens at Baseline, n (%)		
1 Qualifying + any number of Non-Qualifying	2 (2.4)	0
1 Qualifying Only	81 (97.6)	25 (100.0)

Source: Statistical Reviewer Analysis; adsl.xpt;
Abbreviations: Micro-ITT, microbiological intent-to-treat; NTF-S, nitrofurantoin susceptible; SD, standard deviation

The table below summarizes key efficacy endpoint results, including therapeutic response, microbiological response, and clinical response at TOC. The two groups had similar success rates in all analyses. In mITT NTF-S population, the gepotidacin arm had numerically higher success rates in the three types of responses. The nitrofurantoin arm had numerically higher success rate in clinical response at TOC in ITT population.

Table 54. Summary of Efficacy Endpoints, EAGLE-J

Therapeutic Response at TOC, mITT NTF-S	**Gepotidacin N=83**	**Nitrofurantoin N=25**
Success, n (%)	69 (83.1)	17 (68.0)
Adjusted difference in success rate % (95% CI)	14.4 (-2.1, 30.8)	
Microbiological Response at TOC, mITT NTF-S	**Gepotidacin N=83**	**Nitrofurantoin N=25**
Success, n (%)	74 (89.2)	20 (80.0)
Adjusted difference in success rate % (95% CI)	9.6 (-4.8, 24.1)	
Clinical Response at TOC, mITT NTF-S	**Gepotidacin N=83**	**Nitrofurantoin N=25**
Success, n (%)	71 (85.5)	19 (76.0)
Adjusted difference in success rate % (95% CI)	12.2 (-4.0, 28.4)	
Clinical Response at TOC, ITT	**Gepotidacin N=281**	**Nitrofurantoin N=93**
Success, n (%)	223 (79.4)	78 (83.9)
Adjusted difference in success rate % (95% CI)	-3.9 (-12.6, 4.7)	

Source: Statistical Reviewer Analysis; adsl.xpt; adeff.xpt; All adjusted difference and corresponding Miettinen-Nurminen confidence intervals are stratified by actual age category (≤50 years or >50 years) and history of acute cystitis recurrence (nonrecurrent infection or recurrent infection).
Abbreviations: mITT, microbiological intent-to-treat; NTF-S nitrofurantoin susceptible; ITT = Intention-to-treat; TOC, test-of-cure; N, number of participants in treatment group; n, number of participants in specified population or group; CI, confidence interval

17. Clinical Safety

Not applicable

18. Clinical Virology

Not applicable

19. Clinical Microbiology

19.1. Activity in Vitro

Antibacterial Activity

The tables below summarize the in vitro activity of gepotidacin against *N. gonorrhoeae*. This analysis includes 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 *N. gonorrhoeae* including isolates with certain genotypic and phenotypic characteristics. The MIC90 for gepotidacin against 393 *N. gonorrhoeae* isolates with collection dates from 2003-2017 was 0.5-1 mcg/mL.

The in vitro activity of gepotidacin and comparators was tested by agar dilution against 98 *N. gonorrhoeae* isolates. These isolates were from the 2022 gonococcal surveillance study and collected from the United States. The MIC90 for gepotidacin against *N. gonorrhoeae* was 0.5 mcg/mL and the antibacterial activity of gepotidacin and comparators is shown in the table below.

Table 55. Summary of Gepotidacin and Comparator Agents in Vitro Activity Tested by AD Against 98 *N. gonorrhoeae* Isolates From the 2022 Gepotidacin Gonococcal Global Surveillance Study (US)

Antibacterial Agent	Number of isolates	µg/mL			CLSI[a]				US FDA[b]			
		MIC50	MIC90	range	%S	%I	%R	%NS	%S	%I	%R	%NS
GEP	98	0.25	0.5	≤0.06 to 4	-[c]	-	-	-	-	-	-	-
AZM	98	0.12	1.0	≤0.03 to 16	96.9	NA	NA	3.1	-	-	-	-
CFM	98	0.015	0.03	≤0.002 to 0.12	100	NA	NA	0	100	NA	NA	0
CRO	98	0.008	0.015	≤0.002 to 0.03	100	NA	NA	0	100	NA	NA	0
CIP	98	0.004	8	≤0.0005 to 16	67.3	0	32.7	NA	67.3	0	32.7	NA
GEN	98	8	8	≤1.0 to 16	-	-	-	-	-	-	-	-
PEN	98	0.25	2	≤0.06 to >16	8.2	81.6	10.2	NA	8.2	81.6	10.2	NA
SPT	98	16	16	≤4 to 16	100	0	0	NA	100	0	0	NA
TET	98	0.5	16	≤0.12 to 32	27.6	52.0	20.4	NA	27.6	52.0	20.4	NA

Source: m5.3.5.4, GSK Study Report 2024N562388

a. criteria as published by CLSI [CLSI, M100]
b. based on U.S. FDA - https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
c. -, breakpoint not established

Gepotidacin was also tested against drug resistant *N. gonorrhoeae* in vitro. Against 57 ciprofloxacin-resistant (CIP-R) isolates (2012-2017), gepotidacin demonstrated an MIC90 of 1 mcg/mL.

The Applicant studied gepotidacin activity against a subset of *N. gonorrhoeae* isolates with phenotypic drug resistance to other antibacterial drugs from the 2018 to 2021. The gepotidacin surveillance study included isolates from the US (2018-2020), Australia (2012-2021), and India (2018-2021). The MIC90 for CIP-R, Pen-R and Tet-R isolates was 1 mcg/mL and the MIC90 for AZM-NSUS was 2 mcg/mL (data not shown).

Gepotidacin MIC90 for isolates from the cervix/vagina sources was 2 mcg/mL (n=17), which was 1 doubling dilution higher than the MIC90 of 1 mcg/mL from the other body sites tested including the urethra, (n=533) rectum (n=87), and throat (n=74).

The following tables show the MIC50 and/or MIC90 for 252 clinical isolates of *N. gonorrhoeae* that were characterized for mutations in GyrA and ParC or had other genotypic testing.

Table 56. Gepotidacin MIC Range and MIC50 for 252 Clinical Isolates of *N. Gonorrhoeae* and International Reference Strains According to Different Mutation Patterns Observed in the QRDR of *gyrA* and *parC* Genes

Mutation	Number of isolates	Gepotidacin	
		MIC range (µg/mL)	MIC50 (µg/mL)
gyrA[a]			
WT	101	0.03 to 2	0.25
S91F, D95G	107	0.03 to 4[b]	0.5
S91F, D95A	21	0.12 to 2	0.5
S91F, D95N	13	0.06 to 4[c]	0.5
S91F	8	0.25 to 2	-
S91F, D95Y	1	4[d]	-
S91Y	1	1	-
parC			
WT	118	0.03 to 2	0.5
S87R	75	0.03 to 2	0.5
E91G	21	0.12 to 1	0.5
D86N	20	0.5 to 4	2
S87R, S88P	6	0.06 to 0.5	-
S87N, E91Q	3	0.12 to 0.25	-
S87N, E91K	2	0.5	-
S87N	2	0.5, 2	-
S87I	1	0.5	-
S87W	1	0.25	-
E91K	1	4	-
E91Q	1	0.5	-
D86N, S88P	1	4	-

Source: Jacobsson, 2018
MICs (µg/mL) were determined by AD for gepotidacin; "-" = MIC50 not calculated when n<10
a. Of the 151 isolates with any gyrA QRDR mutation, 133 (88.1%) also had a parC QRDR mutation
b. Includes 1 isolate with a gepotidacin MIC of 4 µg/mL, which also had the ParC D86N mutation
c. Includes 1 isolate with a gepotidacin MIC of 4 µg/mL, which also had the ParC D86N and S88P mutations
d. Isolate also had the ParC E91K mutation

Reviewer's Comment

In the table above and below, some of the isolates with characterized mutations had elevated MIC50/90 to gepotidacin at 2 mcg/mL in vitro. D86N was one mutation that appeared to be

associated with higher gepotidacin MIC50/90 of 2 mcg/mL (MIC range of 0.25 – 4 mcg/mL) alone or in combination with other mutations.

This review does not include an analysis of beta-lactamases and PenA/B mutations produced by the *N. gonorrhoeae*. Although some of these genotypes were characterized by the Applicant, they are not directly related to gepotidacin activity.

Table 57. Summary of Gepotidacin Activity Against *N. gonorrhoeae* Genotypic Subsets That Met the MIC Screening Criteria From the 2018 to 2021 Gepotidacin Gonococcal Global Surveillance Study (US [2018 to 2020], AUS [2019-2021], India [2018 to 2021] (Global Data All Body Sites)

N. gonorrhoeae genotypic subgroups[a]	Gepotidacin MIC (µg/mL)				
	n	Min	Max	MIC50[b]	MIC90[b]
β-lactamase gene positive	110	≤0.06	2	1	2
Narrow-spectrum β-lactamases					
TEM-1	73	0.12	2	1	2
TEM-135	35	0.12	2	1	2
PenA mutations	341	≤0.06	2	0.5	1
345 INS "D"	14	1	2	1	1
345 INS "D"; A501T; A516G	32	≤0.06	2	0.5	1
345 INS "D"; A501V; A516G	16	0.12	2	1	2
345 INS "D"; A516G	207	≤0.06	2	0.5	1
I312M; V316T; N513Y; G454S	72	0.12	2	0.5	1
PenB mutations	159	≤0.06	2	0.5	1
G120K;A121D	43	≤0.06	2	0.5	1
G120K;A121N (potentially impactful)	68	≤0.06	2	0.5	1
PIA	39	0.12	2	0.25	1
PonA mutations	161	≤0.06	2	0.5	1
L421P	161	≤0.06	2	0.5	1
QRDR mutations	311	≤0.06	2	0.5	1
GyrA mutations	311	≤0.06	2	0.5	1
S91F,D95A	180	≤0.06	2	0.5	1
S91F,D95G	121	≤0.06	2	0.5	1
ParC mutations	302	≤0.06	2	0.5	1
D86N	106	0.25	2	1	2
S87R[c]	125	≤0.06	2	0.25	0.5
E91G	47	≤0.06	2	0.5	1
S87I[d]	11	0.5	1	1	1
S87N[e]	12	0.25	1	0.5	1
ParE mutations	143	≤0.06	2	0.5	1
P456S[f]	23	0.12	2	0.5	1
R427H	30	≤0.06	2	0.5	1
V89A	78	≤0.06	2	0.25	1
GyrA S91F,D95A and ParC D86N	83	0.25	2	1	2
GyrA S91F,D95A and ParC S87R	83	0.25	2	1	2
GyrA S91F,D95G and ParC D86N	23	0.25	2	1	2
GyrA S91F,D95G and ParC S87R	40	≤0.06	2	0.5	1
GyrA S91F,D95G and ParC S87I	11	0.5	1	1	1
MtrR coding region mutations	320	≤0.06	2	0.5	1
A39T[g]	70	≤0.06	1	0.25	0.5
G45D	32	0.12	2	0.5	1
H105Y	89	≤0.06	2	0.5	1
RpsJ rRNA mutations					
V57M	321	≤0.06	2	0.5	1
23s rRNA mutations	263	≤0.06	2	0.5	1
12A>G, 278C>T, 708T>C, 1074G>T, 1242C>T, 1350A>G, 1655C>T, 2059A>G[h]	241	≤0.06	2	0.5	1
2611C>T	22	0.12	2	0.5	1
Acquired tetracycline genes					
tet(M)-like	64	0.12	2	1	2

N. gonorrhoeae genotypic subgroups[a]	Gepotidacin MIC (µg/mL)				
	n	Min	Max	MIC50[b]	MIC90[b]
MLST[i]					
ST1579	23	≤0.06	2	0.5	1
ST1580	21	0.12	2	0.5	1
ST1901	12	0.12	0.5	0.25	0.5
ST7363	56	≤0.06	2	1	1
ST7822	16	0.12	0.5	0.5	1
ST8143	23	≤0.06	2	0.5	1
ST9363	10	0.5	2	1	2
ST10314	18	≤0.06	0.5	0.25	0.5
ST13266	20	0.5	2	1	2
ST13526	12	0.12	0.5	0.25	0.5
NG-MAST[i]					
ST1407	14	0.25	2	0.5	1
ST12526	18	0.5	2	1	2
ST16391	13	0.5	2	1	2

Source: m5.3.5.4 GSK Study Report 2024N549370

a. Only sequence types with 10 or more isolates are displayed
b. MIC50 and MIC90 refer to the corresponding concentrations required to inhibit 50% and 90% of the strains, respectively.
c. includes 2 isolates with additional S88P mutation
d. includes 3 isolates with additional E91G mutation
e. includes 7 isolates with additional E91K and 2 isolates with additional E91Q mutations
f. includes 4 isolates with additional A96V and 1 isolate with additional R427H mutations
g. includes 2 isolates with additional G45D and 5 isolates with additional H105Y mutations
h. mutations occurred in various combinations
i. MLST, Multilocus sequence type; NG-MAST, *N. gonorrhoeae* multiantigen sequence typing; ST, sequence type. Only sequence types with 10 or more isolates are displayed.

Reviewer's Comment

The Applicant discussed the activity of gepotidacin against *N. gonorrhoeae* isolates with certain ciprofloxacin mutations (e.g., GyrA S91F:D95A, ParC D86N, ParC S87R). However, some of these mutations were in isolates associated with microbiological failures and had increased MIC to gepotidacin in the phase 2 clinical study (e.g., ParC D86N). This will be further discussed in the Clinical Microbiology Analysis of Efficacy subsection of this review.

The effect of mutations on gepotidacin activity varies depending on the amino acid change and the combination of other mutations present. In some cases, there was an elevated MIC to gepotidacin when there was more than one mutation present or the presence of the MtrC-MtrD-MtrE efflux pump, a major mechanism of resistance in *N. gonorrhoeae*.

Epidemiological Cutoff Value

The Epidemiological Cutoff Value (ECV) for gepotidacin was determined for 761 *N. gonorrhoeae* isolates collected from 2015-2021. The Agency's clinical microbiology team determined the ECV to be 0.5 mcg/mL based on visual inspection of the frequency distribution data shown in the frequency distribution table below.

The Applicant used a different ECV value that was based on an aggregate percentage (weighted distribution) and determined that the ECV was 2 mcg/mL for ECV 97.5% and 5 mcg/mL for ECV 99.9%. Moreover, an ECV of 2 mcg/mL encompasses many of the D86N ParC mutations that are known to be associated with elevated MIC values.

Table 58. Frequency Distributions (N) With Cumulative Percent Inhibited (Cum%) for Gepotidacin and Ciprofloxacin at Each MIC mcg (µg/mL) Against 761 *Neisseria Gonorrhoeae* Isolates Used for ECV Determination[a]

Compound		MIC (µg/mL)																		
		≤0.0005	≤0.001	0.001	0.002	0.004	0.008	0.015	0.03	≤0.06[b]	0.06	0.12	0.25	0.5	1	2	4	8	16	32
GEP	N								1	23	5	74	253	271	111	22			1	
	Cum %								0.1	3.2	3.8	13.5	46.8	82.4	97.0	99.9			100	
CIP	N	2	1	2	31	270	47	22	9		2	5	5	10	27	78	135	63	43	9
	Cum %	0.3	0.4	0.7	4.7	40.2	46.4	49.3	50.5		50.7	51.4	52.0	53.4	56.9	67.1	84.9	93.2	98.8	100

Abbreviations: GEP, gepotidacin; CIP, ciprofloxacin
[a]On/off scale values are a result of some sites differing in their testing concentrations and are included for thoroughness.
[b] 23 MIC values of ≤0.06 µg/mL were considered 0.06 µg/mL for ECV/TECOFF calculations.

Source: This submission

Antibacterial Interactions

No interaction was observed for *N. gonorrhoeae* for gepotidacin in combination with the tested antibacterial drugs from the following classifications: fluoroquinolones, cephalosporins, macrolides, tetracyclines, aminoglycosides, pleuromutilins, and aminocyclitols. It was noted that lefamulin was the antimicrobial product tested from the pleuromutilins, and that spectinomycin was listed as an aminocyclitol, although also considered an aminoglycoside antibacterial drug.

Intracellular Activity

Bacteria such as *N. gonorrhoeae* can invade cells and use an intracellular location to help evade the immune system. Intracellular clearance and bactericidal activity of gepotidacin was assessed against cervical cells (ME180), conjunctival cells (Chang) and pharyngeal cells (Detroit). Gepotidacin was tested by the Applicant in comparison to ciprofloxacin and ceftriaxone against intracellular *N. gonorrhoeae* at 0.25, 1 and 4x MIC over time points up to 24 hours. The *N. gonorrhoeae* isolates tested were MS11, FA19, FA1090, H041, and F89. Gepotidacin demonstrated bactericidal activity across all three cell lines. At 24 hours, following exposure to gepotidacin, strains FA19, F89 and FA1090 were killed in cervical cells at all gepotidacin concentrations tested. Strain H041 was killed at 1x MIC gepotidacin and MS11 was killed at 4x MIC gepotidacin. In conjunctiva cells exposed to gepotidacin, strains FA19, FA1090 and F89 were killed at all concentrations tested. Strains H041 and MS11 only persisted at the lowest gepotidacin concentration tested after 24 hours (0.24x MIC). In pharyngeal cells, FA19 and FA1090 were killed after exposure to any of the gepotidacin concentrations tested. Strains H041 and F89 only persisted at the lowest gepotidacin concentration tested. Strain MS11 was cleared at 4x MIC gepotidacin.

Reviewer's Comment

The totality of the data above suggests that gepotidacin has in vitro antimicrobial activity against the indicated pathogen, *N. gonorrhoeae*, with an MIC90 of 0.5-1 mcg/mL and an ECV based on this reviewer's assessment to be 0.5 mcg/mL. Furthermore, gepotidacin has intracellular bactericidal activity.

19.2. Mechanism of Action and Resistance

Gepotidacin inhibits two bacterial enzymes: DNA gyrase and topoisomerase IV. The mechanism of action of gepotidacin was previously reviewed in the original NDA for uncomplicated urinary

tract infections. The dual-targeting mechanism of gepotidacin is also relevant for antimicrobial activity against *N. gonorrhoeae*. The Applicant reported that gepotidacin inhibited DNA supercoiling of wild-type DNA gyrase and the DNA decatenation activity of wild-type topoisomerase IV which had been purified from *N. gonorrhoeae* with magnitudes of 5.1 ± 2.3 µM and 1.8 ± 1.3 µM, respectively. In this study, the Applicant reported that gepotidacin had a reduction in the ability to inhibit ParC D86N topoisomerase IV decatenation (IC50 > 100-fold) and decreased potency for single-strand break enhancement compared to wild-type enzyme and (> 80-fold). GyrA D90N had > 20-fold reduction in inhibition of supercoiling activity and stimulation of DNA cleavage by gepotidacin compared to wild-type enzyme. In a separate study, gepotidacin exhibited concentration-dependent bactericidal activity, with a post-antibiotic effect of 0.7 to 1 hours for *N. gonorrhoeae*.

The mechanisms of resistance were also previously assessed with the original application against indicated bacteria and in this application against *N. gonorrhoeae*. The particular amino acids that are relevant for increased MIC to gepotidacin vary by the organism tested.

The primary resistance mechanisms identified for *N. gonorrhoeae* involve mutations in:

- GyrA: A92T and D90N
- ParC: D86N
- Efflux pumps (MtrCDE upregulation)

The Applicant provided data that included instances when individual mutations showed minimal impact (0- to 4-fold MIC increase), but combinations resulted in significant resistance (16- to >256-fold MIC increase), highlighting the importance of the dual-target mechanism.

In the Applicant's studies of spontaneous mutation frequency, the frequency of mutations in *N. gonorrhoeae* was 10^{-9} to 10^{-10} at 4X and 10X the MIC of gepotidacin, respectively. In time-kill analysis study of 7 clinical *N. gonorrhoeae* isolates from Study BTZ116576, gepotidacin and comparators were tested, and gepotidacin showed bactericidal activity against *N. gonorrhoeae* isolates. A 3 $\log_{10}$ decrease in CFU after 24 hours at 4x and 10x MIC gepotidacin was reported by the Applicant for the isolates tested. Growth of bacteria from 24-hour timepoint plates was assessed for development of resistance to gepotidacin. Increase in gepotidacin resistance was observed for a few isolates (≥ 4-fold increase gepotidacin MIC). One *N. gonorrhoeae* isolate recovered from a 4X MIC plate was isolate #1040859. Resistance development was reported for this isolate with MICs on colony replicates ranging from 1-256 mcg/mL. It was characterized genotypically and found to have mutations in GyrA S91F, D95G and ParC D86N. One isolate tested (#1040855) had a gepotidacin MIC of 16-64 mcg/mL and had mutations in GyrA S91F, A92T, D95G and ParC D86N.

Reviewer's Comment

In some cases, single amino acid mutations tested by the Applicant did not appear to generate increases in gepotidacin MIC values; however, increases in gepotidacin MICs were seen with more than one mutation. It was noted that all mutations have not been tested, and bacteria can have other resistance factors that are known or unknown that may also contribute to gepotidacin resistance. In the Applicant's study of the molecular characterization of *N. gonorrhoeae* isolates from clinical and nonclinical studies with MICs ≥ 2 mcg/mL, many of the isolates had GyrA S91F, D95G in addition to ParC D86N and other mutations. Enzymatic studies of gepotidacin IC50 values also provide further evidence that GyrA D90 and ParC D86 are key residues for

gepotidacin activity against *N. gonorrhoeae*. The Applicant has reported that *N. gonorrhoeae* isolates with GyrA D90N have not been found clinically.

19.3. Susceptibility Test Methods and Interpretive Criteria

The effect of broth microdilution, agar dilution, and disk diffusion test methods were assessed for gepotidacin in previous studies submitted in the original NDA. The information below pertains to *N. gonorrhoeae*.

Susceptibility Testing Methods and Quality Control

Gepotidacin disk diffusion testing of other bacterial species using the 10 mcg disk concentration was previously reviewed in the original NDA. In order to evaluate the appropriateness of the disk for in vitro antimicrobial testing of *N. gonorrhoeae,* gepotidacin and comparator (ciprofloxacin) were evaluated by agar and disk diffusion testing in accordance with CLSI guidelines against 102 clinical isolates of *N. gonorrhoeae*. The quality control isolate, *N. gonorrhoeae* ATCC 49226 was also tested on each day. 101 of the isolates tested exhibited MIC of ≤ 1 mcg/mL and zone diameters ≥ 25mm. The 10 mcg disk appeared appropriate for testing of gepotidacin against *N. gonorrhoeae.*

Disk stability data previously submitted in the original application also tested *N. gonorrhoeae* ATCC 29226 strain and concluded that there was little deterioration of disks from 20 °C to room temperature in content or performance up to 18 months. At higher temperatures gepotidacin 10 mcg disks were within the acceptance limits, except for batches 405141 and 405143 at 9 months stored at room temperature and 37°C respectively falling 1 mm below lower than acceptance limit. Disks were within specification for the test period at the recommended storage temperature 2-8 °C.

CLSI accepted quality control ranges for *N. gonorrhoeae*: ATCC 49226 MIC range 0.25-1 mcg/mL and disk diffusion zone diameter of 32-40 mm. The Applicant determined the effect of various testing parameters on the in vitro activity of gepotidacin and comparator, ciprofloxacin, using disk diffusion against *N. gonorrhoeae*. Two manufacturers were tested (b) (4) and (b) (4) according to CLSI methods using 10 mcg gepotidacin disks. Fifteen World Health Organization reference strains were tested including two gepotidacin-resistant strains. Variables that effected gepotidacin zone diameters were media manufacturer (Oxoid GC agar supplemented with IsoVitalex did not support *N. gonorrhoeae* growth), reduced incubation time, low inoculum concentration and pH. These variables should be controlled during disk diffusion antimicrobial susceptibility testing by using standardized testing methods.

Method equivalency: In accordance with CLSI M23 guidelines, the equivalency between 2 reference antimicrobial susceptibility testing methods was determined for gepotidacin against *N. gonorrhoeae.* Agar dilution and broth microdilution equivalency was not established based on essential agreement of 28.6%. The essential agreement was calculated by the Applicant as the number of broth microdilution and agar dilution MIC values for each isolate that are ± 1 $\log_2$ dilution divided by the total number of isolates. Instances where at least 1 MIC value was

recorded as being off scale were not included in EA calculations. Agar dilution is the method that will be used for antimicrobial susceptibility testing of gepotidacin by MIC of *N. gonorrhoeae* and is the method by which the quality control ranges for *N. gonorrhoeae* ATCC 49226 were accepted by CLSI.

The Applicant determined the effect of various testing parameters on the in vitro activity of gepotidacin and comparators, ciprofloxacin and ceftriaxone, using agar dilution against *N. gonorrhoeae*. Media, low inoculum concentrations, pH and atmospheric conditions (10% CO_2) impacted gepotidacin activity against *N. gonorrhoeae* by agar dilution. Media was the most impacted variable as Remel GC agar supplemented with GCHI did not support the growth of *N. gonorrhoeae.* Also, lower MIC results and poor growth was observed with Oxoid GC agar supplemented with GCHI. It is important to control for these variables using standardized testing methods when doing agar dilution testing with gepotidacin against *N. gonorrhoeae*.

Gepotidacin gradient diffusion strips tested for antimicrobial activity against *N. gonorrhoeae* were verified by (b) (4) and found acceptable by CLSI guidelines. Gepotidacin susceptibility testing by disk diffusion was tested to evaluate the performance of Remel GC Agar Base with 1% GCHI in comparison to (b) (4) GC Agar with IsoVitaleX enrichment media, since this media will be discontinued. The Applicant found good correlation between the manufacturers.

Applicant's Proposed Breakpoints & Rationale

The Applicant proposed an MIC susceptible breakpoint: (b) (4) mcg/mL. The Applicant's rationale was based on (b) (4)

The Applicant's proposed susceptible disk interpretive criteria was (b) (4) mm and the agar dilution MIC-disk correlation data that the Applicant proposed is shown in the figure below. Discrepancy rates were calculated by the Applicant as zero for all MIC ranges assessed. It appears that the horizontal line in the scattergram should have been moved to the left to show that isolates with disk diffusion zone diameters of (b) (4) would be considered susceptible in accordance with their proposed susceptible zone diameter breakpoint (b) (4) However, the Agency is proposing new MIC and disk diffusion breakpoint criteria that were discussed with the Applicant. The Agency's proposed disk diffusion breakpoints and MIC-disk correlation analysis for *N. gonorrhoeae* for antimicrobial susceptibility testing are in the Susceptibility Test Interpretive Criteria (Breakpoints) section of this review.

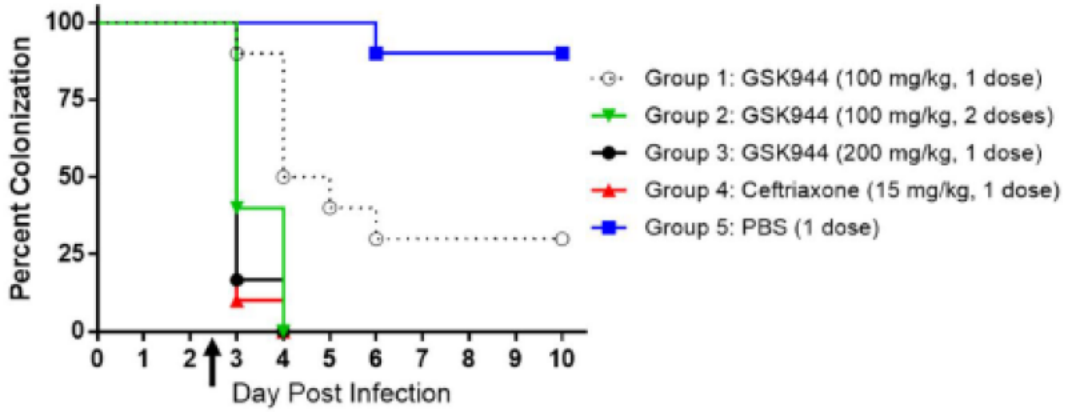
Figure 5. Scattergram of Gepotidacin MICs and DDZDs ((b) (4) and (b) (4) Disks Combined) for *N. Gonorrhoeae* (n=1204) From Study BTZ116577 and the Gepotidacin Gonococcal Global Surveillance Study (2018-2021) Combined (Susceptible-Only MIC Breakpoint of (b) (4) mcg/mL)

(b) (4)

19.4. Activity in Vivo (Animal Studies)

Gepotidacin was evaluated for its in vivo efficacy against *N. gonorrhoeae* MS11 (gepotidacin MIC 1 mcg/mL, ceftriaxone (CRO) MIC 0.015 mcg/mL) in a mouse vaginal colonization model using an immunocompetent female mouse model primed with estradiol. The percent of mice colonized with *N. gonorrhoeae* MS11 over 10 days following treatment with gepotidacin (GSK944), CRO or phosphate-buffered saline (PBS) given on day 2 of infection is shown in the figure below.

Figure 6. Percent of Mice Colonized With *N. gonorrhoeae* MS11 (gepotidacin MIC 1 mcg/mL) Over 10 Days Following Treatment With Gepotidacin (GSK944), CRO or PBS Given on Day 2 of Infection (Arrow)[a]



Source: m5.3.5.4, GSK Study Report 2015N228350
[a]GSK944 = GSK2140944

Reviewer's Comment

Gepotidacin was tested for its in vivo efficacy against various bacteria using animal models reviewed in the original NDA submission. The in vivo efficacy model above showed proof-of concept for gepotidacin's efficacy against *N. gonorrhoeae* in a vaginal colonization model, a

model which has not been fully validated. Therefore, the determination of the efficacy of gepotidacin against *N. gonorrhoeae* will rely on the totality of evidence including human clinical trials discussed in this review.

19.5. Pharmacokinetics/Pharmacodynamics

The pharmacokinetics and pharmacodynamics of gepotidacin were previously reviewed in the original application for the indication of uncomplicated urinary tract infection. In this review of gepotidacin against *N. gonorrhoeae,* the clinical pharmacology reviewer has stated that the "PK/PD index and magnitude predictive of gepotidacin efficacy against *N. gonorrhoeae* remain undefined through conventional preclinical methods. However, subsequent in vitro hollow-fiber infection model studies were conducted to determine resistance suppression targets." Please see the Clinical Pharmacology section of this review for additional information on PK/PD for gepotidacin against *N. gonorrhoeae*.

19.6. Clinical Microbiology Analysis of Efficacy

Please refer to the clinical and statistical sections of this multidisciplinary review for additional information on the clinical study design and efficacy conclusions. Information pertaining to clinical microbiology is discussed below. Since the indication being sought with this sNDA is for uGC, this clinical microbiology review will focus primarily on that indication.

Phase 2 Clinical Study BTZ116576

Genetic characterization of N. gonorrhoeae isolates

Three Baseline urethral isolates with the ParC D86N substitution were associated with microbiological failures, and all had a baseline gepotidacin MIC of 1 mcg/mL. The 5 remaining Baseline urethral isolates with the ParC D86N were microbiological successes, including 2 with a gepotidacin MIC of 1 mcg/mL.

Test of cure (TOC) isolates from all 3 urogenital failures harbored the D86N substitution in ParC and 2 additional mutations in GyrA (S91F and D95G). One of these isolates did not harbor any additional substitutions in GyrA or ParC, exposed to a 1.5 g dose of gepotidacin and had a gepotidacin MIC, at TOC, equivalent to baseline (gepotidacin MIC = 1 mcg/mL). Two of these isolates harbored an additional substitution in GyrA (A92T) at TOC. Both participants received a 3 g dose of gepotidacin and urethral isolates from both participants had elevated gepotidacin MICs (≥ 32 mcg/mL) at TOC, an increase of 32- fold from Baseline.

This data provides two instances of emergence of resistance to gepotidacin on therapy in the phase 2 clinical study BTZ116576 and suggests that the combination of the ParC D86N and GyrA A92T substitutions are likely to be contributing to the reduced susceptibility to gepotidacin. The mutated amino acid residues are thought to be structurally important for binding to gepotidacin. The resistance mutants observed at TOC in the phase 2 study suggest that the gepotidacin concentration of 1.5 g was insufficient/below the threshold for preventing bacteria from developing additional mutations for resistance development.

Reviewer's Comment

In Study BTZ116576, using an unapproved single 3,000 mg dose of gepotidacin, microbiological failures were reported among patients with *N. gonorrhoeae* isolates with baseline MIC of 1 mcg/mL. Two of these isolates had mutations in GyrA and ParC known to be important for gepotidacin binding to the target (ParC D86N, GyrA A92T), and an increase in resistance to gepotidacin (≥32-fold) was also reported at the end of treatment. Using 3,000 mg of gepotidacin followed by a second 3,000 mg dose taken approximately 12 hours later (Study BTZ116577), no *N. gonorrhoeae* resistance to gepotidacin was observed. A description of the phase 3 clinical study BTZ116577 follows.

Phase 3 Clinical Study BTZ116577

In the Phase 3 BTZ116577, urogenital microbiological success (Micro-ITT Population) was observed as 92.6% for gepotidacin and 91.2% for ceftriaxone plus azithromycin.

Participants provided a urogenital sample for bacterial culture at the baseline and test-of-cure (TOC) visits. The primary endpoint was culture-confirmed bacterial eradication of *N. gonorrhoeae* (microbiological success) from the urogenital body site at TOC. Pretreatment pharyngeal and rectal swab specimens were also obtained from consenting participants. Secondary endpoints evaluated bacterial eradication from the rectal and pharyngeal body sites at the TOC visit.

Baseline N. gonorrhoeae isolate characteristics from Study BTZ116577

The most prevalent genotypes among baseline urogenital *N. gonorrhoeae* isolates included:

QRDR mutations GyrA S91F D95 alone and in combination with various ParC mutations. ParC D86N mutation was present in 12% of *N. gonorrhoeae* isolates.

Multi-locus sequence typing (MLSTs): ST9362, ST7822, and ST8156

The microbiological response and outcome of pharyngeal *N. gonorrhoeae* at TOC in Study BTZ116577 were reported by the Applicant for the micro-ITT pharyngeal population. Microbiological success was 77.8% in the gepotidacin arm and 94.1% success in the ceftriaxone plus azithromycin arm. Microbiological failures were 22.2% in the gepotidacin arm and 5.9% in the ceftriaxone plus azithromycin arm. Bacterial persistence was 11.1% in the gepotidacin arm and 0% in the ceftriaxone plus azithromycin arm. Some patients were classified as "unable to determine" for microbiological outcome. These were 11.1% in the gepotidacin arm and 5.9% in the ceftriaxone plus azithromycin arm. Microbiological success of baseline pharyngeal *N. gonorrhoeae* isolates at TOC by genotypic subcategory in the micro ITT population showed 75% microbiological success for gepotidacin at 3000 mg (two doses) and 94.1 % microbiological success for 500 mg ceftriaxone plus azithromycin 1 g. *N. gonorrhoeae* isolates with QRDR mutations had 75% microbiological success including 80% for isolates with GyrA S91F D95A mutations and 60% microbiological success for *N. gonorrhoeae* isolates with MtrCDE promotor and coding mutations. The comparator had 100% microbiological success for these subcategories.

The microbiological profile of pharyngeal *N. gonorrhoeae* isolates from microbiological failures were characterized by the Applicant and had a combination of factors present in their microbiology profile. All four of the isolates had GyrA D95A, S91F and ParC D86N mutations as well as mutations in Mtr efflux operon or coding regions. All of the isolates were MLST type

7363, a strain of *N. gonorrhoeae* that has been associated in the literature with concerning levels of antimicrobial resistance.

The microbiological outcome and response of rectal *N. gonorrhoeae* at TOC in study BTZ1166577 in the micro-ITT rectal population was 100% in the gepotidacin arm and 80% in the ceftriaxone plus azithromycin arm. There was no bacterial persistence of *N. gonorrhoeae* in the gepotidacin arm. Microbiological success of rectal *N. gonorrhoeae* at TOC by baseline *N. gonorrhoeae* phenotypic and genotypic subcategories (micro-ITT population) was evaluated by the Applicant. In the gepotidacin 3000 mg (two doses) arm, for ciprofloxacin-resistant *N. gonorrhoeae* there was 100% microbiological success and in the ceftriaxone 500 mg plus azithromycin 1 g arm there was 80% microbiological success. For the genotypic category of QRDR mutations, including all characterized ParC and GyrA mutations such as GyrA S91F, D95A, the microbiological success for gepotidacin against *N. gonorrhoeae* was 100%. In the comparator arm, microbiological success was 87.5% for *N. gonorrhoeae* isolates with QRDR mutations.

For study BTZ116577, microbiological success in the micro-ITT population was high among urogenital isolates, regardless of isolate characterization by the Applicant. Microbiological success by MIC, phenotypic and genotypic subcategories are shown in the tables (from the Applicant) below. The Applicant reported that the NAAT outcome and response for urogenital *N. gonorrhoeae* at TOC was 88.3% in the gepotidacin arm.

Table 59. Summary of Gepotidacin Microbiological Success at TOC by Baseline Urogenital Gepotidacin MIC for *N. gonorrhoeae* in Study BTZ116577 (micro-ITT Population)

Baseline gepotidacin MIC (µg/mL)	Microbiological Success
≤0.06	13/13 (100%)
0.12	55/58 (95%)
0.25	71/80 (89%)
0.5	37/39 (95%)
1	10/11 (91%)
2	2/2 (100%)
4	
Total	188/203 (93%)
MIC range (µg/mL)	≤0.06 to 2
MIC50 (µg/mL)	0.25
MIC90 (µg/mL)	0.5

Source: m5.3.5.1, BTZ116577 CSR, Table 2.318; m5.3.5.1, BTZ116577 CSR, Table 2.30101
Note:MIC is referring to the Baseline visit MIC for the compound in that respective treatment group. The denominators for each cell are based on the micro-ITT Population and include participants with Baseline *N. gonorrhoeae* isolated from the urogenital body site and with the Baseline MIC result. The numerators include all participants with eradication (success) at the urogenital body site and with the Baseline MIC result. A participant with more than 1 *N. gonorrhoeae* isolate is counted more than once for microbiological response. MICs are based on the AD MICs.

Table 60. Microbiological Success of Baseline Urogenital *N. gonorrhoeae* at TOC by Phenotypic Subcategory, micro-ITT Population

Subcategory	GEP 2 x 3000 mg N=202	CRO 500 mg + AZM 1 g N=204	Difference in % for success rate (95% CI)[1]
Overall	187/202 (92.6%)	186/204 (91.2%)	-0.1% (-5.6%, 5.5%)
Phenotype			
AZM-NSUS	17/17 (100%)	19/20 (95.0%)	5.0% (-14.3%, 24.0%)
CIP-R	103/110 (93.6%)	101/109 (92.7%)	1.0% (-6.2%, 8.3%)
PEN-R	35/36 (97.2%)	30/33 (90.9%)	6.3% (-6.4%, 21.4%)
TET-R	42/49 (85.7%)	47/53 (88.7%)	-3.0% (-17.1%, 10.6%)
CIP-R and PEN-R and TET-R	23/24 (95.8%)	21/23 (91.3%)	4.5% (-13.1%, 23.6%)

Source: m5.3.5.1, BTZ116577 CSR, Table 2.109

Only phenotypic subcategories with ≥10 participants in at least 1 treatment group are displayed. Percentages were based on the number of participants overall or in the respective group by treatment.

[1]MN method adjusting for treatment and pooled actual strata of sex and sexual orientation (men who have sex with men, men who have sex with women, or female) for overall analysis. Unadjusted MN method for analyses within subgroup.

Table 61. Microbiological Success of Baseline Urogenital *N. gonorrhoeae* at TOC by Genotypic Subcategory, micro-ITT Population

Subcategory	GEP 2 x 3000 mg N=202	CRO 500 mg + AZM 1 g N=204	Difference in % for success rate (95% CI)
Overall	187/202 (92.6%)	186/204 (91.2%)	-0.1% (-5.6%, 5.5%)
Genotype			
Beta-lactamase gene positive	24/25 (96.0%)	21/23 (91.3%)	4.7% (-12.4%, 23.7%)
Narrow spectrum β lactamases	24/25 (96.0%)	21/23 (91.3%)	4.7% (-12.4%, 23.7%)
TEM-1	17/18 (94.4%)	20/22 (90.9%)	3.5% (-18.4%, 23.7%)
PenA mutations	28/29 (96.6%)	26/28 (92.9%)	3.7% (-11.2%, 19.9%)
PenB mutations	53/60 (88.3%)	51/57 (89.5%)	-1.1% (-13.3%, 11.2%)
PonA mutations	9/9 (100%)	10/10 (100%)	0.0% (-31.1%, 28.9%)
QRDR mutations	111/119 (93.3%)	112/121 (92.6%)	0.7% (-6.2%, 7.7%)
GyrA mutations	109/117 (93.2%)	111/119 (93.3%)	-0.1% (-7.1%, 6.8%)
S91F, D95A	101/107 (94.4%)	99/106 (93.4%)	1.0% (-6.0%, 8.2%)
S91F, D95G	5/6 (83.3%)	10/11 (90.9%)	-7.6% (-50.6%, 26.9%)
ParC mutations	95/101 (94.1%)	99/107 (92.5%)	1.5% (-5.9%, 9.0%)
D86N	22/24 (91.7%)	20/23 (87.0%)	4.7% (-15.3%, 25.6%)
S87R	68/72 (94.4%)	69/74 (93.2%)	1.2% (-7.6%, 10.1%)
Combination QRDR mutations			
GyrA S91F, D95A and ParC D86N	20/22 (90.9%)	16/19 (84.2%)	6.7% (-15.3%, 30.5%)
GyrA S91F, D95A and ParC S87R	64/67 (95.5%)	65/69 (94.2%)	1.3% (-7.4%, 10.2%)
MtrCDE promoter mutations	64/71 (90.1%)	62/69 (89.9%)	0.3% (-10.3%, 11.1%)
-4A>G, -17G>T, -20C>T, -24C>A, -27delC, -34C>T, -39C>T, -40delG, -41G>C, -43T>A, -45G>A, -51C>T, -52G>T, -57A>G, -58A>G, -59T>C, -65C>T, -66C>T, -70A>G, -71delT, -86A>G, -88T>C, -89A>G, -91G_-90TinsA, -93C>G, -94T>A, -95T>C, -97C>T, -101C>T, -108A>G, -121A>C ,	18/18 (100%)	15/16 (93.8%)	6.2% (-12.4%, 28.8%)

Source: This submission

No reduction in susceptibility (≥ 4-fold increase in study treatment MIC compared with baseline MIC) was observed in the phase 3 study, including among baseline urogenital isolates with ParC D86N substitutions in the gepotidacin treatment group. This was an improvement over the resistance found in the phase 2 study results.

Laboratory methods

Local laboratory testing was used for recovery of *N. gonorrhoeae* for study BTZ116577 with central laboratory confirmation and identification, susceptibility testing and molecular characterization. For whole genome sequencing, a third-party laboratory was used. Baseline local laboratory urogenital *N. gonorrhoeae/C. trachomatis* NAATs were done, and the results were used to guide treatment for *C. trachomatis* at the test-of-cure, if required. For urogenital isolates of *N. gonorrhoeae*, one swab was done for culture and Gram stain, 1 swab or urine for local

laboratory NAAT (baseline only), and 1 urine specimen or swab (depending on if male or female participant) for central laboratory NAAT (also collected at follow up visit if the baseline *M. genitalium* NAAT was positive).

Nucleic Acid Amplification Tests (NAATS)

The emphasis in this review was placed on standard culture-based methods for activity of gepotidacin in vitro and in *N. gonorrhoeae* clinical trials. The Applicant provided information on FDA-cleared tests that were used during the clinical studies for *Chlamydia trachomatis* and *N. gonorrhoeae* detection by PCR and laboratory developed tests for *Mycoplasma genitalium*.

Reviewer's Comment

Urogenital NAAT success was 82.5% favoring gepotidacin against *N. gonorrhoeae*. The NAAT results were exploratory in nature and the details were not included in this review. Use of NAATs can have some disadvantages including the detection of both live and dead cells. Also, NAATs do not give antimicrobial susceptibility testing information which can be obtained from standard culture methods.

19.7. Susceptibility Test Interpretive Criteria (Breakpoints)

The Agency's proposed MIC breakpoints for gepotidacin against *N. gonorrhoeae* are shown in the table below and the Agency's rationale for gepotidacin against. *N. gonorrhoeae* is based on the following parameters:

Pathogen	MIC90	ECV	PK/PD	Clinical Cutoff
N. gonorrhoeae	0.5-1 mcg/mL	0.5 mcg/mL	0.5-1 mcg/mL	1 mcg/mL

The Agency will approve the following Minimum Inhibitory Concentration MIC and Disk breakpoints for *Neisseria gonorrhoeae*.

Table 62. Agency's Breakpoints for Gepotidacin Oral Products

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Neisseria gonorrhoeae	≤ 1	2	≥ 4	≥ 28	23-27	≤ 22

Source: Agency review
Abbreviations: S, susceptible; I, intermediate; R, resistant

The rationale for this proposal is based primarily on the in vitro and clinical trial data. The MIC90 for the in vitro surveillance studies ranged between 0.5-1 mcg/mL. Isolates above 2

mcg/mL have been noted among clinical isolates of *N. gonorrhoeae* (e.g., Jacobsson, 2018[17]). With a greater number of isolates having microbiological success at 1 mcg/mL in the phase 3 trial (10/11, 91%), there is greater confidence in clinical and microbiological success at 1 mcg/mL than with only 2 isolates having microbiological success at 2 mcg/mL. Additionally, using a single 3000 mg dose, failures were reported among patients from the phase 2 clinical study with *N. gonorrhoeae* isolates with baseline MIC of 1 mcg/mL. These isolates had mutations in GyrA and ParC known to be important for gepotidacin binding to the target, and an increase in resistance to gepotidacin (≥ 32-fold) was also reported at the end of treatment.

Therefore, the Agency recommends a susceptible MIC of ≤ 1 mcg/mL which will include the wild-type population. Since isolates with MICs greater than 1 mcg/mL have been characterized for the presence of certain gepotidacin resistance factors, the Agency does not consider that these isolates represent the wild-type population. Furthermore, breakpoints with intermediate and resistant criteria will be beneficial to device manufacturers as the intermediate provides a buffer for laboratory testing errors.

Disk diffusion zone diameter breakpoints have also been proposed by the Agency. The error rate-bounded method was used to calculate the lowest discrepancy rates between MIC and zone diameter results according to Clinical and Laboratory Standards Institute (CLSI) guidelines (M23). The Agency also considered the CLSI M23 recommendation that the minimum intermediate disk diffusion zone diameter range should equal half the relevant quality control strain and no wider than the relevant quality control range. The Agency's reanalysis of the Applicant's scattergram of combined data from Study BTZ116677 and gepotidacin gonococcal global surveillance study 2018-2021 is shown below. For this analysis the Agency's proposed MIC and disk diffusion breakpoints for gepotidacin against *N. gonorrhoeae* are used.

[17] Jacobsson, Susanne; Golparian, Daniel; Scangarella-Oman, Nicole; and Magnus Unemo, In vitro activity of the novel triazaacenaphthylene gepotidacin (GSK2140944) against MDR *Neisseria gonorrhoeae, J Antimicrob Chemother* 2018; 73: 2072–2077 doi:10.1093/jac/dky162.

Table 63. Reanalysis of the Scattergram of Gepotidacin MICs and DDZDs ((b) (4) and (b) (4) Disks Combined) for *N. gonorrhoeae* (N=1204) From Study BTZ116577 and Gepotidacin Gonococcal Global Surveillance Study (2018 to 2021) Combined Using the Agency's Proposed Breakpoints, S|I|R= ≤ 1|2|≥4 mcg/mL

(b) (4)

Source: Modified from the Applicant's figure from this submission. The orange vertical lines show the Agency's proposed disk breakpoints.

Table 64. Discrepancy Rates for the Figure Above Using Agency's Proposed MIC Breakpoints

MIC Range	Number	Very Major	Major	Minor
(b) (4)				

Source: Reviewer's Table

Clinical Microbiology Conclusions

From a clinical microbiology perspective, it is recommended to approve gepotidacin for *N. gonorrhoeae* based on the totality of the evidence provided by the Applicant in their sNDA. However, because of the detection of resistance emergence in the phase 2 clinical study, ongoing surveillance for resistance of *N. gonorrhoeae* to gepotidacin is recommended. Additionally, the Agency will approve MIC and disk diffusion breakpoints for gepotidacin against *N. gonorrhoeae*.

20. Mechanism of Action/Drug Resistance

Refer to the Clinical Microbiology section.

21. Other Drug Development Considerations

Not applicable

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

For this NDA 218230/S-001, three BIMO review-based Good Clinical Practice (GCP) inspections (3 clinical investigators) were conducted in auditing Study BTZ116577:

- Candice J. McNeil, M.D. (Greensboro, North Carolina; Site 241673)
- Aaron C. Ermel, M.D. (Indianapolis, Indiana; Site 240508)
- Rivero Calaf Ángel, M.D. (Barcelona, Spain; Site 241370)

Based on the inspections, the study appears to have been conducted in observance of GCP principles and in compliance with FDA regulations. The data generated by the clinical investigators appear to be acceptable in support of this NDA supplement.

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 currently approved PI and the Applicant's draft PI submitted on June 11, 2025 (Table 65). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) 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.

Table 65. Key Labeling Changes and Considerations

Full PI Sections[1]	Applicant Proposed Labeling	Rationale for Major Changes Incorporated into the Finalized PI[2]
1 INDICATIONS AND USAGE	Added new indication for the treatment of adult and pediatric patients 12 years of age and older weighing more than 45 kilograms (kg) with uncomplicated urogenital gonorrhea caused by susceptible strains of *Neisseria gonorrhoeae* (b) (4)	Indication statement edited to restrict use of Blujepa to treatment of patients with uncomplicated urogenital gonorrhea who have limited or no alternative treatment options. A statement was added that clarified that the indication is based on limited clinical safety data for this indication. Refer to section 7.7.1 of the IAMA for additional details.
2 DOSAGE AND ADMINISTRATION	Revised subsection headings (b) (4)	Revised subsection headings to list each full indication and the respective ages and weights of the population for which the drug is indicated for as follows: (1) uUTI- Female adult and pediatric patients 12 years of age and older weighing at least 40 kg and (2) Uncomplicated urogenital gonorrhea- Adult (male and female) and pediatric patients 12 years of age and older weighing at least 45 kg. This clarification was also added to the text beneath the headings.
4 CONTRAINDICATIONS	No major changes	-
5 WARNINGS AND PRECAUTIONS	Subsection 5.1 QTc Prolongation: Added statement recommending (b) (4)" when Blujepa is administered with moderate CYP3A4 inhibitors and two or more risk factors (low body weight, moderate hepatic impairment, or moderate renal impairment.	Subsection 5.1 QTc Prolongation: Changed the recommendation from "(b) (4)" to "avoid use" of Blujepa in uncomplicated urogenital gonorrhea patients who have concomitant use of moderate CYP3A4 inhibitors or any two or more of the following risk factors for increased gepotidacin exposure and risk of QTc interval prolongation: body weight between 45 kg and 60 kg, moderate renal impairment, or moderate hepatic impairment. Refer to Sections 8.2.2 and 14.5 of the IAMA for additional details. Subsection 5.2 Acetylcholinesterase Inhibition: Syncope was added to the listing of adverse reactions observed in the clinical trials that are potentially attributed to acetylcholinesterase inhibition. Refer to Section 7.6.1 of the IAMA for additional details.
6 ADVERSE REACTIONS	Added new subsection on Clinical Trial Experience in Patients with Uncomplicated Urogenital Gonorrhea	Subsection 6.1 Clinical Trials Experience, subheading “Clinical Trial Experience in Patients with Uncomplicated Urogenital Gonorrhea”:

Full PI Sections[1]	Applicant Proposed Labeling	Rationale for Major Changes Incorporated into the Finalized PI[2]
		Added myalgia and arthralgia as they were noted in 2 gepotidacin uncomplicated urogenital gonorrhea patients. Refer to Section 7.6.1 of the IAMA for additional details.
7 DRUG INTERACTIONS	Subsection 7.1 Effect of Other Drugs on BLUJEPA: Added text for CYP3A4 inhibitors and inducers regarding patients treated for uncomplicated urogenital gonorrhea. (b) (4) " was recommended for concomitant use of a moderate CYP3A4 inhibitor and two or more risk factors.	Changed recommendation from "(b) (4) " to avoid use in patients taking moderate CYP3A4 inhibitors. See changes to subsection 5.1 QTc Prolongation of the PI described above. Refer to Sections 14.5 and 8.2.2 of the IAMA for additional details. Converted the paragraph into a table format for CYP3A4 inhibitor recommendations to clearly differentiate between the different indications (uUTI and uncomplicated urogenital gonorrhea) and different types of CYP3A4 inhibitors (strong and moderate). Separated the recommendations for CYP3A4 inducers based on the different indications. For uUTI -avoid coadministration of Blujepa with strong CYP3A4 inducers. For uncomplicated urogenital gonorrhea- avoid coadministration of Blujepa with strong and moderate CYP3A4 inducers. Refer to Sections 14.5 and 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 Margins to nonclinical studies updated based on new MRHD. Added new headings for Uncomplicated Urogenital Gonorrhea for subsections 8.4 (Pediatric Use) and 8.5 (Geriatric Use).	Subsection 8.1 Pregnancy For margins in 8.1 for nonclinical studies, margins less than one were changed from numerical to "less than the MRHD" and (b) (4) were changed to "approximately equal to the MRHD." Refer to Section 7.1 of the IAMA for additional details. Subsections 8.6 and 8.7 Added the recommendation to avoid use of BLUJEPA in uncomplicated urogenital gonorrhea patients with moderate renal impairment or moderate hepatic impairment when additional risk factors for increased exposure are present.
10 OVERDOSAGE	No edits	-
12 CLINICAL PHARMACOLOGY	Subsection 12.2 Pharmacodynamics, subheading	Subsection 12.2 Pharmacodynamics, subheading Cardiac Electrophysiology

Full PI Sections[1]	Applicant Proposed Labeling	Rationale for Major Changes Incorporated into the Finalized PI[2]
	Cardiac Electrophysiology Added text on the Cmax ratio for between the 1,800 mg IV and 3,000 mg oral doses. Subsection 12.3 Pharmacokinetics Added a column in the PK parameters table for the new dosing regimen. Subsection 12.4 Microbiology • The mechanism of action was updated to include the post-antibiotic effect of gepotidacin as 0.7 to 1 hour for *N. gonorrhoeae*. • Resistance information was updated to add that gepotidacin activity against *N. gonorrhoeae* was unrelated to beta-lactam resistance. • In vitro activity of gepotidacin against certain *N. gonorrhoeae* Multi-locus Sequence Typing was listed. • Interactions with other antimicrobials was updated to include antimicrobial drugs for which gepotidacin had no observed antagonism when used in combination against *N. gonorrhoeae*. • Antimicrobial Activity was updated to included *N. gonorrhoeae* in the first list under the indication of Uncomplicated Urogenital Gonorrhoeae.	The ratio between Cmax of the proposed dose and the Cmax obtained in the TQT study was revised from 1.7-fold to 1.2-fold for the 1500 mg dose and from 1.9-fold to 1.2-fold for the 3000 mg dose. The Cmax ratio change was updated using popPK model-predicted Cmax values for 1500 mg and 3000 mg doses, respectively, that were adjusted by a correction factor of 1.5-fold to account for the difference between observed Cmax in Phase 1 studies and the PK model-predicted Cmax. Refer to Section 5.2 and 14.5 of the IAMA for additional details. Subsection 12.3 Pharmacokinetics The Cmax reported in the Pharmacokinetic Parameters of Gepotidacin was changed from 4.2 to 6.3 mcg/mL for the 1500 mg dose and from 7.4 to 11 mcg/mL for the 3000 mg dose. Refer to Section 5.2 and 14.5 of the IAMA for additional details. The impact of body weight on gepotidacin exposure was revised from "no clinically relevant effect" to "(b) (4) [redacted]" Added the study results for moderate hepatic impairment from the dedicated hepatic study. Refer to Section 5.2 and 14.5 of the IAMA for additional details. Added PBPK modeling and simulation-informed exposure changes pertaining to drug-drug interactions (DDI). Refer to the integrated review for the original NDA dated 03/25/2025. Subsection 12.4 Microbiology: • Information was added about isolates from microbiological failures that had increases in resistance to gepotidacin from the phase 2 clinical study using an unapproved single

Full PI Sections[1]	Applicant Proposed Labeling	Rationale for Major Changes Incorporated into the Finalized PI[2]
		3000 mg dose of gepotidacin. Two isolates had mutations known to be important for gepotidacin binding to target (ParC D86N, GyrA A92T). Using the approved dosage of 3000 mg gepotidacin following by a second 3000 mg dose taken 12 hours later, no *N. gonorrhoeae* resistance to gepotidacin was observed. • (b) (4) were removed because they were not directly related to gepotidacin activity. • (b) (4) were deleted from the description of gepotidacin antimicrobial activity against *N. gonorrhoeae* if they were associated with microbiological failures or found among *N. gonorrhoeae* isolates with elevated gepotidacin MICs alone or when combined with other mutations.
13 NONCLINICAL TOXICOLOGY	Margins to nonclinical studies updated based on new MRHD.	Refer to Section 7.1 of the IAMA for additional details.
14 CLINICAL STUDIES	Added new subsection 14.2 Uncomplicated Urogenital Gonorrhea	Updated language to streamline and rearrange the description of the study design and baseline characteristics. (b) (4) were removed (b) (4) Refer to Section 6 of the IAMA for additional details.
17 PATIENT COUNSELING INFORMATION	Revised text for Diarrhea heading	No major changes
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	No changes were made to Sections 3 or 11 of the PI. Section 16 was updated to include the new presentation for the drug product (i.e., 8 tablets/bottle) and the associated NDC number.	No major changes

Source: Review Team
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row 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.
Abbreviation(s): IAMA, Integrated Assessment of Marketing Application; PI, Prescribing Information

Carton and Container labeling: Refer to the DMEPA review in DARRTS dated 11/7/2025 for details on the changes made.

Medication Guide: Refer to the Patient Labeling review in DARRTS dated 11/10/2025 for details on the changes made.

23.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide
- Container Labeling

24. Postmarketing Requirements and Commitments

The following postmarketing requirement has been requested by FDA and agreed to by the Applicant. Please refer to the approval letter for the final PMR language and timelines.

Conduct an open-label, single-arm, prospective trial for the treatment of uncomplicated gonorrhea to evaluate the safety of Blujepa (gepotidacin).

- *Draft Protocol Submission: 06/2026*
- *Final Protocol Submission: 12/2026*
- *Study Completion: 04/2029*
- *Final Report Submission: 12/2029*

25. Financial Disclosure

Table 66. Covered Clinical Studies: BTZ116577

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 342; Of note this includes 6 sub-investigators who did not complete/return their required investigator financial disclosure forms to the Sponsor.		
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): 0		
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: 0 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: FDA, Food and Drug Administration

26. References

References are denoted with footnotes.

27. Review Team

Table 67. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Christopher Davi
Nonclinical reviewer	Leah Rosenfeld
Nonclinical team leader	Amy Nostrandt
OCP reviewers	Meng Wang, Elyes Dahmane
OCP team leaders	Cristina Miglis, Justin Earp
Clinical reviewer	Rebecca Levorson
Clinical team leader	Mukil Natarajan
Biometrics reviewer	Jie Cong
Biometrics secondary reviewer	Daniel Rubin
Biometrics tertiary reviewer	Scott Komo
Clinical microbiology reviewer	Kerian Grande Roche
Clinical microbiology team leader	Avery Goodwin
Associate director for labeling	Abimbola Adebowale
Cross-discipline team leader	Mukil Natarajan
Deputy division director (pharm/tox)	Terry Miller
Division director (OCP)	Kellie Reynolds
Division director (clinical)	Peter Kim

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 68. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Juliana Quarterman, Dorota Matecka
OPDP	Qumerunnisa Syed
OSI	John Lee
OSE/DMEPA	Deborah Myers
Other	Not applicable

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis

27.1. Reviewer Signatures

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: 12/9/2025 1:45 PM EST** **GUID: 2025129184517**	

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	Mukilan Natarajan OID DAI	Sections: 1-4, 7, 10-11, 22-27	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: 12/9/2025 1:46 PM EST** **GUID: 2025129184629**	

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: 14.5.1, 23	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: 12/9/2025 1:48 PM EST** **GUID: 2025129184820**	

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: 7, 13, 23	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: 12/9/2025 1:51 PM EST** **GUID: 202512918516**	

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	Dmitri Iarikov OID DAI	Sections: 1-27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Dmitri Iarikov

Digitally signed by Dmitri Iarikov

Date: 12/9/2025 1:54 PM EST
GUID: 2025129185441

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	Meng Wang OCP DIDP	Sections: 5.1, 5.2, 6.1, 7.7.3, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Meng Wang

Digitally signed by Meng Wang

Date: 12/9/2025 1:55 PM EST
GUID: 2025129185529

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	Meng Wang OCP DIDP	Sections: 5.1, 5.2, 6.1, 7.7.3, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Meng Wang			**Digitally signed by Meng Wang** **Date: 12/9/2025 1:56 PM EST** **GUID: 2025129185650**	

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: 12/9/2025 1:59 PM EST** **GUID: 2025129185911**	

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	Avery Goodwin OID DAI	Sections: 17-19	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Avery Goodwin			**Digitally signed by Avery Goodwin** **Sign on behalf of Signing for Kerian Grande Roche.** **Date: 12/9/2025 2:00 PM EST** **GUID: 202512919031**	

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: 17-19	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: 12/9/2025 2:01 PM EST** **GUID: 202512919123**	

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	Cristina Miglis OCP DIDP	Sections: 5.1, 5.2, 6.1, 7.7.3, 8, 14, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Cristina Miglis

Digitally signed by Cristina Miglis

Date: 12/9/2025 2:02 PM EST
GUID: 202512919244

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Primary Reviewer	Ying-Hong Wang OCP DPM	Sections: 14.5.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Ying-Hong Wang

Digitally signed by Ying-Hong Wang

Date: 12/9/2025 2:10 PM EST
GUID: 202512919105 3

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: 1,2,3,7,23,25	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: 12/9/2025 2:19 PM EST** **GUID: 2025129191947**	

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 Tertiary Reviewer	Scott Komo OB DBIV	Sections: 6, 15, 16, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Scott Komo			**Digitally signed by Scott Komo** **Date: 12/9/2025 2:20 PM EST** **GUID: 202512919202**	

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: 7, 13, 23	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: 12/9/2025 2:23 PM EST** **GUID: 202512919231**	

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 Tertiary Reviewer	Abimbola Adebowale OID DAI	Sections: 23	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: 12/9/2025 2:27 PM EST** **GUID: 2025129192726**	

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	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: 12/9/2025 2:28 PM EST
GUID: 202512919287

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	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: 12/9/2025 2:28 PM EST
GUID: 2025129192842

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	Scott Komo OB DBIV	Sections: 6, 15, 16, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Scott Komo			**Digitally signed by Scott Komo Sign on behalf of Signing for Daniel Rubin Date: 12/9/2025 2:29 PM EST GUID: 2025129192948**	

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: 12	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: 12/9/2025 2:56 PM EST GUID: 2025129195618**	

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 Division Signatory	Kellie Reynolds OCP DIDP	Sections: 5; 6.1; 7.7.3; 8.1; 8.2; 14	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: 12/9/2025 3:14 PM EST
GUID: 2025129201447

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.	

Signature: Dorota Matecka

Digitally signed by Dorota Matecka

Date: 12/9/2025 7:17 PM EST
GUID: 2025121001714

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	Juliana Quarterman OPQAI DPQAIII	Sections: 9	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Juliana Quarterman			**Digitally signed by Juliana Quarterman** **Date: 12/10/2025 10:11 AM EST** **GUID: 20251210151126**	

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: 7, 13, 23	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: 12/10/2025 11:13 AM EST** **GUID: 20251210161353**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Secondary Reviewer	Yuching Yang OCP DPM	Sections: 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: 12/10/2025 11:51 AM EST** **GUID: 20251210165115**	

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: 6.1,14.5	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: 12/10/2025 1:58 PM EST** **GUID: 20251210185833**	

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
12/10/2025 01:05:43 PM

PETER W KIM
12/10/2025 02:28:53 PM