TITLE PAGE

Protocol Title: A Phase III, Randomized, Multicenter, Open-Label Study in Adolescent and Adult Participants Comparing the Efficacy and Safety of Gepotidacin to Ceftriaxone Plus Azithromycin in the Treatment of Uncomplicated Urogenital Gonorrhea Caused by *Neisseria gonorrhoeae*

Protocol Number: BTZ116577 / Amendment 3

Short Title: Phase III, Comparator-Controlled, Efficacy and Safety Study of Gepotidacin in the Treatment of Uncomplicated Urogenital Gonorrhea; Efficacy of Antibacterial Gepotidacin Evaluated (EAGLE-1)

Compound Number: GSK2140944

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Regulatory Agency Identifying Numbers:
IND 111885
EudraCT 2018-001780-23

Protocol Amendment Number: 3

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Approval Date: 10 Aug 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date of Issue**	**DNG Number**
Amendment 3	10 Aug 2023	TMF-16433266
Amendment 2	16 December 2022	TMF-15064686
Amendment 1	14 December 2021	TMF-14342295
Original Protocol	12 April 2019	2017N317989_00

Amendment 3 (10 Aug 2023)

This global amendment is considered to be non-substantial.

Overall rationale for the current Amendment:

This global amendment revised the definition of the Microbiological ITT (micro-ITT) population to align with the reporting and analysis plan; reference to EUCAST breakpoints was deleted from this population definition in accordance with regulatory agency feedback. The amendment includes wording edits based on the above changes.

Minor editorial edits have been done. Reference list has been updated as one reference was erroneously missed.

List of main change in the protocol and their rationale:

Section # and Name	**Description of Change**	**Brief Rationale**
10.3 Populations for Analyses	The definition of the Microbiological Intent-to-Treat Population has been updated.	Revisions were made to support the planned efficacy analyses per the reporting and analysis plan.
11 References	Reference list for erroneously missed reference has been updated	Reference list has been updated as one reference was erroneously missed.

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1. SYNOPSIS

Protocol Title: A Phase III, Randomized, Multicenter, Open-Label Study in Adolescent and Adult Participants Comparing the Efficacy and Safety of Gepotidacin to Ceftriaxone Plus Azithromycin in the Treatment of Uncomplicated Urogenital Gonorrhea Caused by *Neisseria gonorrhoeae*

Short Title: Phase III, Comparator-Controlled, Efficacy and Safety Study of Gepotidacin in the Treatment of Uncomplicated Urogenital Gonorrhea; Efficacy of Antibacterial Gepotidacin Evaluated (EAGLE-1)

Rationale:

Gonorrhea is the second most prevalent bacterial sexually transmitted infection globally and remains an important clinical and public health problem throughout the world. A variety of antimicrobial agents have been used over the years for the treatment of gonorrhea; however, effective treatment options for gonorrhea have diminished rapidly because of the emergence and worldwide spread of antimicrobial resistance to many drugs previously used or considered first line. Gepotidacin is a first-in-class, novel triazaacenaphthylene antibacterial that has demonstrated in vitro activity against *Neisseria gonorrhoeae* (NG) with gepotidacin MIC_{90} values of 0.25 and 1 µg/mL for ciprofloxacin-susceptible and -resistant strains, respectively. In a Phase II study of urogenital gonorrhea caused by NG, microbiological success (bacterial eradication) was demonstrated for 97% and 95% of participants treated orally with single doses of 1500 and 3000 mg gepotidacin, respectively. This Phase III study aims to evaluate oral gepotidacin compared to intramuscular (IM) ceftriaxone plus oral azithromycin, a currently recommended treatment regimen, for the treatment of uncomplicated urogenital infection caused by NG in adolescent and adult participants.

Objectives and Estimands/Endpoints:

Objectives	Endpoints
Primary • To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with uncomplicated urogenital gonorrhea caused by NG	• Culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit
Secondary • To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with rectal gonorrhea caused by NG • To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with pharyngeal gonorrhea caused by NG • To evaluate the safety and tolerability of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin	• Culture-confirmed bacterial eradication of NG from the rectal body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit • Culture-confirmed bacterial eradication of NG from the pharyngeal body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit • Treatment-emergent adverse events and serious adverse events and change from baseline results for clinical laboratory tests and vital sign measurements

Note: Exploratory objectives are described in the main protocol text.

Estimands:

The primary clinical question of interest is: What is the treatment effect on the culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit after treatment with oral gepotidacin compared to IM ceftriaxone plus oral azithromycin in participants with uncomplicated urogenital gonorrhea and have confirmed NG isolated from baseline culture of their urogenital specimen, regardless of treatment discontinuation for any reason.

The primary estimand is described by the following attributes:

- Population: Participants with uncomplicated urogenital gonorrhea caused by culture-confirmed NG.
- Treatment condition: Gepotidacin 2×3000 mg versus ceftriaxone 500 mg plus azithromycin 1 g, regardless of adherence.
- Variable: Microbiological success: Participants with culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., urogenital microbiological success) at the TOC (Day 4 to 8) Visit without the participant receiving other systemic antimicrobials before this visit.

- Summary measure: Difference in proportions (microbiological success rate in the gepotidacin treatment group - ceftriaxone plus azithromycin treatment group).
- Intercurrent events:
  - Participants who receive systemic antimicrobials before the TOC Visit will be considered microbiological failures (composite strategy).
  - For study treatment discontinuation, the data will be analyzed as collected (treatment policy strategy).

Components of estimands for all secondary endpoints are provided in Table 3.

The rationale for a treatment policy intercurrent event strategy of study treatment discontinuation is that interest lies in the treatment effect irrespective of whether the full course of treatment was taken or not, this is reflective of how patients may be treated in clinical practice.

The rationale for using a composite strategy for the intercurrent event of antimicrobial use is because usage could affect bacterial culture response; thus, a conservative approach has been adopted and if a participant receives systemic antimicrobials before the TOC Visit, the participant will be assumed to be a microbiological failure. Note: The intercurrent event of antimicrobial use is not applicable for the safety estimands.

Overall Design:

- BTZ116577 is a Phase III, open-label (sponsor-blinded), parallel-group, multicenter, comparator-controlled, noninferiority study in adolescent and adult participants comparing the efficacy and safety of oral gepotidacin to IM ceftriaxone plus oral azithromycin in the treatment of uncomplicated urogenital gonorrhea caused by NG.
- Participants will be stratified by sex and sexual orientation combination and age; and will be randomly assigned to receive either oral gepotidacin or IM ceftriaxone plus oral azithromycin.
- Appropriate safety and microbiological assessments will be conducted at the Baseline (Day 1) Visit and repeated at the TOC (Day 4 to 8) and Follow-up (Day 14 to 21) Visits.
- “Test-of-Cure” microbiological success will be defined by body site (i.e., urogenital and, as appropriate, pharyngeal and/or rectal) as culture-confirmed bacterial eradication of NG observed at the TOC (Day 4 to 8) Visit.

Number of Participants:

Approximately 620 participants will be screened and randomized to achieve approximately 400 participants with culture-confirmed urogenital gonorrhea in the Microbiological Intent-to-Treat (micro-ITT) Population, for an estimated total of 200 participants per treatment group in the micro-ITT Population. Enrollment will continue until the target number of participants in the micro-ITT Population has been reached.

Treatment Groups and Duration:

- Participants will receive 1 of the following treatments:
  - Gepotidacin: 3000 mg administered orally at the study site during the Baseline (Day 1) Visit followed by self-administration of a second oral 3000-mg dose as an outpatient 10 to 12 hours after the first dose; however, for participants who weigh <50 kg or have moderate renal impairment, the second dose should be taken approximately 12 hours after the first dose). (Note: Each dose should be taken after food consumption and with water to assist with tolerability.)
  - Ceftriaxone plus azithromycin: A single IM 500-mg dose of ceftriaxone plus a single oral 1-g dose of azithromycin administered at the study site during the Baseline (Day 1) Visit. (Note: Azithromycin should be taken after food consumption and with water.)
- The duration of study participation is approximately 21 days with 3 planned study visits:
  - Baseline (Day 1) Visit
  - TOC (Day 4 to 8) Visit
  - Follow-up (Day 14 to 21) Visit

Data Monitoring or Other Committee: Yes; an internal GSK Safety Review Team will monitor blinded safety data and an internal Microbiology Review Team will monitor blinded microbiological data instream. No external data monitoring review committees are planned for the study.

2. SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities

Visit[a]	Baseline		TOC[b]	Follow-up[c]	Early Withdrawal
Study Day	1		4 to 8	14 to 21	NA
Procedure	**Predose**	**Postdose**	**NA**	**NA**	**NA**
Written informed consent/assent	X				
IRT – Screening module	X				
Inclusion and exclusion criteria	X				
Participant demography	X				
Participant social and sexual history[d]	X				
Medical/surgical history	X				
Diagnosis of presumptive uncomplicated urogenital gonorrhea	X				
Bacteriology samples[e]	X		X	X	X
NAAT assay samples[f]	X		X	X	X
Physical examination (including height and weight at Baseline only)[g]	X		X		
12-lead electrocardiogram[h]	X				
Vital sign measurements[i]	X		X		
Hematology, chemistry, and urinalysis	X		X		
Serology (hepatitis B and C and HIV)[j]	X				
Urine pregnancy test[k]	X[k]		X		X
Drug and alcohol screen	X				
IRT – Randomization module	X				
Administer oral gepotidacin[l]		X[l]			
Administer IM ceftriaxone plus oral azithromycin[m]		X[m]			
Sexual history since last visit[d]			X	X	X
Serious adverse events[n]	X	X	X	X	X
Adverse events[o]		X	X	X	X
Concomitant medication review	X	X	X	X	X
Schedule TOC and Follow-up Visits	X[p,q]		X[q]	X[p]	
Treatment for CT and/or Mgen infection[r]			X	X	X
Genetic sample[s]	X				

CT=*Chlamydia trachomatis*; HIV=human immunodeficiency virus; IM=intramuscular; IRT; interactive response technology; Mgen=*Mycoplasma genitalium*; NA=not applicable; NAAT=nucleic acid amplification test; TOC=Test-of-Cure.

a. For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the Study Reference Manual. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit.
b. TOC (Day 4 to 8) Visit: Participants will be instructed to return to the study site within 3 to 7 days after study treatment administration. This visit may occur earlier if participants experience an adverse event.
c. Participants will be instructed to return to the study site from Day 14 to 21 for a Follow-up Visit. The investigator and/or study site staff should make every effort to ensure the participant returns for this visit. If the participant is unable to return to the study site, the visit assessments may be completed via telephone, with the exception of assessments requiring sample collection for laboratory testing.
d. Refer to the Study Reference Manual for information to collect for social and sexual history.
e. See Table 2 for collection of bacteriology samples. Also refer to the laboratory manual.
f. See Table 2 for collection of NAAT assay samples. Also refer to the laboratory manual.
g. A complete physical examination will be performed at the Baseline Visit and a gonorrhea-focused examination will be performed at the TOC Visit (see Section 9.4.1). Height and weight will only be measured and recorded at the Baseline Visit (before dosing).
h. See Section 6.2 for electrocardiogram exclusion criterion for participants aged ≥12 to <18 years. For additional details see Section 8.1.2 and Section 9.4.3.
i. Take measurement of temperature, blood pressure, and pulse rate. See Section 9.4.2.
j. If serology testing was performed within 3 months prior to the first dose of study treatment and results were **positive**, testing at Baseline **is not required**. If testing was performed within 3 months and any result was **negative**, testing at Baseline **is required**.
k. For women of childbearing potential, a negative urine pregnancy test is sufficient for eligibility. See Appendix 6 for Baseline urine test sensitivity requirements and associated contraception requirements.
l. During the Baseline Visit, participants randomly assigned to gepotidacin will receive their first oral dose (3000 mg) at the study site. Participants will self-administer their second dose (3000 mg) as an outpatient 10 to 12 hours after the first dose; however, for participants who weigh <50 kg or have moderate renal impairment, the second dose should be taken approximately 12 hours after the first dose). See Section 7.1. Each dose should be taken after food consumption and with water to assist with tolerability. Participants will be contacted to confirm that they took their second gepotidacin dose. See Section 7.6.
m. During the Baseline Visit, participants randomly assigned to ceftriaxone plus azithromycin will receive a single IM dose of ceftriaxone (500 mg) plus a single oral dose of azithromycin (1 g). See Section 7.1. Azithromycin should be taken after food consumption and with water.
n. Record serious adverse events from the time of consent/assent in order to fulfill international regulatory requirements.
o. Record adverse events from the time of the first dose of study treatment.
p. Confirm return day/time for the TOC and Follow-up Visits.
q. Previsit reminder: Study site staff will contact the participant 24±4 hours before the respectively scheduled Baseline (if applicable), TOC, or Follow-up Visit.
r. Participants who tested positive for CT and/or Mgen per NAAT results at the Baseline Visit should be treated per local standard of care at or after the TOC Visit or at the Follow-up Visit (if treatment has not already been initiated), as required, after all study procedures at the visit have been completed.
s. Collect sample only if the participant has a signed consent/assent specific for this purpose. The Baseline Visit is the recommended time to collect the sample; however, it can be collected at any time during the study.

Table 2 Collection of Bacteriology and NAAT Microbiological Specimens

Visit	Baseline	TOC[a]	Follow-up	Early Withdrawal
Study Day	**1**	**4 to 8**	**14 to 21**	**NA**
Collection Type **Anatomical Site[b] – Organism**	**Predose**	**NA**	**NA**	**NA**
Bacteriology sample collection[b]				
Urogenital – NG[c]	X	X		X
Pharyngeal – NG[d]	X	X	X[e]	X
Rectal – NG[d]	X	X		X
NAAT assay sample collection[f]				
Urogenital – NG and CT[g]	X	X[h]		X
Urogenital – Mgen[g]	X		X[i]	X
Pharyngeal – NG and CT[j]	X	X	X[k]	X
Rectal – NG and CT[j]	X	X		X

CT=*Chlamydia trachomatis*; Mgen=*Mycoplasma genitalium*; NA=not applicable; NAAT=nucleic acid amplification test; NG=*Neisseria gonorrhoeae*; TOC=Test-of-Cure.

a. Any participant that withdraws before TOC should have all bacteriology and NAAT assay collections performed as indicated at the TOC Visit.
b. Multiple swab specimens and types may need to be obtained from each anatomical site; refer to the laboratory manual.
c. Collect a pretreatment urogenital swab specimen from all participants for Gram stain (males and females), bacterial culture, and in vitro susceptibility testing at Baseline. At TOC, a urogenital swab specimen will be collected for Gram stain, bacterial culture, and in vitro susceptibility testing. Note: **All** urogenital swab specimens will be processed for Gram stain testing following inoculation of the culture plates.
d. Pretreatment rectal and pharyngeal swab specimens for bacterial culture and in vitro susceptibility testing will be obtained from participants who are willing to provide such specimens, regardless of known exposure. At TOC, swab specimens will be collected from pharyngeal and/or rectal sites that were collected at Baseline for bacterial culture and in vitro susceptibility testing. Note: **None** of the rectal or pharyngeal swab specimens will be processed for Gram stain testing.
e. At Follow-up, pharyngeal swab specimens will be obtained for bacterial culture and in vitro susceptibility testing from participants who had a positive NAAT assay for pharyngeal NG at **both** Baseline and TOC. Results from the NAAT assay will be available to the study sites by the Follow-up Visit.
f. See the laboratory manual for local versus central laboratory details and the number and type of specimens to collect.
g. Pretreatment baseline urogenital specimens will be obtained from all participants for detection of NG, Mgen, and CT by NAAT. At Baseline, while detection of NG and CT by NAAT may be performed using the same urogenital sample, 2 separate samples must be obtained (1 for the local laboratory and 1 for the central laboratory).
h. Urogenital specimens will be obtained from all participants for detection of NG and CT by NAAT at the TOC Visit.
i. At Follow-up, a urogenital specimen will be collected for the detection of Mgen only by NAAT from participants who had a positive NAAT assay for Mgen at Baseline. Results from the NAAT assay will be available to the study sites by the Follow-up Visit.
j. Pretreatment baseline pharyngeal and rectal specimens for detection of NG and CT by NAAT will be obtained from participants who are willing to provide such specimens, regardless of known exposure. At TOC, a specimen will be collected from pharyngeal and/or rectal sites that were collected at Baseline.
k. At Follow-up, a pharyngeal specimen will be collected for detection of NG and CT by NAAT from participants whose NAAT assay had the presence of nucleic acid for NG at **both** Baseline and TOC. NAAT assay results will be available to the study sites by the Follow-up Visit.

3. INTRODUCTION

Gepotidacin (GSK2140944) is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action [Gibson, 2019; Bax, 2010] and equally and independently binds to 2 different type II topoisomerase enzymes [Oviatt, 2022].

This provides activity against most strains of *Escherichia coli* and *Staphylococcus saprophyticus*, including isolates resistant to current antibiotics [Biedenbach, 2016; Mushtaq, 2019]. Due to the equal and independent binding at both enzymes, mutations in both enzymes are needed to significantly affect gepotidacin susceptibility [Oviatt, 2022].

Gepotidacin has been evaluated in Phase II studies for the treatment of ABSSSIs, uncomplicated urogenital gonorrhea, and uncomplicated UTI. Phase III studies are ongoing to evaluate oral gepotidacin for the treatment of uncomplicated urogenital gonorrhea and uncomplicated UTI (acute cystitis).

Gepotidacin selectively inhibits bacterial DNA replication by interacting in a unique way on the GyrA subunit of bacterial DNA gyrase and the ParC subunit of bacterial topoisomerase IV. This interaction appears to be highly specific to bacterial topoisomerases as evidenced by weak in vitro inhibition of human topoisomerase IIα, supporting the selective activity of gepotidacin against the bacterial target. The novel mode of action of this new class antibacterial affords in vitro activity against most target pathogens resistant to established antibacterials, including fluoroquinolones.

3.1. Study Rationale

This study is being conducted based on the need to identify new and effective antibiotic treatment options for gonorrhea as antimicrobial resistance continues to rise worldwide (see Section 3.2) and based on the results of an open-label, dose-ranging Phase II study of gepotidacin for the treatment of adults with uncomplicated urogenital gonorrhea caused by NG.

Study BTZ116576 was a Phase II, randomized, multicenter, open-label, dose-ranging study evaluating the efficacy, safety, and tolerability of gepotidacin therapy in adult participants with uncomplicated urogenital gonorrhea caused by NG. Participants were administered single oral doses (1500 or 3000 mg) of gepotidacin on Day 1 with a Test-of-Cure (TOC) (Day 4 to 8) Visit. A total of 69 participants (1500 mg: 30 participants; 3000 mg: 39 participants) were included in the Microbiologically Evaluable Population. The primary aim of the study was to provide evidence for 95% bacterial eradication of urogenital NG in the Microbiologically Evaluable Population at the TOC Visit (cure rate) and to exclude the null hypothesis that the cure rate was 80% or less. Microbiological success was achieved by 97% and 95% of participants (lower 1-sided exact 95% confidence interval [CI] bound, 85.1% and 84.7%, respectively) in the 1500- and 3000-mg treatment groups, respectively. Microbiological success (bacterial eradication) was also evaluated for pharyngeal and rectal NG, with 1 of the 2 participants with pharyngeal NG and all 3 participants with rectal NG achieving microbiological success. In Study BTZ116576, gepotidacin was active in vitro

against the 69 baseline urogenital NG isolates recovered, with a gepotidacin minimum inhibitory concentration (MIC) range of ≤0.06 to 1 µg/mL and 50th and 90th percentile minimum inhibitory concentration (MIC_{50} and MIC_{90}) values of 0.12 and 0.5 µg/mL, respectively. Additional study results demonstrated that some baseline urogenital NG isolates were resistant to ciprofloxacin, penicillin, and/or tetracycline.

This Phase III study (BTZ116577) aims to evaluate oral gepotidacin compared to intramuscular (IM) ceftriaxone plus oral azithromycin, a currently recommended treatment regimen, for the treatment of uncomplicated urogenital infection caused by NG in adolescent and adult participants.

3.2. Background

Gonorrhea is the second most prevalent bacterial sexually transmitted infection globally and remains an important clinical and public health problem throughout the world. In 2012, an estimated 78 million cases of gonorrhea occurred among 15- to 49-year-olds worldwide with a global incidence rate of 19 per 1000 females and 24 per 1000 males [WHO, 2016]. Gonococcal infections following sexual and perinatal transmission are a major source of morbidity worldwide [Barry, 2009]. Infections can involve cervicitis, proctitis, urethritis, pelvic inflammatory disease, and pharyngitis. Complications include infertility, ectopic pregnancy, chronic pelvic pain, adverse outcomes of pregnancy, disseminated gonococcal infection, and increased susceptibility to and transmission of human immunodeficiency virus [Workowski, 2008; Barry, 2009].

A variety of antimicrobial agents have been used over the years for the treatment of gonorrhea; however, effective treatment options for gonorrhea have diminished rapidly because of the emergence and worldwide spread of antimicrobial resistance to many drugs previously used or considered first line, i.e., penicillins, narrow-spectrum cephalosporins, tetracyclines, macrolides, and fluoroquinolones [Workowski, 2008; Barry, 2009]. At the start of the present study, the recommended treatment for urogenital gonorrhea per the European Union, United States (Centers for Disease Control and Prevention [CDC]), and World Health Organization (WHO) guidelines is an IM injection of ceftriaxone combined with a single oral dose of azithromycin [Bignell, 2013; CDC, 2015; WHO, 2016]. As of Dec 2020, the CDC now recommends an IM injection of ceftriaxone based on body weight and an oral regimen of doxycycline if chlamydia infection has not been ruled out [CDC, 2021]. While these guidelines may help delay the emergence of cephalosporin-resistant gonorrhea by using combination antibacterial therapy, they are not able to eliminate this impending threat. Therefore, drug-resistant NG has been labeled at a threat level of urgent by the CDC and as a high priority by WHO; both agencies have urged scientists and private sector drug developers to prioritize the identification and study of new, effective antibiotic treatment options for gonorrhea [CDC, 2019; CDC, 2015; WHO, 2017].

Gepotidacin is a first-in-class, novel triazaacenaphthylene antibacterial that has demonstrated in vitro activity against NG with gepotidacin MIC_{90} values of 0.25 and 1 µg/mL for ciprofloxacin-susceptible and -nonsusceptible strains, respectively (see Section 4.2.1.3 in the investigator's brochure [IB]). In a Phase II study of uncomplicated urogenital gonorrhea caused by NG, microbiological success (bacterial eradication) was demonstrated for 97% and 95% of participants treated orally with single doses of 1500 and 3000 mg gepotidacin, respectively. With its unique ability to selectively inhibit bacterial DNA replication by a means not utilized by any currently approved human therapeutic agent, gepotidacin warrants further study in order to address an unmet medical need by providing a new and effective oral treatment option for gonorrhea.

A detailed description of the chemistry, pharmacology, efficacy, and safety of gepotidacin is provided in the IB. Details on the active comparator in this study, ceftriaxone plus azithromycin, may be found in locally approved prescribing information.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) may be found in the IB for gepotidacin and in locally approved prescribing information for ceftriaxone and azithromycin.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gepotidacin (GSK2140944)		
Cardiovascular Effects Based on nonclinical data, cardiovascular effects were reversible increase in heart rate and blood pressure (dog and monkey); reversible 10 to 21 msec (4% to 9%) increase in QTc (monkey); and at the highest dose, a reversible 2 to 3 msec (6% to 8%) increase in QRS (monkey). Based on a thorough QTc clinical study, gepotidacin may cause mild, reversible heart rate effects and QT prolongation.	In a thorough QTc study, infusion of gepotidacin at doses of 1000 and 1800 mg over 2 hours caused a mild increased heart rate effect of approximately 6 to 10 bpm and QT prolongation measured as ΔΔQTcF of 12 to 22 msec. The QT prolongation evolved during the infusion and was quickly reversed over 2 hours after the end of the infusion (see Section 5.2.6 and Section 6 of the IB). In Phase I and II studies, concentration-dependent QT prolongation has been observed during clinical trials with gepotidacin; however, this increase has not translated into medically significant QTc values or changes from baseline (QTcF >500 msec or change from baseline >60 msec) or cardiovascular safety concerns. In Phase I and II studies, gepotidacin did not have a clinically relevant effect on cardiac conduction (PR and QRS intervals).	See Section 6.2 for excluded cardiac conditions. Close monitoring of clinical parameters and AEs (Section 2, Table 1) will be conducted, and treatment monitoring and evaluation criteria (Section 8.1.2) will be utilized to mitigate cardiovascular effects. Participants taking medications known to increase QT or potent CYP3A4 inhibitors will be excluded (Section 7.7.2). See also the Hepatic and Renal sections within this table below.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal Effects Based on nonclinical data, gastrointestinal effects were mild ulceration of the nonglandular mucosa and minimal erosion and/or mural inflammation of the glandular mucosa in stomach (rat, oral study); moderate cecal ulceration and minimal colonic erosion (rat, IV study); and vomiting (dog). Lower gastrointestinal effects (soft stools, flatulence, and diarrhea) are among the most common AEs reported in gepotidacin clinical studies. Nausea and vomiting AEs have also been commonly observed in gepotidacin clinical studies.	See also the Acetylcholinesterase Inhibition section within this table below. *Clostridium difficile*-associated diarrhea has been observed in clinical trials with gepotidacin.	See Section 6.2 for excluded medical conditions. Close monitoring of clinical parameters and AEs (Section 2, Table 1) will be conducted to mitigate and assess gastrointestinal effects. Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Appendix 10.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Acetylcholinesterase Inhibition In vitro testing showed gepotidacin to be a rapidly reversible inhibitor of acetylcholinesterase in the clinical plasma concentration range. Based on clinical data, caution should be used in participants who have a condition requiring treatment with anticholinergic medications or who have certain medical conditions that may be exacerbated by the acetylcholinesterase inhibition activity of gepotidacin.	Increased cholinergic effects can potentially be associated with more severe symptoms including atrioventricular block, seizure/convulsions, bronchospasm, and vasovagal syncope. No causal relationship between these events and the use of gepotidacin has been established during clinical trials to date. Adverse events possibly consistent with acetylcholinesterase inhibition, including diarrhea, nausea, vomiting, gastrointestinal cramping and pain, dyspnea, bradycardia, lacrimation, salivation, dysarthria, and diaphoresis/sweating have been reported during clinical trials with gepotidacin. The majority of these AEs have been mild and transient and have been reported in clinical trials with comparable Cmax levels expected in this study.	Participants who have medical conditions or require medications that may be impacted by inhibition of acetylcholinesterase will be excluded from participation in this study. See Section 6.2, for excluded medical conditions and Section 7.7.2, Prohibited Medications and Nondrug Therapies, for prohibited medications. Close monitoring of clinical parameters and AEs will be conducted to assess effects potentially related to acetylcholinesterase inhibition (Section 2, Table 1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatic Effects In preclinical studies, increases in ALT, GLDH, alkaline phosphatase, and total bilirubin were observed in some rat studies of varying exposure.	Elevations in ALT have occurred in a few participants with pre-existing hepatitis C infection, but none were felt related to study treatment. The type and pattern of elevation in liver transaminases observed has not been suggestive of an adverse effect of gepotidacin and none were considered related to study treatment. A substantial increase in Cmax and AUC and decrease in clearance was observed in volunteer participants with severe hepatic impairment.	Participants with severe hepatic impairment are excluded from Phase III trials. See Section 6.2 for excluded medical conditions. Monitoring and stopping criteria liver events have been implemented.
Renal Effects In preclinical trials, mild to moderate tubular degeneration was noted in the rat and proteinuria in the dog. Proteinuria was also observed in humans.	No clinical evidence of renal toxicity has been seen in clinical trials to date. A substantial increase in Cmax and AUC and decrease in clearance was observed in severe renal impairment/ESRD participants not on hemodialysis and in ESRD participants requiring hemodialysis (note: gepotidacin may have been administered at any time other than when receiving dialysis).	Participants with severe renal impairment/ESRD (including those who may require dialysis) are excluded from Phase III trials. See Section 6.2 for excluded medical conditions. Monitoring criteria have been implemented.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Reproductive System Effects Preclinical studies demonstrated that gepotidacin was not genotoxic and no drug-related malformations were observed. Although positive in vitro findings for clastogenicity, consistent with a mechanism related to mammalian topoisomerase II inhibition were found, in vivo data from rat micronucleus and COMET assays suggest that gepotidacin does not pose a genotoxic hazard to humans. Gepotidacin effects on embryofetal development were limited to decreased fetal weights for male and female fetuses in rats and decreased fetal weights and increased fetal resorptions (fetal deaths) in mice, both at maternally toxic doses. These occurred at clinically relevant exposures (65 µg.h/mL in rat and 35 µg.h/mL in mouse).	There are no data on the use of gepotidacin in pregnant women.	Gepotidacin is not recommended in pregnant or nursing mothers. Pregnancy testing requirements in this study minimize the risk of exposure to a fetus. See Appendix 6 for contraceptive measures and for required pregnancy testing.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
Ceftriaxone	Intramuscular administration of ceftriaxone may be associated with local injection site reactions, including pain, warmth or induration, or tenderness. Some of the risks summarized for gepotidacin also apply to ceftriaxone, including the occurrence of gastrointestinal effects (diarrhea or loose stools) and the need to monitor for *C. difficile*-associated diarrhea. Other adverse effects include hepatic (AST and ALT elevations) and hematologic (eosinophilia, thrombocytosis, and leukopenia). Additionally, ceftriaxone should not be reconstituted using diluents containing calcium, such as Ringer's solution or Hartmann's solution, because a precipitate can form. Refer to the locally approved ceftriaxone prescribing information for specific details relating to ceftriaxone.	Close monitoring of clinical parameters and AEs (Section 2, Table 1) will be conducted, and treatment monitoring and evaluation criteria (Section 8.1.1) will be utilized to mitigate hepatic effects. Participants with a history of sensitivity to ceftriaxone, or components thereof, will not be allowed to enroll in the study (Section 6.2). Participant's medical history will be carefully evaluated for a history of hypersensitivity. Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Appendix 10. Precautions related to ceftriaxone solution preparation are included in Section 7.5 and summarized in detail in the Study Reference Manual.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Azithromycin	Some of the risks summarized for gepotidacin also apply to azithromycin, including the occurrence of gastrointestinal effects (diarrhea or loose stools) and the need to monitor for *C. difficile*-associated diarrhea and prolongation of the QT interval. Azithromycin may also exacerbate muscle weakness in participants with myasthenia gravis. Other adverse effects include allergic and skin reactions and hepatotoxicity, which may be serious (including fatal).	Close monitoring of clinical parameters and AEs (Section 2, Table 1) will be conducted. Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Appendix 10. See Section 6.2 for excluded cardiac conditions. Monitoring and evaluation criteria (Section 8.1.2) will be utilized to mitigate cardiovascular effects. In addition, participants taking QT-prolonging drugs or strong CYP3A4 inhibitors will be excluded. Participants with myasthenia gravis will be excluded. Participants with a history of sensitivity to azithromycin, erythromycin, and any macrolide or ketolide drug will be excluded (Section 6.2). Participant's medical history will be carefully evaluated for a history of hypersensitivity. Participants with a history of cholestatic jaundice or hepatic dysfunction associated with prior use of azithromycin will be excluded (Section 6.2). Treatment monitoring and evaluation criteria (Section 8.1.1) will be utilized to mitigate hepatic effects.

bpm=beats per minute; ABSSSI=acute bacterial skin and skin structure infection; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the drug concentration-time curve; Cmax=maximum concentration; CYP3A4=cytochrome P450 enzyme 3A4; ECG=electrocardiogram; ESRD=end-stage renal disease; GLDH=glutamate dehydrogenase; IC_{50}=inhibitory concentration inhibiting 50% of microbial isolates; IB=investigator's brochure; IV=intravenous; ΔΔQTcF=placebo-corrected change from baseline in corrected QT interval using the Fridericia formula; QTc=corrected QT interval; QTcB=QT interval corrected for heart rate according to Bazett; QTcF=interval corrected for heart rate according to Fridericia.

3.3.2. Benefit Assessment

Given the results of the previous Phase II study in adult participants with uncomplicated urogenital gonorrhea and the demonstrated in vitro activity of gepotidacin against NG, including ciprofloxacin-resistant strains (see Section 3.1 and Section 4.2.1.1 in the IB), as well as human safety data and the pharmacokinetic (PK) profile, it is anticipated that gepotidacin will benefit participants with uncomplicated urogenital gonorrhea.

The active comparator in this study is ceftriaxone plus azithromycin, both of which are marketed antibiotics that have demonstrated effectiveness for eradication of NG and *Chlamydia trachomatis* (CT), respectively (refer to locally approved ceftriaxone and azithromycin prescribing information). Participants randomly assigned to this treatment group are also expected to experience treatment benefits.

It is expected that gepotidacin will have a similar efficacy profile to ceftriaxone plus azithromycin and may have a better tolerability profile, as gepotidacin will be administered orally and ceftriaxone will be administered IM, possibly resulting in fewer treatment-related AEs associated with oral gepotidacin dose administration.

Overall, all participants in this study will not only receive routine medical monitoring for uncomplicated urogenital gonorrhea, but they will also receive heightened monitoring, including detection and treatment of any co-occurring infections caused by CT or *Mycoplasma genitalium* (Mgen), to ensure safety when participating in a clinical study.

3.3.3. Overall Benefit:Risk Conclusion

The ability of NG to develop resistance to antimicrobials has complicated the management of treatment for gonorrhea, leading to an urgent need for new treatment options [CDC, 2015; WHO, 2016]. However, even in the face of increasing drug resistance to existing agents, few new antibiotics with novel mechanisms of action are being developed. Gepotidacin selectively inhibits bacterial DNA replication by a means not utilized by any currently approved human therapeutic agent. Clinical results from a Phase II study in adult participants showed that gepotidacin is an effective treatment for uncomplicated urogenital gonorrhea, including most ciprofloxacin-resistant strains. Gepotidacin, therefore, represents a potential new oral treatment option for gonorrhea and an opportunity to address an unmet medical need.

None of the potential or identified risks seen to date in participants dosed with gepotidacin preclude further clinical development. Mitigation strategies have been implemented to promptly identify and appropriately address risks in order to protect participant safety and to better characterize the safety profile of the study treatments (see Section 3.3.1). Furthermore, an internal GSK Safety Review Team (SRT) will monitor blinded safety data instream. Careful safety monitoring should also identify any emerging safety issues for gepotidacin and contribute to the benefit-risk profile of ceftriaxone plus azithromycin.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with gepotidacin and ceftriaxone plus azithromycin are justified by the anticipated benefits that may be afforded to participants with uncomplicated urogenital gonorrhea caused by NG.

4. OBJECTIVES AND ESTIMANDS/ENDPOINTS

Objectives	Endpoints
Primary • To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with uncomplicated urogenital gonorrhea caused by NG	• Culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit
Secondary • To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with rectal gonorrhea caused by NG • To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with pharyngeal gonorrhea caused by NG • To evaluate the safety and tolerability of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin	• Culture-confirmed bacterial eradication of NG from the rectal body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit • Culture-confirmed bacterial eradication of NG from the pharyngeal body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit • Treatment-emergent AEs and serious AEs (SAEs) and change from baseline results for clinical laboratory tests and vital sign measurements
Exploratory • To assess the clearance or persistence of NG nucleic acid (by nucleic acid amplification test [NAAT] assay) from urogenital specimens for oral gepotidacin compared to IM ceftriaxone plus oral azithromycin	• Urogenital NG NAAT results at the TOC (Day 4 to 8) Visit
• To assess the clearance or persistence of NG nucleic acid (NAAT assay) from pharyngeal specimens for oral gepotidacin compared to IM ceftriaxone plus oral azithromycin	• Pharyngeal NG NAAT results at the TOC (Day 4 to 8) and Follow-up (Day 14 to 21) Visits, where only participants who did not receive other systemic antimicrobials at or after the TOC (Day 4 to 8) Visit will be evaluated at the Follow-up Visit
• To assess the clearance or persistence of NG nucleic acid (NAAT assay) from rectal specimens for oral gepotidacin compared to IM ceftriaxone plus oral azithromycin	• Rectal NG NAAT results at the TOC (Day 4 to 8) Visit

Objectives	Endpoints
• To assess the clearance or persistence of Mgen nucleic acid (by NAAT assay) from urogenital specimens for oral gepotidacin compared to IM ceftriaxone plus oral azithromycin	• Urogenital Mgen NAAT results at the Follow-up (Day 14 to 21) Visit, where only participants who did not receive other systemic antimicrobials at or after the TOC (Day 4 to 8) Visit will be evaluated
• To evaluate the microbiological characteristics and antimicrobial susceptibility profile of NG from urogenital, pharyngeal, or rectal specimens	• Gram stain (urogenital specimens only), bacterial culture, and in vitro susceptibility test results from urogenital, pharyngeal, or rectal specimens at the Baseline (Day 1), TOC (Day 4 to 8), and Follow-up (Day 14 to 21) Visits, as data permit

Estimands:

The primary clinical question of interest is: What is the treatment effect on the culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit after treatment with oral gepotidacin compared to IM ceftriaxone plus oral azithromycin in participants with uncomplicated urogenital gonorrhea and have confirmed NG isolated from baseline culture of their urogenital specimen, regardless of treatment discontinuation for any reason.

Prespecified estimands with related attributes are presented in Table 3 for the primary and key secondary objectives.

Table 3 Estimands

Estimand Category	Estimand				
	Variable/Endpoint	**Population**	**Treatment Condition**	**Summary Measure**	**Intercurrent Event Strategy**
Primary Objective: To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with uncomplicated urogenital gonorrhea caused by NG					
Primary	Microbiological success: Participants with culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., urogenital microbiological success) at the TOC (Day 4 to 8) Visit without the participant receiving other systemic antimicrobials Refer to Table 5 for further details on the endpoint definition, including the missing data strategy for participants who do not return for the TOC Visit	Participants with uncomplicated urogenital gonorrhea caused by culture-confirmed NG	Gepotidacin 2×3000 mg versus Ceftriaxone 500 mg plus azithromycin 1 g, regardless of adherence	Difference in proportions (microbiological success rate in the gepotidacin treatment group - ceftriaxone plus azithromycin treatment group)	Participants who receive systemic antimicrobials before the TOC Visit will be considered microbiological failures (composite strategy) For study treatment discontinuation, the data will be analyzed as collected (treatment policy strategy)

Estimand Category	Estimand				
	Variable/Endpoint	**Population**	**Treatment Condition**	**Summary Measure**	**Intercurrent Event Strategy**
Secondary Objective: To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with rectal gonorrhea caused by NG					
Secondary	Participants with culture-confirmed bacterial eradication of NG from the rectal body site (i.e., rectal microbiological success) at the TOC (Day 4 to 8) Visit without the participant receiving other systemic antimicrobials Refer to Table 5 for further details on the endpoint definition, including missing data strategy for participants who do not return for the TOC Visit	Participants with uncomplicated urogenital and rectal gonorrhea caused by culture-confirmed NG	Gepotidacin 2×3000 mg versus Ceftriaxone 500 mg plus azithromycin 1 g, regardless of adherence	Difference in proportions (microbiological success rate in the gepotidacin treatment group - ceftriaxone plus azithromycin treatment group)	Participants who receive systemic antimicrobials before the TOC Visit will be considered microbiological failures (composite strategy) For study treatment discontinuation, the data will be analyzed as collected (treatment policy strategy)

Estimand Category	Estimand				
	Variable/Endpoint	**Population**	**Treatment Condition**	**Summary Measure**	**Intercurrent Event Strategy**
Secondary Objective: To evaluate the efficacy of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin to treat participants with pharyngeal gonorrhea caused by NG					
Secondary	Participants with culture-confirmed bacterial eradication of NG from the pharyngeal body site (i.e., pharyngeal microbiological success) at the TOC (Day 4 to 8) Visit without the participant receiving other systemic antimicrobials Refer to Table 5 for further details on the endpoint definition, including the missing data strategy for participants who do not return for the TOC Visit	Participants with uncomplicated urogenital and pharyngeal gonorrhea caused by culture-confirmed NG	Gepotidacin 2×3000 mg versus Ceftriaxone 500 mg plus azithromycin 1 g, regardless of adherence	Difference in proportions (microbiological success rate in the gepotidacin treatment group - ceftriaxone plus azithromycin treatment group)	Participants who receive systemic antimicrobials before the TOC Visit will be considered microbiological failures (composite strategy) For study treatment discontinuation, the data will be analyzed as collected (treatment policy strategy)

Estimand Category	Estimand				
	Variable/Endpoint	**Population**	**Treatment Condition**	**Summary Measure**	**Intercurrent Event Strategy**
Secondary Objective: To evaluate the safety and tolerability of oral gepotidacin compared to IM ceftriaxone plus oral azithromycin					
Secondary (Safety)	Treatment-emergent AEs and serious AEs and change from baseline results for clinical laboratory tests and vital sign measurements	Participants with uncomplicated urogenital gonorrhea	Gepotidacin 2×3000 mg versus Ceftriaxone 500 mg plus azithromycin 1 g, regardless of adherence	The proportions for treatment-emergent AEs and serious AEs will be produced for each arm **separately**. The means for change from baseline results (clinical laboratory results and vital sign measurements) will be produced for each arm **separately**.	For study treatment discontinuation, the data will be analyzed as collected (treatment policy strategy)

AE=adverse events; NG=*Neisseria gonorrhoeae*; TOC=Test-of-Cure.

The rationale for a treatment policy intercurrent event strategy of study treatment discontinuation is that interest lies in the treatment effect irrespective of whether the full course of treatment was taken or not, this is reflective of how patients may be treated in clinical practice.

The rationale for using a composite strategy for the intercurrent event of antimicrobial use is because usage could affect bacterial culture response; thus, a conservative approach has been adopted and if a participant receives systemic antimicrobials before the TOC Visit, the participant will be assumed to be a microbiological failure. Note: The intercurrent event of antimicrobial use is not applicable for the safety estimands.

5. STUDY DESIGN

5.1. Overall Design

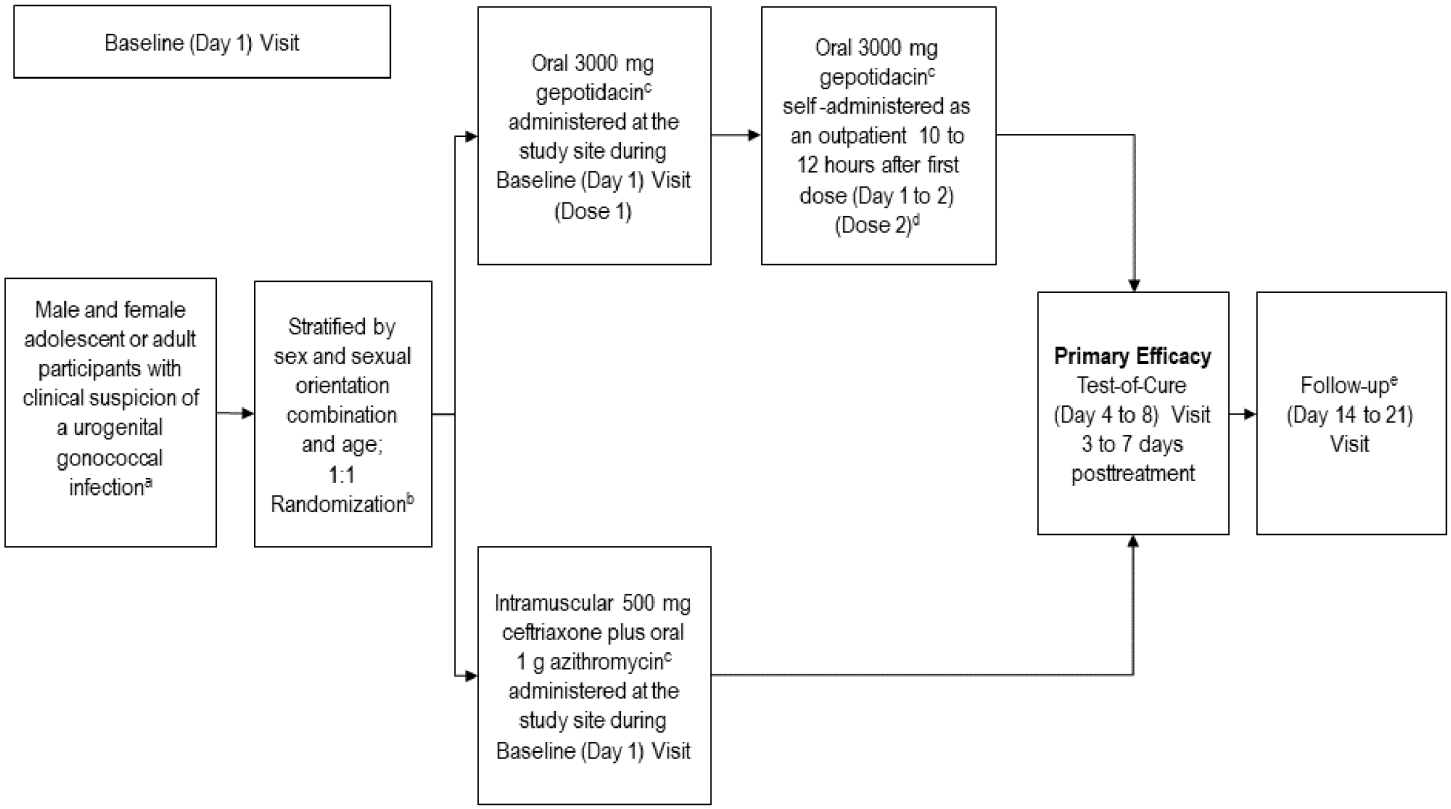
- BTZ116577 is a Phase III, open-label (sponsor-blinded), parallel-group, multicenter, comparator-controlled, noninferiority study in adolescent and adult participants comparing the efficacy and safety of oral gepotidacin to IM ceftriaxone plus oral azithromycin in the treatment of uncomplicated urogenital gonorrhea caused by NG.
- Participants will be stratified by sex and sexual orientation combination (men who have sex with men [MSM], men who have sex with women [MSW], or female) and age (<18 years, ≥18 to 65 years, or >65 years). The MSM category will include MSM and bisexual males (i.e., male participants who have sex with both males and females). Participants will be randomly assigned to receive 1 of the following treatments (see Section 7.1):
  - Gepotidacin: 3000 mg administered orally at the study site during the Baseline (Day 1) Visit followed by self-administration of a second oral 3000-mg dose as an outpatient 10 to 12 hours after the first dose; however, for participants who weigh <50 kg or have moderate renal impairment, the second dose should be taken approximately 12 hours after the first dose. (Note: Each dose should be taken after food consumption and with water to assist with tolerability.)
  - Ceftriaxone plus azithromycin: A single IM 500-mg dose of ceftriaxone plus a single oral 1-g dose of azithromycin administered at the study site during the Baseline (Day 1) Visit. (Note: Azithromycin should be taken after food consumption and with water.)
- Appropriate safety and microbiological assessments will be conducted at the Baseline (Day 1) Visit and repeated at the TOC (Day 4 to 8) and Follow-up (Day 14 to 21) Visits.
- "Test-of-Cure" microbiological success will be defined by body site (i.e., urogenital and, as appropriate, pharyngeal and/or rectal) as culture-confirmed bacterial eradication of NG observed at the TOC (Day 4 to 8) Visit, which is 3 to 7 days posttreatment per Food and Drug Administration (FDA) guidance [DHHS, 2015].
- Participants may return to the study site before the TOC Visit due to AEs.

- Participants who test positive for a CT and/or Mgen infection per baseline NAAT results should be treated per local standard of care at or after the TOC Visit or at the Follow-up Visit (if treatment has not already been initiated), as required, after all study procedures at the visit have been completed (see Section 7.8).
- Participants will be instructed to return to the study site anytime from Day 14 to 21 for a Follow-up Visit. The investigator and/or study site staff should make every effort to ensure a participant returns for this visit. If it is determined that the participant is unable to return to the study site, the Follow-up Visit assessments may be completed via telephone, with the exception of assessments requiring sample collection for laboratory testing (see Table 1).
- The duration of study participation is approximately 21 days with 3 planned study visits (see Section 9 for study visit details):
  - Baseline (Day 1) Visit
  - TOC (Day 4 to 8) Visit
  - Follow-up (Day 14 to 21) Visit

A study design schematic is depicted in Figure 1.

Refer to Appendix 11 for details regarding allowed revisions to study conduct and/or monitoring due to coronavirus disease (COVID-19). For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the Study Reference Manual (SRM). Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit.

Figure 1 Study Design Schematic



a. Refer to Inclusion Criterion #2 for details regarding urogenital gonococcal infection eligibility requirements.
b. Stratification will be performed before randomization to ensure that treatment groups are balanced with regard to sex and sexual orientation combination and age.
c. Study treatment will be administered under open-label conditions. All doses of oral study treatment should always be taken after food consumption and with water.
d. Participants randomly assigned to gepotidacin will self-administer their second dose (3000 mg) as an outpatient 10 to 12 hours after the first dose; however, for participants who weigh <50 kg or have moderate renal impairment, the second dose should be taken approximately 12 hours after the first dose.
e. Participants will return to the study site anytime from Day 14 to 21 for a Follow-up Visit. The investigator and/or study site staff should make every effort to ensure a participant returns for this visit. If it is determined that a participant is unable to return to the study site, the Follow-up Visit assessments may be completed via telephone, with the exception of assessments requiring sample collection for laboratory testing.

5.2. Number of Participants

Approximately 620 participants will be screened and randomized to achieve approximately 400 participants with culture-confirmed urogenital gonorrhea in the Microbiological Intent-to-Treat (micro-ITT) Population, for an estimated total of 200 participants per treatment group in the micro-ITT Population. Enrollment will continue until the target number of participants in the micro-ITT Population has been reached.

5.3. Participant and Study Completion

A participant is considered to have completed study treatment if he or she has taken all doses of the randomly assigned study treatment and completed the TOC Visit. A participant is considered to have completed the study if he or she has completed all study visits including the Follow-up Visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

The study design follows the FDA guidance for industry for developing drug treatments for uncomplicated gonorrhea [DHHS, 2015] and the European Medicines Agency (EMA) guideline on the evaluation of medicinal products indicated for treatment of bacterial infections [EMA, 2011].

The selected gepotidacin dose in this study (oral 3000-mg dose taken twice, with the second dose administered 10 to 12 hours after the first dose) was informed by the safety and efficacy results in the Phase II study, where single doses of 1500 and 3000 mg gepotidacin were efficacious against NG with gepotidacin MICs <1 µg/mL, including isolates resistant to ciprofloxacin (see Section 3.1). A comparison of gepotidacin MICs and the corresponding gepotidacin dose against NG demonstrated 100% microbiological success rate in both treatment groups for participants with baseline urogenital NG isolates with gepotidacin MICs ≤0.5 µg/mL. There were no unexpected safety signals at either dose in this study. As further described in Section 5.5, based on PK modeling, gepotidacin will be administered as 2 single oral 3000-mg doses, with 10 to 12 hours between doses, to provide higher daily systemic exposures that allow coverage of NG isolates with higher gepotidacin MIC values, which are likely to be observed in this global Phase III study, and reduce the risk of resistance emergence.

Both adult and adolescent (≥12 to <18 years) eligible participants will be enrolled in this open-label (sponsor-blinded) study. Adolescent participants will only be enrolled at study sites where investigators have experience in this population and if allowed per the study site's institutional ethic committees and local country/national guidelines and enrollment will be contingent upon such approvals. Adolescent assent forms and adult consent forms will be developed with oversight from local governing institutional review boards (IRBs)/independent ethics committees (IECs) (see Appendix 3). Randomization by sex and sexual orientation combination (MSM, MSW, or females) and age will be employed in this study. The effectiveness of gepotidacin is not expected to be different for the

participants in the stratification categories, but the randomization has been planned such that the treatment groups are balanced within each category.

Given the method of study treatment administration (oral gepotidacin versus IM ceftriaxone plus oral azithromycin) blinding of the study was not feasible. A double-blind, double-dummy design would require all participants randomized to oral gepotidacin to receive a placebo IM injection, which is considered unnecessary because the primary endpoint is based on objective microbiological laboratory assessments rather than subjective clinical assessments.

Ceftriaxone plus azithromycin was chosen as the comparator based on the recommended treatment regimen for uncomplicated gonorrhea by authoritative bodies. At the time of study start, both the CDC and WHO recommend a dual antibiotic regimen consisting of a single IM 250-mg dose of ceftriaxone and a single oral 1-g dose of azithromycin [CDC, 2015; WHO, 2016], while in Europe and Australia the recommended dose of ceftriaxone is a single IM 500-mg dose and either a single oral 2-g (Europe) or 1-g (Australia) dose of azithromycin [Bignell, 2013; ASHA, 2016]. As of Dec 2020, the CDC now recommends an IM injection of ceftriaxone based on body weight (500-mg IM if <150 kg and 1-g IM if ≥150 kg) and an oral regimen of doxycycline if chlamydia infection has not been ruled out [CDC, 2021]. For this study, a single IM 500mg- dose of ceftriaxone with a single oral 1-g dose of azithromycin has been chosen (for dose justification see Section 5.5).

In this study, participants who test positive for CT and/or Mgen infection per baseline NAAT results should be treated per local standard of care at or after the TOC Visit or at the Follow-up Visit, as required, after all study procedures at the visit have been completed. Treatment with alternate antibiotic therapy for these co-infections is needed, as gepotidacin and ceftriaxone are not active in vitro against CT, not all participants will receive azithromycin study treatment (an effective treatment for CT), and the study treatment regimen may be insufficient for treatment of Mgen infection. At study entry, any participant suspected or confirmed to have a CT infection will not be allowed to enroll in the study if, per the investigator's judgement, standard-of-care treatment for this infection cannot be safely postponed until the TOC Visit.

Participants meeting eligibility criteria will be treated prior to the availability of culture data to confirm infection. Culture-confirmed bacterial eradication of NG will be assessed 3 to 7 days after the initial treatment per FDA guidelines [DHHS, 2015]. Problems in studies of gonococcal infection include lower culture-confirmed pathogen recovery rates from NG cultures in certain patient populations and the risk for participants to not return for the TOC Visit. In order to maximize the efficiency of this study while minimizing discomfort and inconvenience to participants consenting to this protocol, an internal GSK SRT will monitor blinded safety data instream, while an internal Microbiology Review Team will monitor blinded pathogen identification and susceptibility data instream.

5.5. Dose Justification

In the Phase II study, both single oral doses of 1500 and 3000 mg gepotidacin were ≥95% efficacious (bacterial eradication) against urogenital NG with no unexpected safety signals at either dose. A total of 3 participants failed therapy at the urogenital body site (all with a baseline gepotidacin MIC of 1 μg/mL, which was among the highest MIC for gepotidacin), and analysis of the posttreatment cultures identified 2 isolates that had become resistant to gepotidacin (TOC gepotidacin MICs ≥32 μg/mL). Further analysis revealed that both isolates also had a pre-existing D86N polymorphism in the topoisomerase IV gene at Baseline. Following treatment, both isolates showed a second mutation, an A92T substitution in the DNA gyrase enzyme, which resulted in reduced susceptibility to gepotidacin. Of the 8 participants in the study with D86N-positive baseline urogenital NG isolates, 5 were microbiological successes (bacterial eradication), including 2 that were infected with baseline organisms with the higher gepotidacin MIC of 1 μg/mL. These data suggest that the 3000-mg single dose may provide close to an effective exposure and that this genotype may be overcome with appropriate dosing.

In the current study, gepotidacin will be administered as 2 oral 3000-mg doses. The two 3000-mg doses, administered 10 to 12 hours apart, compared with the single 3000-mg dose used in the Phase II study, is expected to provide 2-fold higher systemic exposures that allow coverage of NG isolates with higher gepotidacin MIC values, which are likely to be observed in this global Phase III study, and also to reduce the risk of resistance emergence.

Previous studies with antibacterials have shown that attaining a target exposure that correlates with bacterial reduction endpoints in preclinical models is predictive of good clinical outcome in participants with bacterial infections [Ambrose, 2007]. However, due to lack of validated preclinical models for NG, the PK/pharmacodynamic (PD) parameter and magnitude predictive of gepotidacin efficacy has not been established in preclinical models for this infection or pathogen. In the Phase II study, the bacterial cure rate was 100% when the free drug area under the concentration-time curve/MIC (*f*AUC/MIC) was approximately 48 or higher and the free mean time above the MIC (*f*T>MIC) was ≥42% (10 hours) for NG isolates with gepotidacin MICs up to 0.5 μg/mL. Based on PK modeling, including PK data in adults and adolescents (Study 209611), the dosing strategy of 2 gepotidacin 3000-mg doses (administered 10 to 12 hours apart) is expected to limit the occurrence of maximum plasma exposures ≥14 μg/mL, which is necessary from a safety perspective due to corrected QT interval (QTc) increases and acetylcholinesterase inhibition. This dosing strategy also supports an *f*AUC/MIC of 40 with an *f*T>MIC of 58% to 63% (14 to 15 hours), which will maximize the probability for efficacy against NG isolates with gepotidacin MICs up to 1 μg/mL. A set of duplicate 10-day hollow fiber infection model studies was also completed using a NG isolate with a gepotidacin MIC of 1 μg/mL and a D86N mutation in ParC to determine if the exposure achieved by 2 gepotidacin 3000-mg doses (administered 8 or 12 hours apart) prevented amplification of a resistant subpopulation when a pre-existing single step mutation was already present. An inverted-U shaped function described the relationship between drug resistance amplification and gepotidacin dose with total daily gepotidacin doses ≥4500 mg (including the 2 gepotidacin 3000-mg doses [administered either 8 or 12 hours apart]) preventing resistance amplification to gepotidacin for NG in the hollow fiber

infection model. Therefore, 2 gepotidacin 3000-mg doses (administered 8 or 12 hours apart) are expected to prevent amplification of resistance against NG isolates with gepotidacin MICs up to 1 μg/mL. However, it should be noted, any emergence of resistance to gepotidacin is not expected to limit or affect standard-of-care treatment for gonorrhea or a participant's future treatment options in this study.

At the start of this study, both the CDC and WHO recommend a dual antibiotic regimen that includes a single 250-mg IM ceftriaxone dose plus a single 1-g oral dose of azithromycin for the treatment of uncomplicated gonococcal infections [CDC, 2015; WHO, 2016]. The CDC now recommends an IM injection of ceftriaxone based on body weight and an oral regimen of doxycycline only if chlamydia infection has not been ruled out [CDC, 2021]. The selected ceftriaxone dose in this study is 500 mg IM. This higher ceftriaxone dose was selected because this dose allows for higher systemic exposures, which are predicted to offer additional coverage of NG isolates with higher ceftriaxone MIC values, should the prevalence of such isolates increase and be observed in this global Phase III study. A single 500-mg IM dose of ceftriaxone is within the prescribing limits, which states the total daily dose for ceftriaxone should not exceed 4000 mg, and is consistent with treatment guidance for Europe and from the Australian regulatory authority [Bignell, 2013; ASHA, 2016]. The selected azithromycin dose in this study is 1 gm administered orally. The azithromycin dose is in alignment with the CDC, WHO, and Australian uncomplicated gonorrhea treatment recommendations [CDC, 2015; WHO, 2016; ASHA, 2016]. Lastly, with approximately 99% efficacy [CDC, 2021], the dual-therapy comparator arm of 500 mg ceftriaxone plus a single 1 g dose of azithromycin is expected to be at least as efficacious as 500 mg ceftriaxone monotherapy.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Weight

1. The participant is ≥12 years at the time of signing the informed consent/assent and has a body weight >45 kg.

   Note: Although participants as young as 12 years may enroll in the study, study sites must follow their institutional ethics committee and local country/national regulatory guidelines and enrollment will be contingent upon such approvals regarding the allowed lower age limit for clinical study participants.

Type of Participant and Disease Characteristics

2. The participant has clinical suspicion of a urogenital gonococcal infection (which can include sexual contact within the past 14 days with a partner who has a confirmed gonococcal infection) with or without pharyngeal and/or rectal gonococcal infection and has 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 has 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 has 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 has not received any treatment for this infection).

   Note: A urogenital specimen will be taken from **all** participants (males and females) for NG culture at the Baseline Visit; however, these results will not be used to determine participant eligibility for enrollment in the study. The culture results will be used to identify the primary analysis population.

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.

Sex

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 as detailed in Appendix 6 of this protocol from the Baseline Visit through completion of the TOC Visit.

   b. Female participants:

   A female participant is eligible to participate if she is a woman of childbearing potential (WOCBP) who is not pregnant as confirmed by a high sensitivity urine pregnancy text at Baseline (Day 1) **regardless of current or prior contraception use or abstinence**, is not breastfeeding, or is not a WOCBP. **Note:** Pregnancy testing requirements, contraceptive guidance, and WOCBP definitions are provided in Appendix 6.

Informed Consent

5. The participant is capable of giving signed informed consent/assent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF)/assent form and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions and History

1. The participant is a male with a current diagnosis of epididymitis and/or orchitis at the time of the Baseline Visit.
2. The participant is suspected or confirmed to have a CT 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 has a body mass index ≥40 kg/m^2 or has 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 has a history of sensitivity to the study treatments, or components thereof, or a history of a drug (including erythromycin and any macrolide or ketolide drug) or other allergy that, in the opinion of the investigator or medical monitor, contraindicates his or her participation.
5. The participant is immunocompromised or has altered immune defenses that may 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.

Note: Participants taking pre-exposure prophylactics for human immunodeficiency virus (HIV) are allowed to enroll. HIV-infected participants are allowed to enroll, as long as their CD4 count is ≥200 cells/mm^3. Use of strong cytochrome P450 enzyme 3A4 (CYP3A4) inhibitors during the study is prohibited (see Exclusion Criterion 15).

6. The participant has any of the following:
   - Medical condition that requires 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 does not include a history of childhood febrile seizures)

   OR

   - Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study treatment (e.g., ileostomy or malabsorption syndrome).
7. The participant has 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 has a serious underlying disease that could be imminently life threatening, or the participant is unlikely to survive for the duration of the study period.

Cardiac Exclusions

10. The participant has congenital long QT syndrome or known prolongation of QTc.
11. The participant has uncompensated heart failure.
12. The participant has severe left ventricular hypertrophy.
13. The participant has a family history of QT prolongation or sudden death.
14. The participant has a recent history of vasovagal syncope or episodes of symptomatic bradycardia or bradyarrhythmia within the last 12 months.

15. The participant is 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 is taking a strong CYP3A4 inhibitor.

Cardiac ECG Exclusions

16. For any participant ≥12 to <18 years, the participant has an abnormal ECG reading.
17. The participant has a QTc >450 msec or a QTc >480 msec for participants with bundle-branch block.

    Note:

    – The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), or Fridericia's (QTcF) formula, and/or another method. It is either machine read or manually overread.

    – The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

18. The participant has a documented or recent history of uncorrected hypokalemia within the past 3 months.

Hepatic Exclusions

19. The participant has a known history of cholestatic jaundice or hepatic dysfunction associated with prior use of azithromycin.
20. The participant has a known alanine aminotransferase (ALT) value >2 × upper limit of normal (ULN).
21. The participant has a known bilirubin value >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
22. The participant has 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).

    Note: Participants with asymptomatic viral hepatitis are eligible for study participation.

Prior/Concurrent Clinical Study Experience Exclusions

23. The participant has been previously randomized in this study or has previously been treated with gepotidacin.
24. The participant has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer.

Gonococcal Infection Exclusions

25. The participant has any of the following gonococcal infections that require 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

Prior Antibiotic/Antifungal Use and Concomitant Medication Exclusions

26. The participant has received any antibacterial therapy for the treatment of a gonococcal infection within 14 days before the Baseline Visit.
27. The participant has received any systemic, topical, or intravaginal antibiotics 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.

6.3. Lifestyle Restrictions

Participants will be instructed to abstain from sexual activity from the Baseline Visit through the TOC Visit to prevent possible re-infection with NG. If a participant refuses to abstain and is sexually active, male participants as well as male partners of female participants, of both childbearing and nonchildbearing potential, must use a male condom during intercourse from the Baseline Visit through completion of the TOC Visit. Details for contraception requirements are included in Appendix 6.

6.3.1. Meals and Dietary Restrictions

Gepotidacin and azithromycin should be taken with food (a meal or snack) (see Section 7.1).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Participants who are screen failures are not allowed to be rescreened for the same infection episode; however, participants who were screen failures for an earlier infection episode may be newly screened for a second infection episode ≥4 weeks later and participate in the study if they meet all of the inclusion and exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

7. TREATMENTS

All doses of oral study treatment should always be taken after food consumption and with water. Study treatment is defined as any investigational treatments or marketed products intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	**Gepotidacin**	**Ceftriaxone**	**Azithromycin**[a]
Dosage Formulation:	Tablets containing gepotidacin and inactive formulation excipients	Sterile powder for reconstitution with appropriate diluent	Tablets[a]
Unit Dose Strengths/ Dosage Levels:	4 × 750-mg tablets	500-mg equivalent	2 × 500-mg tablets[a]
Route of Administration:	Oral	IM	Oral
Dosing Instructions:	Administer first oral dose at the study site. Participant self-administers the second dose as an outpatient 10 to 12 hours after the first dose; however, for participants who weigh <50 kg or have moderate renal impairment, the second dose should be taken approximately 12 hours after the first dose Dose 1: 3000 mg – 4 tablets Dose 2: 3000 mg – 4 tablets Each dose should be taken after food consumption and with water.	Administer one 500-mg IM dose at the study site (volume administered will be dependent on the amount of diluent[b] added and resulting concentration; see Study Reference Manual).	Administer one 1-gm oral dose at the study site. Dose should be taken after food consumption and with water.

Study Treatment Name:	Gepotidacin	Ceftriaxone	Azithromycin[a]
Packaging and Labeling:	Gepotidacin tablets will be provided in bottles. Each bottle will be labeled as required per country requirement.	Ceftriaxone will be provided by PPD and labeled as required per country requirement.	Azithromycin tablets[a] will be provided by PPD and labeled as required per country requirement.
Manufacturer:	CCI [redacted]	May be sourced locally or centrally within individual countries but will be supplied by PPD and labeled as per the regulatory requirements in all participating countries.	May be sourced locally or centrally within individual countries but will be supplied by PPD and labeled as per the regulatory requirements in all participating countries.

IM=intramuscular.

a. The total oral dose of azithromycin must be 1 gm. Based on locally or centrally sourced available supplies and tablet/capsule strengths, the number of tablet/capsules may be adjusted to reach the 1-gm dose of azithromycin.
b. Study sites will be responsible for procurement of diluent and injection supplies.

The labeling, distribution, procurement, and/or drug returns for comparator investigative products were supported by Almac US, Almac UK, PPD Athlone (Germany and Spain), Flinders (Australia), World Courier Mexico, Clinigen (Australia, EMEA, and US), Bionical LTDA (UK), and Oncomedic (Mexico).

7.2. Dose Modification

The study design does not allow for dose modifications.

7.3. Method of Treatment Assignment

Participants will be stratified by sex and sexual orientation combination (MSM, MSW, or females) and age (<18 years, ≥18 to 65 years, or >65 years) to ensure that treatment groups are balanced within each category. The MSM category will include MSM and bisexual males (i.e., male participants who have sex with both males and females). Within each stratum, participants will be centrally randomized in a 1:1 ratio to either gepotidacin or ceftriaxone plus azithromycin using an interactive response technology (IRT) in accordance with the randomization schedule generated by or under the direction of GSK's Clinical Statistics. Before the study is initiated, information and directions for the IRT will be provided to each study site.

Each participant scheduled to receive study treatment will receive a randomization number at the time of randomization. This randomization number will be used to identify the participant and indicate the treatment to be administered to that participant.

For those participants randomly assigned to gepotidacin, the first dose will be administered at the study site during the Baseline Visit and the second dose will be dispensed to participants during this visit for self-administration 10 to 12 hours after the

first dose (see Section 7.1). Participants randomly assigned to ceftriaxone plus azithromycin will be administered a single IM dose of ceftriaxone plus a single oral dose of azithromycin during the Baseline Visit.

Returned gepotidacin should not be re-dispensed to other participants.

7.4. Blinding

This is an open-label (sponsor-blinded) randomized study. The specific treatment to be taken by a participant will be assigned using an IRT using central randomization. The study site will contact the IRT prior to the start of study treatment administration for each participant. The study site will record the treatment assignment on the applicable electronic case report form (eCRF), if required. Potential bias will be reduced by the use of central randomization.

The GSK SRT, which will monitor safety data instream, will remain blinded to participant treatment assignment throughout the study (see Appendix 3). A Microbiology Review Team will monitor blinded pathogen identification and susceptibility data instream as well as the number of participants eligible for the micro-ITT Population. Blinded monitoring of pathogens will be conducted, to determine whether end-of-study targets are likely to be achieved. Provision will be made for a limited degree of unblinding of a minority of participant sample data should this be viewed as appropriate for planning closure of trial enrollment. Procedures will be described in a separate microbiology sample monitoring plan, and no impact on trial integrity is expected.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of gepotidacin or azithromycin is required.

A pharmacist or other qualified professional will prepare the ceftriaxone solution using a fixed volume of an appropriate diluent to reconstitute the ceftriaxone powder. Full details of the methods and materials required for ceftriaxone solution preparation are provided in the SRM.

The following considerations must be made with regard to study treatment preparation, handling, storage, and accountability in this study:

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized study site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to the study site staff. For ceftriaxone solution, take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure, notify the monitor, medical monitor, and/or GSK study contact.

A Material Safety Data Sheet or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- Participants dosed at the study site will receive study treatment (oral dose of gepotidacin or single IM dose of ceftriaxone plus an oral dose of azithromycin) directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the study site will be recorded in the source documents and reported in the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.
- Participants will self-administer the second oral dose of gepotidacin as an outpatient (see Section 7.1). Compliance with gepotidacin will be assessed by contacting the participant via telephone, email, or text message. The participants should confirm that the second dose was taken. Study site staff will also query the participant during the TOC Visit and document whether the second dose was taken. A record of the number of gepotidacin tablets dispensed to each participant must be recorded and reconciled with study treatment and compliance records. The date and time of each dose will also be recorded in the eCRF.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving within 30 days prior to the Baseline Visit or receives during the study must be recorded in the eCRF. In addition, any antibiotic use within 6 months prior to the Baseline Visit or during the study must be recorded in the eCRF. The concomitant therapy name must be recorded in the eCRF along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Permitted Medications and Nondrug Therapies

Participants testing positive for CT and/or Mgen per NAAT results at the Baseline Visit will be permitted to receive local standard of care at or after the TOC Visit or at the Follow-up Visit (if treatment has not already been initiated), as required, after all study procedures at the visit have been completed. **Note**: If at Baseline a participant is suspected or confirmed to have a CT infection and per the investigator's judgement standard-of-care treatment for this infection cannot be safely postponed until the TOC Visit, the participant should not be enrolled in the study (see Section 6.2).

The use of H_1 antihistaminics not associated with QT prolongation is allowed (e.g., loratadine, cetirizine, ebastine, and fexofenadine). Use of pre-exposure prophylaxis for HIV is allowed. The use of nonsystemic antifungals (e.g., topical, intravaginal) is allowed throughout the study. Please also refer to Appendix 9.

A list of permitted medications commonly used for nausea, vomiting, pain, and diarrhea per investigator discretion is provided in Appendix 9.

A further detailed list of medications will be provided in the SRM.

7.7.2. Prohibited Medications and Nondrug Therapies

At the time of enrollment and/or during the study, the participant is prohibited from use of the following medications and nondrug therapies:

- An investigational product within 30 days or 5 half-lives, whichever is longer, of Baseline Visit.
- Any antibacterial therapy for the treatment of a gonococcal infection within 14 days before the Baseline Visit.
- Any systemic, topical, or intravaginal antibiotics or any systemic antifungals within 7 days before the Baseline Visit.
- 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).
- With the exception of azithromycin study treatment, QT-prolonging drugs or drugs with known TdP risk, per the www.crediblemeds.org "Known Risk of TdP" category, at the time of their Baseline Visit, which cannot be safely discontinued from the Baseline Visit to the TOC Visit. Details regarding website access are provided in the SRM; additional guidance is provided in Appendix 9. Of note, ondansetron is not allowed from the Baseline Visit to the TOC Visit due to its known TdP risk. Alternative antiemetics that are permitted per investigator discretion are listed in Appendix 9.

  Note: Crediblemeds.org categorizes drugs into 4 categories. The only category for exclusion in this study is the "Known Risk of TdP" category; participants taking drugs that meet criteria of other categories are NOT excluded from participation.

- St John's wort or other strong CYP3A4 inhibitors within 14 days before the Baseline Visit through the TOC Visit (a list of strong CYP3A4 inhibitors is provided in the SRM).
- Ergot derivatives from within 14 days before the Baseline Visit through the TOC Visit.

Due to the gepotidacin's property of acetylcholinesterase inhibition, the concomitant use of succinylcholine or other nondepolarizing paralytic agents is also prohibited. Caution should be used in participants who have a condition requiring medication that may exacerbate the inhibition of acetylcholinesterase, or neuromuscular blocking agents.

7.8. Treatment After the End of the Study

Participants testing positive for CT and/or Mgen per NAAT results at the Baseline Visit should be treated per local standard of care at or after the TOC or at Follow-up Visit (if treatment has not already been initiated), as required, after all study procedures at the visit have been completed. Treatment with alternate antibiotic therapy for these co-infections is needed, as gepotidacin and ceftriaxone are not active in vitro against CT, not all participants will receive azithromycin study treatment (an effective treatment for CT), and the study treatment regimen may be insufficient for treatment of Mgen infection. **Note**: If at Baseline a participant is suspected or confirmed to have a CT infection and per the investigator's judgement standard-of-care treatment for this infection cannot be safely postponed until the TOC Visit, the participant should not be enrolled in the study (see Section 6.2).

Participants with culture-confirmed bacterial persistence of urogenital and, as appropriate, pharyngeal and/or rectal NG at the TOC Visit should receive appropriate alternative therapy per the investigator's choice.

Participants will not receive any additional treatment for urogenital, pharyngeal, and/or rectal NG from GSK after they discontinue or complete the study (i.e., after the Follow-up Visit). However, the investigator is responsible for ensuring that consideration has been given to the poststudy care of the participant's medical condition, whether or not GSK is providing specific poststudy treatment.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants may voluntarily discontinue study treatment at any time. The investigator may also, at his or her discretion, discontinue the participant from study treatment at any time and initiate appropriate alternative therapy.

Reasons for study treatment discontinuation may include the following:

- Adverse event
- Protocol deviation
- Termination of the study by GSK
- Investigator discretion

The reason for study treatment discontinuation will be recorded in the eCRF. Participants who discontinue study treatment for the reasons above will not be considered withdrawn from the study and should return to the study site to complete the TOC and Follow-up Visits (see Table 1).

8.1.1. Liver Chemistry Evaluation Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

The stopping criteria for discontinuing dosing of study treatment due to liver chemistry parameters have limited application in this study, as study treatment is administered as 2 oral doses of gepotidacin over a 24-hour period starting on Day 1 or as a single dose IM dose of ceftriaxone plus an oral dose of azithromycin on Day 1. However, if participants are found to have values consistent with the usual stopping parameters, it is appropriate to institute evaluation and monitoring criteria according to standard GSK criteria. Therefore, liver function tests should be evaluated according to stopping criteria and laboratory evaluation instituted if defined parameters are reached.

Phase III liver chemistry evaluation criteria are presented in Table 4.

Table 4 Liver Chemistry Evaluation Criteria

	Liver Chemistry Evaluation Criteria – Liver Event
ALT Absolute	ALT ≥8 × ULN
ALT Increase	ALT ≥5 x ULN but <8 x ULN persists for ≥2 weeks ALT ≥3 x ULN but <5 x ULN persists for ≥4 weeks
Bilirubin	ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin)
INR	ALT ≥3 × ULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥5 x ULN but <8 x ULN and cannot be monitored weekly for ≥2 weeks ALT ≥3 x ULN but <5 x ULN and cannot be monitored weekly for ≥4 weeks
Symptomatic	ALT ≥3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

ALT=alanine aminotransferase; INR=international normalized ratio; ULN=upper limit of normal.

Liver safety required actions and follow-up assessments section can be found in Appendix 8.

8.1.2. QTc Stopping Criteria

- This protocol only requires an ECG evaluation at the Baseline Visit. Should further ECG monitoring or evaluation be needed for an individual participant, per investigator discretion, the following should be considered:
- Further monitoring and/or evaluation should be considered in any participant who meets either of the bulleted criteria below:
  - QTc >500 msec OR uncorrected QT >600 msec
  - Change from baseline of QTc >60 msec

For participants with underlying bundle-branch block, follow the evaluation criteria listed below:

Baseline QTc With Bundle-Branch Block	**Criteria for Further Evaluation and Monitoring of QTc With Bundle-Branch Block**
<450 msec	>500 msec
450 to 480 msec	≥530 msec

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for the study and whether further evaluation and/or monitoring are necessary. This formula may not be changed or substituted once the participant has been enrolled. (Note: Ideally, all ECGs for a participant should be performed with the same ECG machine.)
  - For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
  - Once the QT correction formula has been chosen for a participant's eligibility, the same formula must continue to be used for that participant for all QTc data being collected for data analysis. Safety ECGs and other nonprotocol-specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5- to 10-minute) recording period.

8.1.3. Gastrointestinal Evaluation Criteria

If a participant meets the clinical criteria outlined in Appendix 10, *Clostridium difficile* toxin detection should be conducted and the specific eCRF page completed. *C. difficile* infection or colitis is considered an AE of special interest (Section 9.2.5).

8.2. Withdrawal From the Study

- A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Reasons for study withdrawal include:
  - Participant lost to follow-up
  - Participant withdrew consent
  - Termination of the study by GSK
  - Investigator discretion
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Participants who withdraw from the study should be encouraged to return for the TOC and/or Follow-up Visits. Refer to Table 1 for data to be collected at these visits.
- The reason for participant withdrawal will be recorded in the eCRF. Participants who were randomly assigned to gepotidacin should return all unused study treatment.

8.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Table 1.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment (only applicable to participants randomly assigned to gepotidacin).
- Adherence to the study design requirements, including those specified in Table 1, is essential and required for study conduct.
- All baseline screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in Table 1.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 150 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The study will comprise the following 3 planned study visits:

Note: For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the SRM. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit.

- **Baseline (Day 1) Visit**: The Baseline Visit will be performed before dosing on Day 1. Assessments will be performed as shown in Table 1, including the following:
  - If applicable, the Baseline Visit will be preceded by a documented reminder contact from the study site to the participant 24±4 hours before the scheduled appointment time per the method (e.g., text message, telephone call, e-mail) confirmed with the study site staff.
  - Demographic data such as year of birth, sex, sexual orientation, race, and ethnicity will be recorded in the participant's eCRF. The collection of sex, sexual orientation, race, and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population. The year of birth is collected to stratify the population.
  - The participant's medical/surgical history will be obtained by interviewing the participant and/or the participant's legally authorized representative and/or review of the participant's medical records. Any pre-existing conditions, signs and/or symptoms present prior to the first dose of study treatment will be recorded in the eCRF.
  - Pretreatment baseline specimens for microbiological testing will be collected as described in Section 9.1 and Table 2.
  - Following completion of all pretreatment assessments, eligible participants will be randomly assigned to treatment as described in Section 7.3.
  - The first oral gepotidacin dose (3000 mg) or the IM ceftriaxone dose (500 mg) plus the oral azithromycin dose (1 g) will be administered at the study site. Oral study treatment (gepotidacin and azithromycin) should be taken after food consumption and with water to assist with tolerability. After dose administration, Day 1 posttreatment assessments will be performed, as shown in Table 1. Any AEs or clinically significant changes should be followed accordingly.
  - Participants randomly assigned to gepotidacin will self-administer the second 3000-mg oral dose as an outpatient 10 to 12 hours after the first dose; however, for participants who weigh <50 kg or have moderate renal impairment, the second dose should be taken approximately 12 hours after the first dose. Gepotidacin study treatment should be taken after food consumption and with water to assist with tolerability. **Note**: The second dose may occur on Day 1 or Day 2, depending on the time at which the first dose was taken. Participants randomly assigned to gepotidacin will be contacted to confirm that they took their second gepotidacin dose (see Section 7.6).

  - The TOC and Follow-up Visits should be scheduled before the participant leaves the study site on Day 1 (as indicated in Table 1); the planned return day/time should be at the convenience of the participant and also the availability of the study site staff.

- **TOC (Day 4 to 8) Visit**: Participants will be instructed to return to the study site 3 to 7 days following study treatment administration at Baseline in order to complete the TOC Visit. Assessments will be performed as shown in Table 1, including the following:
  - The TOC Visit will be preceded by a documented reminder contact from the study site to the participant 24±4 hours before the scheduled appointment time per the method (e.g., text message, telephone call, e-mail) confirmed with the study site staff prior to departing the study site on Day 1.
  - Specimens for microbiological testing will be collected as described in Section 9.1 and Table 2.
  - Participants may return to the study site before the scheduled TOC Visit due to AEs.
  - Participants testing positive for a CT and/or Mgen infection per baseline NAAT results should be treated, as required, per local standard of care at the TOC Visit only after completion of all visit procedures or at any point after the TOC Visit.
  - Participants with culture-confirmed bacterial persistence of urogenital and, as appropriate, pharyngeal and/or rectal NG should receive appropriate alternative therapy per the investigator's choice either on or after the TOC Visit, based on availability of results.
- **Follow-up (Day 14 to 21) Visit**: Participants will be instructed to return to the study site 14 to 21 days following study treatment administration at Baseline in order to complete the Follow-up Visit. Assessments will be performed as shown in Table 1, including the following:
  - The Follow-up Visit will be preceded by a documented reminder contact from the study site to the participant 24±4 hours before the scheduled appointment time per the method (e.g., text message, telephone call, e-mail) confirmed with the study site staff prior to departing the study site on Day 1.
  - The investigator and/or study site staff should make every effort to ensure a participant returns for this visit. If it is determined that the participant is unable to return to the study site, the Follow-up Visit assessments may be completed via telephone, with the exception of assessments requiring sample collection for laboratory testing.
  - Specimens for microbiological testing will be collected as described in Section 9.1 and Table 2.
  - Participants may return to the study site before the scheduled Follow-up Visit due to AEs or if they feel they are not responding to any alternative therapy started after the TOC Visit.

– Participants testing positive for a CT and/or Mgen infection per baseline NAAT results should be treated, as required, per local standard of care (if treatment has not already been initiated) only after completion of all Follow-up Visit procedures.

9.1. Efficacy Assessments

Microbiological efficacy laboratory assessments were performed at PPD Global Clinical Laboratory and JMI Laboratories. Addresses for the central laboratories, as well as all local laboratories, are provided in the List of Clinical Laboratories Used for Human Biological Sample Analysis, which will be stored in the trial master file.

9.1.1. Bacteriology Samples for Culture

Multiple swab specimens and types may need to be obtained from each anatomical site; refer to the laboratory manual. See Table 2 for collection of bacteriology samples.

At the Baseline Visit, a pretreatment urogenital swab specimen must be obtained from all participants for Gram stain (male and females) and bacteriological culture for NG. Pretreatment pharyngeal and rectal swab specimens will also be obtained from participants who are willing to provide such specimens, regardless of known exposure, for bacteriological culture for NG.

At the TOC Visit, specimens will be obtained for Gram stain (urogenital specimens only) and bacteriological culture for NG only from all body sites collected at Baseline.

At the Follow-up Visit, only pharyngeal swab specimens will be obtained for bacteriological culture for NG from participants who had a positive NAAT assay for pharyngeal NG at **both** Baseline and TOC.

Gram stain and bacteriological cultures will be performed at a designated laboratory(ies). Confirmation of identification and susceptibility testing by agar dilution will be conducted at a designated laboratory(ies) for all isolates of NG recovered at all visits from all body sites. Instructions for sample collection, processing, and shipment are provided in the SRM and the laboratory manual. Laboratories should follow the Microbiology Procedures section of the laboratory manual to minimize potential contamination of the specimens or isolates.

Only those participants who have NG confirmed by a designated laboratory(ies) from their baseline bacteriology specimen will be evaluated for microbiological outcome and response. The microbiological outcome and response to the study treatment will be determined programatically at GSK before breaking of the study blind. (**Note**: The sponsor is blinded to participant treatment assignment; see Section 7.4.)

The microbiological outcome is determined by comparing the baseline culture results to the respective culture results at each subsequent visit. The corresponding microbiological response (success or failure) “by participant” will then be assigned, as shown in Table 5.

Table 5 Determining Microbiological Outcome and Response at the TOC Visit

Defining Criteria	Microbiological Outcome	Microbiological Response
Culture-confirmed elimination of baseline NG pathogen from a bacteriology sample taken at the TOC Visit, without the participant receiving other systemic antimicrobials before this visit	Bacterial eradication	Microbiological success
Culture-confirmed persistence of baseline NG pathogen from a bacteriology sample taken at the TOC Visit, without the participant receiving other systemic antimicrobials before this visit	Bacterial persistence	Microbiological failure
1) A determination of the TOC NG pathogen microbiological outcome cannot be made (e.g., no bacteriology sample taken for culture, sample lost, visit did not occur) 2) The participant received other systemic antimicrobials before the TOC Visit	Unable to determine	Microbiological failure

NG=*Neisseria gonorrhoeae*; TOC=Test-of-Cure.
Note: A bacteriological specimen refers to either a urogenital, pharyngeal, or rectal sample obtained for bacteriological culture. Microbiological outcomes are determined on a per-pathogen and per-specimen source basis.

9.1.2. NAAT Assay

Refer to the laboratory manual for local versus central laboratory details and the number and type of specimens to collect for NAAT assay. See Table 2 for collection of NAAT assay samples.

Pretreatment urogenital specimens will be obtained from all participants for NAAT assay to detect the presence of NG, Mgen, and CT nucleic acids at the Baseline Visit. Urogenital specimens will also be obtained from all participants for NAAT assay to detect the presence of NG and CT nucleic acids at the TOC Visit. At the Follow-up Visit, a urogenital specimen for NAAT assay will be collected for detection of Mgen only from participants who had a positive NAAT assay for Mgen at Baseline.

In addition, pretreatment baseline pharyngeal and rectal specimens for NAAT assay for detection of NG and CT will be obtained from participants who are willing to provide such specimens, regardless of known exposure. Specimens will also be collected for NAAT assay for detection of NG and CT at the TOC Visit from all body sites collected at the Baseline Visit. At the Follow-up Visit, a pharyngeal specimen for NAAT assay will be collected for detection of NG and CT from participants whose NAAT assay had the presence of nucleic acid for NG at **both** Baseline and TOC.

The NAAT assay will be performed at a designated laboratory(ies). Participants testing positive for CT or Mgen nucleic acid by NAAT assay at the Baseline Visit should be treated per local standard of care at or after the TOC Visit or at the Follow-up Visit (if treatment has not already been initiated), as required, after all study procedures for the visit have been completed.

Only those participants who have NG or Mgen nucleic acid detected from their baseline NAAT specimen will be evaluated for NAAT outcome and response. The NAAT outcome and response to study treatment will be determined by an algorithm at GSK before breaking of the study blind (**Note**: Sponsor is blinded to participant treatment assignment; see Section 7.4).

For the exploratory objectives, the NAAT outcome is determined by comparing the baseline NAAT result with the respective NAAT result at each subsequent visit. The corresponding NAAT response (success or failure) "by participant" will then be assigned, as shown in Table 6 and Table 7.

Table 6 Determining NAAT Outcome and Response at the Test-of-Cure Visit (NG Only)

Defining Criteria	NAAT Outcome	NAAT Response
Clearance of baseline pathogen nucleic acid from a specimen taken at the TOC Visit, without the participant receiving other systemic antimicrobials before this visit	Nucleic acid clearance	NAAT success
Persistence of baseline pathogen nucleic acid from a specimen taken at the TOC Visit, without the participant receiving other systemic antimicrobials before this visit	Nucleic acid persistence	NAAT failure[a]
1) A determination of the nucleic acid outcome from a specimen taken at the TOC Visit cannot be made (e.g., no sample taken, sample lost, visit did not occur) 2) The participant received other systemic antimicrobials before the TOC Visit	Unable to determine	NAAT failure[a]

NAAT=nucleic acid amplification test; NG=*Neisseria gonorrhoeae*; TOC = Test-of-Cure.
Note: Specimen refers to either a urogenital, pharyngeal, or rectal specimen obtained for NAAT. The NAAT outcomes are determined on a per-pathogen basis.
a. Participants who are a "NAAT failure" at the TOC Visit assessment yet are not switched to other systemic antimicrobials are evaluable at subsequent time points.

Table 7 Determining NAAT Outcome and Response at the Follow-Up Visit (Pharyngeal NG and Mgen Only)

Defining Criteria	NAAT Outcome	NAAT Response
Clearance of baseline pathogen nucleic acid from a specimen taken at the Follow-up Visit, without the participant receiving other systemic antimicrobials before this visit	Nucleic acid clearance	NAAT success
Persistence of baseline pathogen nucleic acid from a specimen taken at the Follow-up Visit, without the participant receiving other systemic antimicrobials before this visit	Nucleic acid persistence	NAAT failure
A determination of the nucleic acid outcome from a specimen taken at the Follow-up Visit cannot be made (e.g., no sample taken, sample lost, visit did not occur) *Note: Any participants who received other systemic antimicrobials before the Follow-up Visit will not be evaluated for NAAT outcome or response at the Follow-up Visit*	Unable to determine	NAAT failure

Mgen=*Mycoplasma genitalium*; NAAT=nucleic acid amplification test; NG=*Neisseria gonorrhoeae*.
Note: Specimen refers to either a urogenital or pharyngeal specimen obtained for NAAT. The NAAT outcomes are determined on a per-pathogen basis and will only be conducted if both the Baseline (NG and Mgen) and TOC (NG only) NAAT assay showed the presence of nucleic acid for the respective pathogen and specimen.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or from the study (see Section 8). PPD was responsible for the safety oversight for this study.

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the Follow-up Visit at the time points specified in Table 1 (Section 2).
- All AEs will be collected from the start of treatment until the Follow-up Visit at the time points specified in Table 1 (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the medical history/current medical conditions section of the eCRF and not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 4. The

investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 9.2.5) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Adverse Events of Special Interest

Predefined AEs of special interest for this study are cardiovascular (CV) events, gastrointestinal events, *C. difficile* infection or colitis events, and AEs related to acetylcholinesterase inhibition (see Section 3.3.1), which will be identified by a prespecified list of coded terms or determined by algorithm, as described in the reporting and analysis plan (RAP). Additional details are provided in Appendix 4.

C. difficile specimens were analyzed at IHMA, Inc. Addresses for the central laboratories, as well as all local laboratories, are provided in the List of Clinical Laboratories Used for Human Biological Sample Analysis, which will be stored in the trial master file.

9.2.6. Cardiovascular and Death Events

For any CV events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific CV and death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV section of the eCRF within 1 week of receipt of a CV event data query prompting its completion.

The death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

9.2.7. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and through the Follow-up Visit.
- If a pregnancy is reported, the investigator should inform GSK/PPD within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

In the ceftriaxone plus azithromycin treatment group, only 1 dose of ceftriaxone and 1 dose of azithromycin are administered during the study, and both are administered at the study site. Although 2 doses of gepotidacin will be administered in the study, participants will not have access to more than the required gepotidacin dose at each dosing time point. At the Baseline Visit, the first gepotidacin dose is administered at the study site and the study site staff will dispense to the participant only the number of tablets required for the second dose (self-administered as an outpatient 10 to 12 hours after the first dose). Therefore, overdoses of either study treatment are not anticipated in this study.

There is no specific antidote for overdose with a bacterial topoisomerase inhibitor. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

There is no specific antidote for an overdose of ceftriaxone or azithromycin. Treatment of an overdose should be symptomatic (refer to the locally approved ceftriaxone and azithromycin prescribing information).

9.4. Safety Assessments

Planned time points for all safety assessments are provided in Table 1.

9.4.1. Physical Examinations

- A complete physical examination will be performed at the Baseline Visit and a gonorrhea-focused physical examination will be performed at the TOC Visit. At Baseline, the complete physical examination will include assessments of the respiratory, CV, abdominal, gastrointestinal, and urogenital systems, as well as pharyngeal and rectal examinations with collections of microbiology specimen(s) as appropriate (see Section 9.1). Height and weight will only be measured and recorded at the Baseline Visit (before dosing). The gonorrhea-focused physical examination at the TOC visit will include urogenital systems, as well as pharyngeal and rectal examinations with collections of microbiology specimen(s) as appropriate (see Section 9.1).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Clinically significant changes from baseline or clinically significant new clinical signs will be reported as AEs.

9.4.2. Vital Signs

- Vital signs will be measured at the time points indicated in Table 1.
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.
  - Vital sign measurements should be obtained before any blood draws scheduled on the same assessment day.
  - Clinically significant changes from baseline will be reported as AEs.

9.4.3. Electrocardiograms

- Triplicate 12-lead ECGs (over an approximate 5- to 10-minute period) will be performed at the Baseline Visit using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- This protocol only requires an ECG evaluation at the Baseline Visit. Ideally, ECGs will be obtained before any vital sign measurements or blood draws scheduled on the same assessment day; however, sites may perform procedures in an order per their standard of care, as long as participants return to a resting state prior to the start of the ECG collections. Subsequent ECGs only need to be triplicate if the initial one is prolonged.
- If clinically significant changes occur during the study, they will be reported as AEs.
- Equipment provided qualified ECG machines and supportive maintenance during the study to sites that required provision.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to Table 1 for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and Table 1.
- All safety laboratory tests will be performed at PPD Global Clinical Laboratory. Addresses for the central laboratories, as well as all local laboratories, are provided in the List of Clinical Laboratories Used for Human Biological Sample Analysis, which is stored in the trial master file.

9.5. Pharmacokinetics

No PK samples will be collected in this study except as potentially required for liver safety follow-up assessments as described in Appendix 8. Any PK samples will be performed by PPD Bioanalytical Lab.

9.6. Pharmacodynamics

Microbiological assessments will include the determination of gepotidacin MICs and other antibacterial MICs for urogenital, pharyngeal, and rectal NG isolates in this study. The MIC values will be used in the PD analysis.

9.7. Genetics

A 6-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in Appendix 7.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics or Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

Full details of all data handling conventions and statistical analyses conducted for this study will be provided in the RAP.

10.1. Statistical Hypothesis

The study is designed to demonstrate that gepotidacin administered orally is noninferior compared to ceftriaxone plus azithromycin on the primary efficacy endpoint of culture-confirmed eradication of NG from the urogenital body site (i.e., microbiological success) at the TOC Visit.

The following are null and alternative hypotheses for the primary analysis of the microbiological success rates at the prespecified noninferiority margin of -10%:

H_0: Microbiological success rate of gepotidacin – Microbiological success rate of ceftriaxone plus azithromycin $\leq$-10.0%

H_1: Microbiological success rate of gepotidacin – Microbiological success rate of ceftriaxone plus azithromycin >-10.0%

Gepotidacin will be declared noninferior to treatment with ceftriaxone plus azithromycin if the lower limit of the 2-sided 95% CI for the difference between the microbiological success rate of gepotidacin and ceftriaxone plus azithromycin at the TOC Visit is above -10.0%. Superiority of gepotidacin will be declared if the lower end of the CI is above 0%.

The difference in the microbiological success rate between the 2 treatment groups and the corresponding CI will be computed using the Miettinen and Nurminen method [Miettinen, 1985].

10.2. Sample Size Determination

10.2.1. Justification of Sample Size

Approximately 400 participants will be needed for the primary analysis population (i.e., the micro-ITT Population, as defined in Section 10.3) to demonstrate efficacy of gepotidacin in this study.

A conservative estimate of a 90% microbiological success rate has been assumed for ceftriaxone 500 mg IM plus azithromycin 1 g orally. Participants not returning for TOC will be considered a microbiological failure in this study.

Assuming a 90% microbiological success rate of ceftriaxone plus azithromycin and the same value for the actual success rate of gepotidacin, a sample size of 400 urogenital microbiological evaluable participants (200 participants in each treatment) will provide approximately 91% power to demonstrate noninferiority of gepotidacin and ceftriaxone plus azithromycin in adolescents and adults with uncomplicated gonorrhea caused by NG with a 0.025 one-sided significance level and a -10% noninferiority margin.

Approximately 620 participants will be enrolled and randomized 1:1 to gepotidacin and ceftriaxone plus azithromycin in order to identify approximately 400 participants that meet the definition of the micro-ITT Population.

10.2.2. Sample Size Sensitivity

Sensitivity of the sample size has been explored considering various microbiological success rates. The assumed reference microbiological success rate affects the power for a target number of participants in the study. Table 8 shows the power with the target number of participants in this clinical trial under different assumptions of the microbiological success rate.

Table 8 Power of the Study for the Target Microbiological Intent-to-Treat Population at Various Microbiological Success Rates

Microbiological Success Rate of Ceftriaxone Plus Azithromycin	Microbiological Success Rate of Gepotidacin	Total Number of Participants in the Primary Analysis	Number of Participants in the Primary Analysis in Each Treatment Group	Power
92%	92%	400	200	95%
90%	90%	400	200	91%
89%	89%	400	200	89%
88%	88%	400	200	86%
87%	87%	400	400	84%

The power of the study will remain above 84% if the true microbiological success rate in the 2 treatment groups is the same and 87% or higher.

10.3. Populations for Analyses

For purposes of analysis, the following key populations are defined:

Population	Description
Screened Population	All participants who were screened for eligibility.
Intent-to-Treat (ITT) Population	All participants randomly assigned to study treatment. Participants will be analyzed according to their randomized study treatment arm.
Microbiological ITT (micro-ITT) Population	All participants randomly assigned to study treatment who receive at least 1 dose of study treatment and have confirmed NG isolated that is ceftriaxone-susceptible from baseline culture of their urogenital specimen. Participants will be analyzed according to their randomized study treatment arm. This is the primary analysis population.
Micro-ITT Rectal 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 rectal specimen. Participants will be analyzed according to their randomized study treatment arm.
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. Participants will be analyzed according to their randomized study treatment arm.
Microbiologically Evaluable (ME) Population	Participants who meet the definition of the micro-ITT Population and follow important components of the study (i.e., [1] receive all planned doses as randomized and actual treatment is the same as randomized, [2] have a urogenital specimen collected at the TOC Visit, with available culture results, [3] have not taken any other systemic antibiotic prior to the TOC Visit, unless it was taken for the current infection, and [4] have no major deviation that prevents evaluation of efficacy). Participants will be analyzed according to their randomized study treatment arm.
Safety Population	All participants who receive at least 1 dose of study treatment. Participants will be analyzed according to their actual treatment received.

Mgen=Mycoplasma genitalium; NG=Neisseria gonorrhoeae; TOC=Test-of-Cure.

10.4. Statistical Analyses

10.4.1. General Considerations

Any additional analysis populations or supplemental analyses will be detailed in the RAP. Any additional analyses or outputs needed as a result of COVID-19 on the study will be detailed in the RAP.

10.4.2. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary analysis will be performed using the micro-ITT Population. • The primary efficacy endpoint is culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., microbiological success) at the TOC (Day 4 to 8) Visit. For this analysis, participants who do not return for the TOC (Day 4 to 8) Visit will be treated as failures. • The number and percentage of participants with culture-confirmed bacterial eradication of NG from the urogenital body site (i.e., microbiological success) will be summarized, along with 95% CIs, at the TOC (Day 4 to 8) Visit by treatment group. • The difference in microbiological success rates between gepotidacin and ceftriaxone plus azithromycin for culture-confirmed bacterial eradication of urogenital NG at the TOC Visit will be summarized, along with 95% CIs. • Gepotidacin will be declared noninferior to treatment with ceftriaxone plus azithromycin if the lower limit of the 2-sided 95% CI for the difference between the microbiological success rate of gepotidacin and ceftriaxone plus azithromycin at the TOC Visit is above -10.0%. Superiority of gepotidacin will be declared if the lower end of the CI is above 0%. The Miettinen and Nurminen method will be used for the analysis adjusting for treatment and stratification factors of sex and sexual orientation combination (i.e., MSM, MSW, or female). • A further supplementary analysis on the primary endpoint may be performed based on the Microbiologically Evaluable Population. Additional sensitivity analysis, if warranted, will be described in the RAP. • The microbiological success in each treatment group along with the difference in microbiological success rates for culture-confirmed bacterial eradication of urogenital NG at the TOC Visit between gepotidacin and ceftriaxone plus azithromycin will be summarized (along with 95% CI) by subgroups based on sex and sexual orientation combination (MSM, MSW, or female). Further analyses may be performed based on the observed differences between the treatment groups in these subgroups; additional details will be provided in the RAP.

Endpoint	Statistical Analysis Methods
Secondary	Secondary analyses will be performed using the micro-ITT Population subset to only include participants with confirmed NG isolated from baseline culture of their rectal/pharyngeal specimen, respectively, unless otherwise specified. • The microbiological success rates for culture-confirmed bacterial eradication of rectal NG at the TOC Visit will be summarized by treatment group and sex and sexual orientation combination. • The microbiological success rates for culture-confirmed bacterial eradication of pharyngeal NG at the TOC Visit will be summarized by treatment group and sex and sexual orientation combination. • Additional details will be provided in the RAP.
Exploratory	• Gram stain (urogenital specimens only), bacterial culture, and in vitro susceptibility test results and NAAT results at the Baseline, TOC (Day 4 to 8), and Follow-up (Day 14 to 21) Visits will be summarized as data permit. • Details regarding exploratory analyses, including additional exploratory analyses not defined in the protocol, will be described in the RAP.

PPD, in conjunction with GSK, will perform the analysis of the primary and secondary endpoints.

10.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population. The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) criteria for adult toxicity assessment [DMID, 2007a], with the exception of serum creatinine adolescent laboratory data, which will be assessed using pediatric toxicity criteria [DMID, 2007b] (Appendix 5). All reported AEs will be coded using MedDRA and summarized by system organ class and preferred terms.

Endpoint	Statistical Analysis Methods
Secondary	• The number and percentage of treatment-emergent AEs, study treatment related AEs, deaths, SAEs, and AEs leading to study treatment or study withdrawal will be provided. • Treatment-emergent AEs will be summarized by severity. • Change from baseline over time in laboratory parameters and vital signs will be summarized with descriptive statistics. • The frequency of laboratory abnormality events along with the shift from baseline to the worst-case postbaseline value will be provided. Abnormal liver chemistry results will be determined using increases above the upper limit of normal. Changes from baseline values will be summarized with descriptive statistics. • The severity of specified AEs and laboratory abnormalities will be graded according to the modified DMID toxicity grading system (Appendix 5). Data will be tabulated and reported by absolute grade for Grades 3 and higher and shift tables, as appropriate. • Adverse events of special interest will include CV, gastrointestinal, and *C. difficile* infection or colitis events. In addition, AEs associated with acetylcholinesterase inhibition are also considered special interest. As described in the RAP, manual and programmatic reviews of AEs/preferred terms will be used to assess these events. • Baseline ECG results will be provided in a listing.

10.4.4. Other Analyses

Pharmacodynamic analysis will be performed to examine the potential relationship between MIC values for the treatment/isolate pairings in this study and microbiological response at the TOC Visit. The full details will be described in the RAP.

10.5. Interim Analysis

No interim analysis is planned for this study.

10.6. Data Monitoring Committee or Other Review Board

An internal GSK Safety Review Team will monitor blinded safety data and an internal Microbiology Review Team will monitor blinded microbiological data instream. No external data monitoring review committees are planned for the study. For details on these internal review teams, refer to Appendix 3.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	adverse event
ALT	alanine aminotransferase
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease
CRF	case report form
CT	*Chlamydia trachomatis*
CV	cardiovascular
CYP3A4	cytochrome P450 enzyme 3A4
DMID	Division of Microbiology and Infectious Diseases
EAGLE	Efficacy of Antibacterial Gepotidacin Evaluated
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EU	European Union
*f*AUC	free drug area under the concentration-time curve
FDA	Food and Drug Administration
*f*T>MIC	free mean time above the minimum inhibitory concentration
FU	Follow-up
GCP	Good Clinical Practice
HIV	human immunodeficiency virus

IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-Treat
IV	intravenous
Kg	Kilogram
M	Meter
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Mgen	*Mycoplasma genitalium*
MIC	minimum inhibitory concentration
MIC_{50}	50th percentile minimum inhibitory concentration
MIC_{90}	90th percentile minimum inhibitory concentration
micro-ITT	Microbiological Intent-to-Treat
Min	Minute
mL	Milliliter
Mm	Millimeter
Msec	Millisecond
MSM	men who have sex with men
MSW	men who have sex with women

NAAT	nucleic acid amplification test
NG	*Neisseria gonorrhoeae*
PD	Pharmacodynamic
PK	pharmacokinetic
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
RAP	reporting and analysis plan
SAE	serious adverse event
SRM	Study Reference Manual
SRT	Safety Review Team
TdP	torsades de pointes
TOC	Test-of-Cure
µg	Microgram
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

Trademark Information

Trademarks of the GSK group of companies
NONE

Trademarks not owned by the GSK group of companies
FIRST RESPONSE
MedDRA

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the central laboratory.
  - Local laboratory results are only required in the event that the central laboratory results are not available in time for response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC Count With Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	Blood urea nitrogen	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total protein
	Glucose, nonfasting	Calcium	Alkaline phosphatase	Albumin
	Chloride	Magnesium		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Urine hCG pregnancy test (as needed for women of childbearing potential)[b] • Serology (HBsAg, hepatitis C virus antibody, and HIV). If serology testing was performed within 3 months prior to the first dose of study treatment and results were positive, testing at Baseline is not required. If testing was performed within 3 months and any result was negative, testing at Baseline is required.			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic case report form; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=while blood cell.

a. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 8. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event.

b. See Appendix 6 for urine test requirement details. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or the Institutional Review Board/Independent Ethics Committee.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
    - The protocol, protocol amendments, informed consent form (ICF)/assent form/eConsent (if applicable), investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board/independent ethics committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.*
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes are made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC*
  - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures*
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

  ***Note**: In countries where the responsibility to perform these submissions and notifications resides with the sponsor rather than the investigator, GSK or their designee PPD (as described in the applicable powers of attorney) will take these responsibilities.

Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent/Assent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. Participants should advise their sexual partner of their infection; this will be discussed with participants as part of the informed consent process and will be documented in the medical chart by the study site staff.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent and/or eConsent (if applicable) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent and/or eConsent (if applicable) was obtained before the participant was enrolled in the study and the date informed consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s)/eConsent during their participation in the study.
- A copy of the ICF(s)/eConsent must be provided to the participant or the participant's legally authorized representative.
  - Adolescent participants should be asked for their written assent or eConsent (if appliable) to participate in the study.
  - As applicable, the IRB/IEC will be consulted before assent form development for guidance around age-appropriate groupings and any specific IRB/IEC requirements or local laws for conducting and documenting assent.

Participants who are rescreened are required to sign a new ICF or provide eConsent (if applicable).

Study Conduct Materials and Support

The following vendors will be used to support study conduct, translations, participant recruitment, stipends, and transportation:

Vendor Name	Vendor Service
Medable	Telemedicine and teleconsent provider
Proforma ProClinix	Central advertising/printing/patient recruitment materials
Signant Health	Patient Texting Service
Transperfect	Translations (including labels & patient cards)
TAKSEE	Patient Transportation in Spain
SERMES	Patient Reimbursement in Spain
Jumo Health	Study Website

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law and as described in the ICF. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

To protect the safety interests of participants, an internal GSK Safety Review Team will review blinded safety data instream on a regular basis throughout study conduct. Data reviewers will include but are not limited to the following participants: medical monitor, safety team lead, statistician, clinical team lead, and data quality lead.

An internal Microbiology Review Team will monitor blinded pathogen identification and susceptibility data instream.

No external data monitoring review committees are planned for the study.

Provision will be made for a limited degree of unblinding of a minority of participant sample data should this be viewed as appropriate for planning closure of trial enrollment. Procedures will be described in a separate microbiology sample monitoring plan.

Written documentation regarding key decisions made by the review teams/committee will be promptly distributed to participating investigators and IRB/IECs.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocol summaries prior to study start and target results summaries submission within 12 months of the primary/study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
  - Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report, and will be provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of study results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed case report forms (CRFs) or electronic CRFs (eCRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process can be found in the Data Validation Manual.
- Document review of financial disclosures, site staff changes, and a list of investigators was also supported by Tata Consulting Services.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
  - Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final clinical study report/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
  - The Electronic Data Capture system was provided by Medidata Rave.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.
  - The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
  - The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Copies of documents are shared with external third parties contracted by GSK/PPD for review by a central reader mechanism (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • A treatment-emergent AE is an event that emerges during treatment having been absent pretreatment or worsens relative to the pretreatment state.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious AE (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of an SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term "life threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any untoward medical occurrence that, at any dose:
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Cardiovascular Adverse Events of Special Interest and Cases of *Clostridium Difficile*

Investigators will be required to fill out the specific event page of the electronic case report form (eCRF) for the following cardiovascular AEs and SAEs, and for cases of *Clostridium difficile:*

Cardiovascular Events:
• Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AEs and SAEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK/PPD in lieu of completion of the GSK/PPD AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases criteria for adult toxicity assessment [DMID, 2007a], with the exception of serum creatinine adolescent laboratory data, which will be assessed using pediatric toxicity criteria [DMID, 2007b] (Appendix 5). An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated. • The investigator will also consult the investigator's brochure and/or product information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK/PPD. However**, it is very important that**

AE and SAE Recording
the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK/PPD. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to GSK/PPD within 24 hours of receipt of the information.

Reporting of SAE to GSK/PPD

SAE Reporting to GSK/PPD via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK/PPD will be the electronic data collection tool. • The study site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically qualified subinvestigator must show evidence within the eCRF (e.g., check review box, signature, etc) of review and verification of the relationship of each SAE to study treatment/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given study site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study site can report this information to the medical monitor or SAE coordinator by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual.

12.5. Appendix 5: Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment

ESTIMATING SEVERITY GRADE: For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (<48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs: ANY clinical event deemed by the investigator to be serious or life-threatening should be considered a Grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, and severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the Division of Microbiology and Infectious Diseases (DAIDS) and modified to better meet the needs of participants in Division of Microbiology and Infectious Diseases (DMID) trials.
- For parameters not included in the following Toxicity Tables, study sites should refer to the "Guide for Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.

Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

Note: Adult DMID toxicity criteria will be applied for all laboratory parameters, with the exception of serum creatinine adolescent laboratory data, which will be assessed using pediatric DMID toxicity criteria. The DMID pediatric toxicity table may be accessed at https://www.niaid.nih.gov/sites/default/files/dmidpedtox.pdf.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 to 10.5 gm/dL	8.0 to 9.4 gm/dL	6.5 to 7.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count	1000 to 1500 /mm^3	750 to 999 /$mm^{3`}$	500 to 749 /mm^3	<500 /mm^3
Platelets	75,000 to 99,999 /mm^3	50,000 to 74,999 /mm^3	20,000 to 49,999 /mm^3	<20,000 /mm^3
White Blood Cells	11,000 to 13,000 /mm^3	13,000 to 15,000 /mm^3	15,000 to 30,000 /mm^3	>30,000 or <1000 /mm^3
% Polymorphonuclear Leukocytes + Band Cells	>80%	90 to 95%	>95%	N/A
Abnormal Fibrinogen	Low: 100 to 200 mg/dL High: 400 to 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL High: N/A	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 to 40 mcg/mL	41 to 50 mcg/mL	51 to 60 mcg/dL	>60 mcg/dL
Prothrombin Time (PT)	1.01 to 1.25 x ULN	1.26 to 1.5 x ULN	1.51 to 3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APTT)	1.01 to 1.66 x ULN	1.67 to 2.33 x ULN	2.34 to 3 x ULN	>3 x ULN
Methemoglobin	5.0 to 9.9%	10.0 to 14.9%	15.0 to 19.9%	>20%

N/A=not applicable; ULN=upper limit of normal.

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to 135 mEq/L	123 to 129 mEq/L	116 to 122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146 to 150 mEq/L	151 to 157 mEq/L	158 to 165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 to 3.4 mEq/L	2.5 to 2.9 mEq/L	2.0 to 2.4 mEq/L or intensive replacement therapy of hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6 to 6.0 mEq/L	6.1 to 6.5 mEq/L	6.6 to 7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55 to 64 mg/dL	40 to 54 mg/dL	30 to 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 to 160 mg/dL	161 to 250 mg/dL	251 to 500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 to 7.8 mg/dL	7.7 to 7.0 mg/dL	6.9 to 6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 to 1.2 mEq/L	1.1 to 0.9 mEq/L	0.8 to 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 to 2.4 mg/dL	1.5 to 1.9 mg/dL or replacement Rx required	1.0 to 1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 to <1.25 x ULN	1.25 to <1.5 x ULN	1.5 to 1.75 x ULN	>1.75 x ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 to <1.5 x ULN	1.5 to <2.0 x ULN	2.0 to 3.0 x ULN	>3.0 x ULN
Blood urea nitrogen	1.25 to 2.5 x ULN	2.6 to 5 x ULN	5.1 to 10 x ULN	>10 x ULN
Hyperuricemia (uric acid)	7.5 to 10.0 mg/dL	10.1 to 12.0 mg/dL	12.1 to 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 to 1.5 x ULN	1.6 to 3.0 x ULN	3.1 to 6.0 x ULN	>6 x ULN or dialysis required

Rx=therapy; ULN=upper limit of normal.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Aspartate aminotransferase (AST)	1.1 to <2.0 x ULN	2.0 to <3.0 x ULN	3.0 to 8.0 x ULN	>8.0 x ULN
Alanine aminotransferase (ALT)	1.1 to <2.0 x ULN	2.0 to <3.0 x ULN	3.0 to 8.0 x ULN	>8.0 x ULN
Gamma to glutamyl transferase (GGT)	1.1 to <2.0 x ULN	2.0 to <3.0 x ULN	3.0 to 8.0 x ULN	>8.0 x ULN
Alkaline Phosphatase	1.1 to <2.0 x ULN	2.0 to <3.0 x ULN	3.0 to 8.0 x ULN	>8.0 x ULN
Amylase	1.1 to 1.5 x ULN	1.6 to 2.0 x ULN	2.1 to 5.0 x ULN	>5.1 x ULN
Lipase	1.1 to 1.5 x ULN	1.6 to 2.0 x ULN	2.1 to 5.0 x ULN	>5.1 x ULN

ULN=upper limit of normal.

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg to 1 gm loss/day	2 to 3+ or 1 to 2 gm loss/day	4+ or 2 to 3.5 gm loss/day	Nephrotic syndrome or >3.5 gm loss/day
Hematuria	Microscopic only <10 RBC/HPF	Gross, no clots >10 RBC/HPF	Gross, with or without clots, or red blood cells casts	Obstructive or required transfusion

HPF=high powered field; RBC=red blood cells.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac rhythm	N/A	Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required	Unstable dysrhythmia; hospitalization and treatment required
Hypertension	Transient increase >20 mm/Hg; no treatment	Recurrent, chronic increase >20 mm/Hg; treatment required	Acute treatment required; outpatient treatment or hospitalization possible	End organ damage or hospitalization required
Hypotension	Transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mmHg systolic BP. No treatment required	Symptoms due to orthostatic hypotension or BP decreased by <20 mmHg systolic; correctable with oral fluid treatment	Requires IV fluids; no hospitalization required	Mean arterial pressure <60 mmHg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion; pain; EKG changes	Tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	Microscopic/occult	Mild, no transfusion	Gross blood loss; 1 to 2 units transfused	Massive blood loss; >3 units transfused

BP=blood pressure; IV=intravenous; EKG=electrocardiogram; N/A=not applicable; Rx=therapy.

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient; no treatment	Persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	N/A
Bronchospasm, Acute	Transient; no treatment; FEV_1 70 to 80% of peak flow	Requires treatment; normalizes with bronchodilator; FEV_1 50 to 70% of peak flow	No normalization with bronchodilator; FEV_1 25 to 50% of peak flow; or retractions present	Cyanosis: FEV_1 <25% of peak flow; or intubation necessary
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring oxygen therapy

FEV_1=forced expiratory volume in 1 second; N/A=not applicable.

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	Mild or transient; maintains reasonable intake	Moderate discomfort; intake decreased significantly; some activity limited	No significant intake; requires IV fluids	Hospitalization required
Vomiting	1 episode in 24 hours	2 to 5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	Requiring stool softener or dietary modification	Requiring laxatives	Obstipation requiring manual evacuation or enema	Obstruction or toxic megacolon
Diarrhea	Mild or transient; 3 to 4 loose stools/day or mild diarrhea lasting <1 week	Moderate or persistent; 5 to 7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization
Oral discomfort/ Dysphagia	Mild discomfort; no difficulty swallowing	Some limits on eating/drinking	Eating/talking very limited; unable to swallow solid foods	Unable to drink fluids; requires IV fluids

IV=intravenous.

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	Slight incoordination dysdiadochokinesis	Intention tremor, dysmetria, slurred speech; nystagmus	Locomotor ataxia	Incapacitated
Psychiatric	Mild anxiety or depression	Moderate anxiety or depression; therapy required; change in normal routine	Severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	Acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle strength	Subjective weakness; no objective symptoms/signs	Mild objective signs/symptoms; no decrease in function	Objective weakness; function limited	Paralysis
Paresthesia (burning, tingling, etc.)	Mild discomfort; no treatment required	Moderate discomfort; non- narcotic analgesia required	Severe discomfort; or narcotic analgesia required with symptomatic improvement	Incapacitating; or not responsive to narcotic analgesia
Neurosensory	Mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or	Moderate impairment (moderately decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or	Severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e., upper and lower extremities)	Sensory loss involves limbs and trunk; paralysis; or seizures

	change in taste, smell, vision, and/or hearing	mild impairment that is not symmetrical		

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	Mild pain not interfering with function	Moderate pain, analgesics and/or pain interfering with function but not with ADL	Severe paid; pain and/or analgesics interfering with ADL	Disabling pain
Arthritis	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling; interfering with function but not with ADL	Severe pain with inflammation, erythema or joint swelling, and interfering with ADL	Permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	Muscle tenderness (at other than injection site) or with moderate impairment of activity	Severe muscle tenderness with marked impairment of activity	Frank myonecrosis

ADL=activities of daily living.

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	Erythema; pruritus	Diffuse, maculo papular rash, dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15 mm	15 to 30 mm	>30 mm	N/A
Erythema	<15 mm	15 to 30 mm	>30 mm	N/A
Edema	<15 mm	15 to 30 mm	>30 mm	N/A
Rash at injection site	<15 mm	15 to 30 mm	>30 mm	N/A
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching over entire body	N/A

N/A=not applicable.

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic reaction	Pruritus without rash	Localized urticarial	Generalized urticarial; angioedema	Anaphylaxis
Headache	Mild, no treatment required	Transient, moderate; treatment required	Severe; responds to initial narcotic therapy	Intractable; requires repeated narcotic therapy
Fever: oral	37.7 to 38.5°C or 100.0 to 101.5°F	38.6 to 39.5°C or 101.6 to 102.9°F	39.6 to 40.5°C or 103 to 105°F	>40°C or >105°F
Fatigue	Normal activity reduced <48 hours	Normal activity decreased 25 to 50%; >48 hours	Normal activity decreased >50%; cannot work	Unable to care for self

12.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the study site personnel's review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative urine pregnancy test.
- Pregnancy testing will be performed at Baseline (Day 1) before study treatment administration. The urine pregnancy test at Baseline will determine study contraception and abstinence requirements as follows:
  - Pregnancy testing at Baseline (Day 1) should be performed using the urine test kit provided to the study site (FIRST RESPONSE Early Result Pregnancy Test with a high sensitivity of ≤6.3 mIU/mL). Participants with a negative urine pregnancy test result from this test kit may be included in the study with no pretreatment contraception or abstinence requirements.

  Note: ***ONLY*** if the study-specific pregnancy kit provided to the study site is unavailable, a standard urine pregnancy test with a sensitivity of 25 mIU/mL may be used as an exception. A participant with a negative urine pregnancy test result from

the standard test may be included in the study ***only*** if the participant has used a highly effective contraception method as described in Table 10 or has practiced abstinence from penile/vaginal intercourse for at least 14 days before receiving study treatment.

- A pregnancy test will also be performed at the Test-of-Cure (Day 4 to 8) Visit.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Urine pregnancy test kits were provided by PPD except for sites in Australia where urine pregnancy test kits were provided by Flinders and Zuellig Pharma.

Contraception Guidance – Male and Female Participants

See the section directly above regarding pregnancy testing for female participants at Baseline (Day 1) and associated pretreatment contraception and abstinence requirements. Female participants of childbearing potential who enter the study using contraception must continue to do so throughout the study.

For male and female participants, the only contraception requirement from the Baseline Visit through the TOC Visit is abstinence or the use of a male condom during intercourse. As described in Section 6.3, all participants will be instructed to abstain from sexual activity from the Baseline Visit through the TOC Visit to prevent possible re-infection with NG. If a participant refuses to abstain and is sexually active, male participants as well as male partners of female participants, of **both childbearing and nonchildbearing potential**, must use a male condom during intercourse from the Baseline Visit through completion of the TOC Visit.

Table 10 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• implantable progestogen-only hormonal contraception associated with inhibition of ovulationb • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion

Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* ***Note****: Male partners of female participants, of both childbearing and nonchildbearing potential, must use a male condom during intercourse from the Baseline Visit through completion of the TOC Visit.)*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

WOCBP=woman of childbearing potential.

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

Collection of Pregnancy Information

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK/PPD within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious AE (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a poststudy pregnancy that is considered reasonably related to the study treatment by the investigator will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study treatment.

12.7. Appendix 7: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and institutional review board/independent ethics committee allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to gepotidacin or urogenital gonorrhea and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to gepotidacin and urogenital gonorrhea. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (or analysis of the entire genome) (as appropriate).
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to gepotidacin or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on gepotidacin (or study treatments of this class) or urogenital gonorrhea continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

12.8. Appendix 8: Liver Safety: Required Actions and Follow-up Assessments

Phase III liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

The stopping criteria for discontinuing dosing of study treatment due to liver chemistry parameters have limited application in this study, as study treatment is only administered as 2 doses of gepotidacin over a 24-hour period starting on Day 1 or as a single intramuscular dose of ceftriaxone plus an oral dose of azithromycin on Day 1. However, if participants are found to have values consistent with the usual stopping parameters, it is appropriate to institute evaluation and monitoring criteria according to standard GSK criteria. Therefore, if defined parameters are reached, liver function tests should be evaluated as shown in the table below, which is in keeping with the liver stopping criteria, and laboratory evaluation should be instituted.

Phase III liver chemistry evaluation criteria and required follow-up assessments

<table>
<tr><th colspan="2">Liver Chemistry Evaluation Criteria – Liver Event</th></tr>
<tr><td>ALT Absolute</td><td>ALT ≥8 x ULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥5 x ULN but <8 x ULN persists for ≥2 weeks
ALT ≥3 x ULN but <5 x ULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[a,b]</td><td>ALT ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[b]</td><td>ALT ≥3 x ULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥5 x ULN but <8 x ULN and cannot be monitored weekly for ≥2 weeks
ALT ≥3 x ULN but <5 x ULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[c]</td><td>ALT ≥3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[b]
• Perform liver event follow-up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)</td><td>• Viral hepatitis serology[d]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen),</td></tr>
</table>

Liver Chemistry Evaluation Criteria – Liver Event	
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline	quantitative hepatitis B DNA, and hepatitis delta antibody[e] • Obtain blood sample for PK analysis, within 24 hours after last dose[f] • Serum creatine phosphokinase and lactate dehydrogenase • Fractionate bilirubin, if total bilirubin ≥2 x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over-the-counter medications • Record alcohol use on the liver event alcohol intake eCRF page **<u>For bilirubin or INR criteria:</u>** • Antinuclear antibody, antismooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China.** • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or liver biopsy eCRFs.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic case report form; HPLC=high-performance liquid chromatography; IgM=immunoglobulin M; INR=international normalized ratio; PK=pharmacokinetic; SAE=serious adverse event; ULN=upper limit of normal.

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
b. All events of ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN (>35% direct bilirubin) or ALT ≥ 3 x ULN **and** INR >1.5, if INR measured which may indicate severe liver injury (possible "Hy's Law"), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants.
c. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
d. Includes: hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen, and hepatitis B core antibody (IgM); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody
e. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction of hepatitis D RNA virus (where needed) [Le Gal, 2005].
f. The PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

Phase III liver chemistry increased monitoring criteria

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5 x ULN and <8 x ULN **and** bilirubin <2 x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3 x ULN and <5 x ULN **and** bilirubin <2 x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If ALT decreases from ALT ≥5 x ULN and <8 x ULN to ≥3 x ULN but <5 x ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3 x ULN and bilirubin <2 x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

References

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 2009;37:1779-1784.

Le Gal F, Gordien E, Affolabi D, et al. Quantification of hepatitis delta virus RNA in serum by consensus real-time PCR indicates different patterns of virological response to interferon therapy in chronically infected patients. J Clin Microbiol. 2005;43:2363-2369.

12.9. Appendix 9: Additional Guidance on Permitted and Prohibited Medications and Crediblemeds.org

For quick reference, a list of some common concomitant medications that are permitted for participants to take during the study for nausea, vomiting, pain, diarrhea, etc. per investigator discretion is provided below. A list of some of the commonly used medications that are prohibited is also provided in this appendix. Lastly, a topline overview of how to use crediblemeds.org is also provided.

A further detailed list of medications will be provided in the Study Reference Manual.

List of Concomitant Medications Permitted During the Study:

Generic Name[a]	**Common Therapeutic Use(s)**
Dolasetron	Nausea, vomiting
Granisetron	Nausea, vomiting
Metoclopramide	Nausea, vomiting
Palonosetron	Nausea, vomiting
Promethazine	Nausea, vomiting
Tropisetron (Only on Non-US markets)	Nausea, vomiting
Acetaminophen or paracetamol	Pain
Tramadol	Pain
Hydrocodone ER	Pain, severe
Lidocaine (solution for intramuscular injection only)	Anesthetic
Loperamide	Diarrhea
Cetirizine	Antihistamine (H_1)
Ebastine	Antihistamine (H_1)
Fexofenadine	Antihistamine (H_1)
Loratadine	Antihistamine (H_1)
Clotrimazole	Antifungal – ***topical, nonsystemic only***
Tolnaftate	Antifungal – ***topical, nonsystemic only***
Ketoconazole	Antifungal – ***topical, nonsystemic only***
Tenofovir and emtricitabine	Pre-exposure prophylaxis for HIV

ER=extended release; HIV=human immunodeficiency virus; US=United States.
a. Check within each local country to assess if other generic names apply.
Note: See also Section 7.7.1 for other permitted medications.

List of Concomitant Medications Prohibited During the Study:

Generic Name[a]	Common Therapeutic Use(s)
Ondansetron	Nausea, vomiting
Other investigational products	Various
Systemic antibiotics (e.g., ciprofloxacin, amoxicillin/clavulanate, cephalexin, doxycycline)	Antibiotic – ***all systemic***
Topical and intravaginal antibiotics (e.g., clindamycin, Neomycin, polymyxin, clotrimazole, tolnaftate, ketoconazole, metronidazole)	Antibiotic – ***all topical and intravaginal***
Systemic antifungals (e.g., itraconazole, fluconazole)	Antifungal – ***all systemic***
Prednisolone or equivalent (refer to Section 7.7.2 for details)	Immunosuppressive therapy
Strong CYP3A4 inhibitors	See Study Reference Manual
St John's wort	Herbal, various
Succinylcholine and other nondepolarizing paralytic agents	Muscle relaxation, muscle paralysis

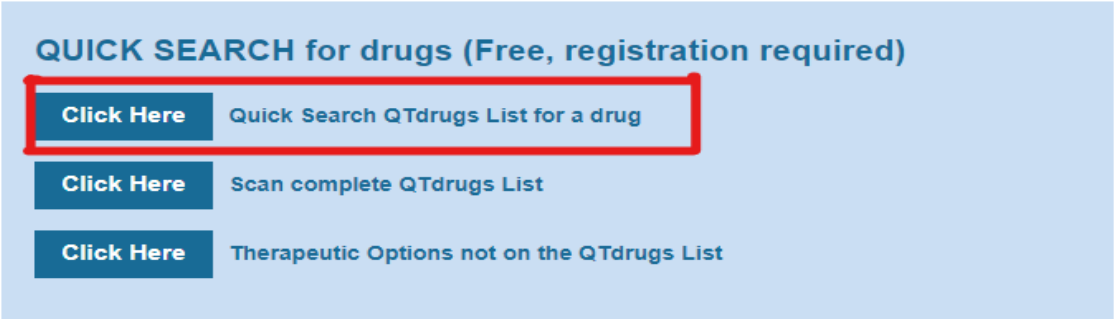
CYP3A4=cytochrome P450 enzyme 3A4.
a. Check within each local country to assess if other generic names apply.
Note: See also Section 7.7.2 for other prohibited medications.

Crediblemeds.org Instructions

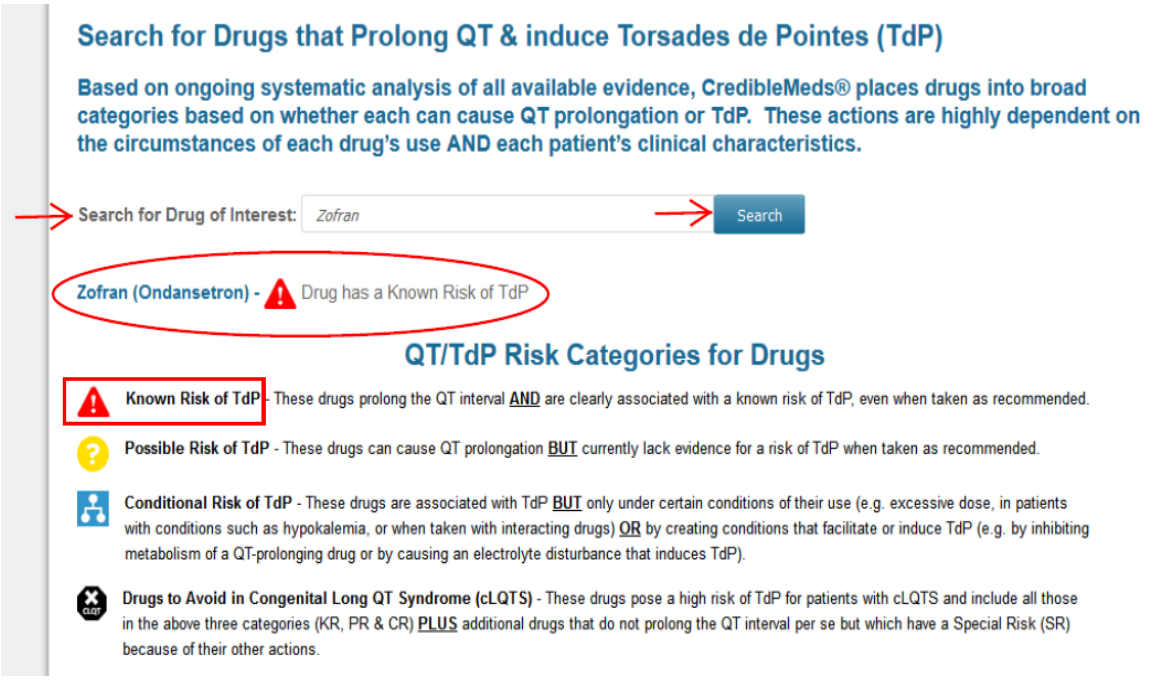
Instructions for accessing www.crediblemeds.org and searching for an exclusionary drug due to its "Known Risk of Torsades de Pointes (TdP)" category are summarized below.

To access www.crediblemeds.org, copy and paste this link into the internet search bar: https://www.crediblemeds.org/

On the main home page, there are 3 search options available. Choose the first option to search for 1 drug at a time. Free registration is required by the website.

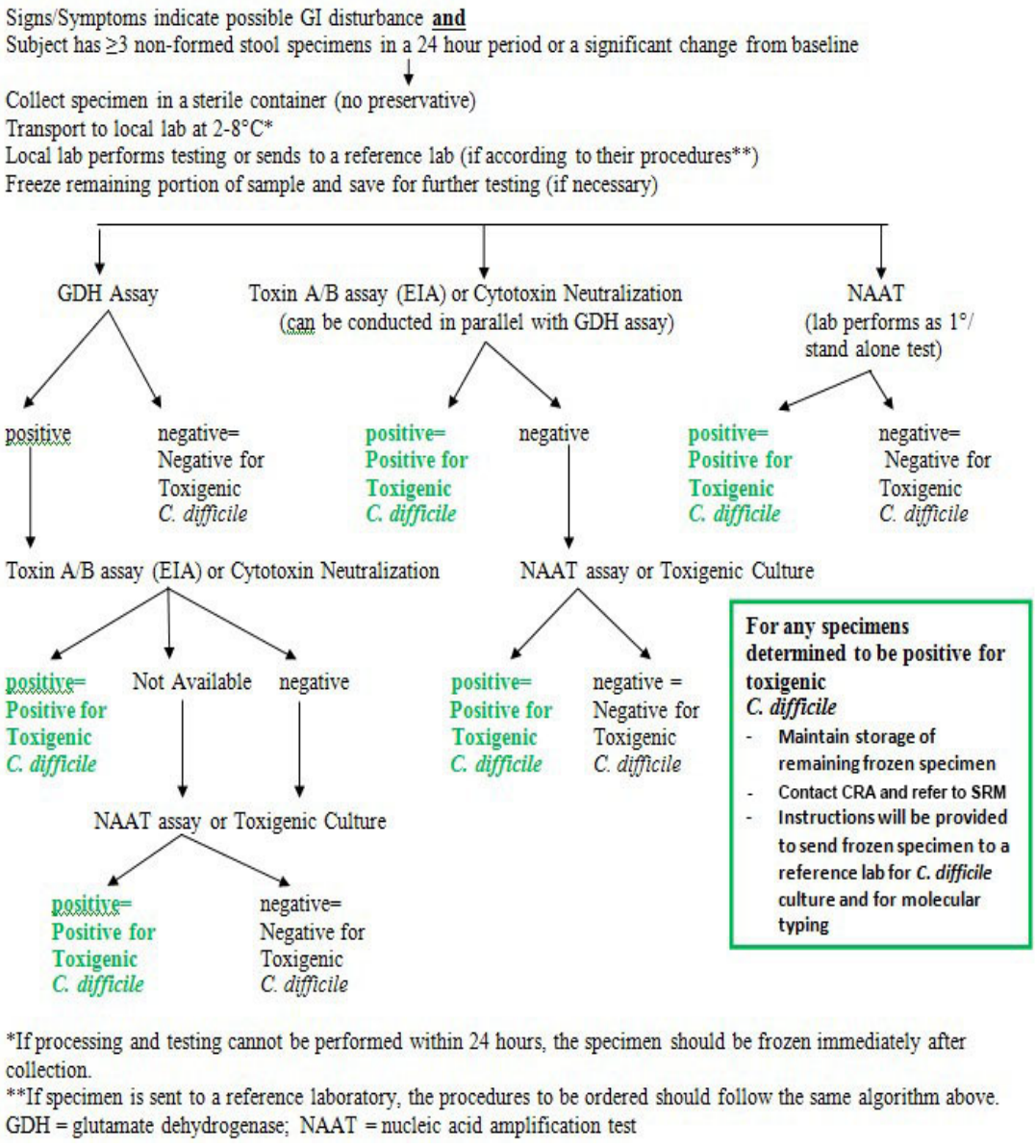


Choosing that option brings you to a screen that allows for you to enter a generic or brand drug name and choose Search. If it has a Known risk of TdP (i.e., is a prohibited exclusionary medication), it will show a red triangle with an exclamation point as shown here:



Always check the www.crediblemeds.org website for the most up-to-date information on drugs with a Known Risk of TdP for participant safety.

12.10. Appendix 10: *Clostridium Difficile* Testing Procedure and Algorithm



*If processing and testing cannot be performed within 24 hours, the specimen should be frozen immediately after collection.
**If specimen is sent to a reference laboratory, the procedures to be ordered should follow the same algorithm above.
GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test
CRA = clinical research associate (PPD site monitor); SRM = Study Reference Manual

Note: This algorithm is subject to investigator discretion when the clinical presentation and time course of diarrhea (e.g., during or within 12 hours immediately after dosing) do not fit the Clostridium difficile associated diarrhea definition; consideration should be given to diarrhea occurring in this early time frame to be suggestive of a cholinergic effect.

12.11. Appendix 11: COVID-19 Protocol Information

12.11.1. Overall Rationale for this Appendix

The COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures.

This appendix outlines measures that may be applicable for any study site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity. These measures are expected to be temporary and study sites will be notified of any change to these allowances as the COVID-19 pandemic evolves.

12.11.2. Study Procedures During the COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, sites should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit/risk when making enrollment and treatment decisions for study participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow-up assessments; however, when not possible, for the duration of these special circumstances, the following measures may be implemented:

- For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the Study Reference Manual. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit.
- Clinical investigators should document in site/participant/source files how restrictions related to COVID-19 led to changes in study conduct, the duration of those changes, and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol-required data/visits due to COVID-19 should be noted in site/participant/source files and recorded as a COVID-19 protocol deviation.

Specifically for data management and monitoring the following will apply:

- If on-site monitoring is no longer permitted, GSK/PPD will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK/PPD will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign-Off Process: The principal investigator is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The principal investigator may sign/re-sign the eCRF from any computer/location by accessing the validated system using his/her unique eCRF log-in credentials. The principal investigator may delegate this activity to another medically qualified and trained subinvestigator and this must be documented on the Delegation of Responsibilities Log. It is recommended that the principal investigator identifies a subinvestigator as a back-up for eCRF signatures and that appropriate training on the protocol and eCRF requirements is provided and documented.
- Essential Document Sign-Off Process: If an investigator is unable to print and sign essential documents such as Protocol/Amendment signature page then e-mail approval can be accepted by replying to the relevant e-mail that is sent by GSK/PPD.

12.12. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 2 16 December 2022

This global amendment is considered to be non-substantial.

Overall rationale for the current Amendment:

This global amendment increased the total enrollment sample size; revised and added key populations for analyses to support the planned efficacy analyses per the current reporting and analysis plan; and removed the covariate age at Baseline from the primary efficacy analyses. The amendment includes minor updates to gepotidacin introductory and risk text for consistency with the current investigator's brochure, and revised crediblemeds.org instructions for consistency with the current website. The amendment also includes minor administrative and wording edits and editorial text additions per the current protocol template.

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief Rationale
Synopsis 5.2 Number of Participants 10.2.1 Justification of Sample Size	Increased the total number of enrolled participants from approximately 600 to approximately 620.	Based on the microbiological evaluability rate, the total sample size was increased to ensure the number of participants in the micro-ITT Population was reached.
10.3 Populations for Analyses	The key populations for analyses have been updated and added.	Revisions were made to support the planned efficacy analyses per the current reporting and analysis plan.
10.4.2 Efficacy Analyses	Excluded the covariate "Age at Baseline" from the primary efficacy analyses. Of note, there is no change to the randomization stratification.	Based on current enrollment projections, there will be an insufficient number of participants in the <18 and >65 years age categories in each treatment group at the end of the study; thus, the sample size in those categories will not be sufficient to support the primary analysis.
Section 3 Introduction	Updated gepotidacin text based on the investigator's brochure.	Revised for consistency with the investigator's brochure.

Section # and Name	Description of Change	Brief Rationale
Section 3.3.1 Risk Assessment	Minor text updates were made to the QTcF, acetylcholinesterase-inhibition, and reproduction sections for gepotidacin.	Revised for clarification and consistency with current investigator's brochure.
Section 9 Study Assessments and Procedures	The demographic data that is collected at the Baseline Visit was clarified and rationale text was added.	Information was added per the current GSK protocol template.
12.3 Appendix 3: Study Governance Considerations	Clarified that redaction of source documents will be performed by study sites before documents are shared with outside vendors. Study Conduct Materials and Support subsection was added.	Information was added per the current GSK protocol template.
12.4 Appendix 4: Adverse Events Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Definition of a treatment-emergent adverse event was added.	Information was added per the current GSK protocol template.
12.9 Appendix 9: Additional Guidance on Permitted and Prohibited Medications and Crediblemeds.org	Updated the text and picture to indicate free registration is now required.	Revised for consistency with the current website.
Throughout	Vendor information was added.	Information was added per the current GSK protocol template.
Throughout	Minor editorial and document formatting revisions, including the addition of text per the current protocol template.	Minor, therefore, have not been summarized. Updated text added per the current GSK protocol template provided further clarification of the original text.

Amendment 1 14 December 2021

This global amendment was considered to be non-substantial.

Overall Rationale for the Amendment:

This global amendment revised the primary analysis to be performed using the Miettinen and Nurminen method instead of the Cochran-Mantel-Haenszel method; added estimand

text; indicated study operational allowances with regard to COVID-19; incorporated past administrative and site notification letters; provided minor clarifications to the microbiology and NAAT defining criteria in the response and outcomes tables; indicated the total enrollment population will be approximately 600 participants; added micro-ITT subpopulations for participants with NG isolated in their rectal/pharyngeal specimen; and incorporated updates per the most recent safety and PK data known for gepotidacin, which included removal of P-glycoprotein inducers from the prohibited medications. Minor clarifications were also made throughout the protocol including, but not limited to, the Schedule of Activities table, inclusion and exclusion criteria, primary and secondary objectives, randomization stratification text, and adverse events of special interest. The amendment also includes additional minor administrative and wording edits.

Summary of changes table of previous amendments:

Section # and Name	Description of Change	Brief Rationale
Synopsis 4 Objectives and Estimands/Endpoints Table 3 Estimands	Added estimands for the primary and secondary objectives and endpoints	To meet current ICH guidelines on estimands
Synopsis 5.1 Overall Design Figure 1 Study Design Schematic 5.4 Scientific Rationale for Study Design 7.3 Method of Treatment Assignment 10.4.2 Efficacy Analyses	Updated text to clarify that participants will be stratified by "sex and sexual orientation combination" and age	Text clarification as the stratification factor of "gender" (i.e., male/female) was inadvertently being used interchangeably for sex characteristics that are biologically defined. To avoid confusion, the term "sex" will be used from this point forward.
Synopsis 4 Objectives and Estimands/Endpoints	Removed the analysis population (i.e., micro-ITT) from the primary and secondary objectives	Not a requirement in the objectives text and the analysis populations are further described in Section 10 of the protocol
Synopsis 5.2 Number of Participants 10.2.1 Justification of Sample Size	Revised the target number of randomized participants to approximately 600	To reflect currently known safety database requirements for regulatory authorities

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities (Table 1)	Divided the "Interactive response technology" row into 2 separate rows specific for the screening and randomization modules; removed the "Randomization" row accordingly	To align with how the interactive response is being used at study sites and to more closely follow the expected order of procedures
2 Schedule of Activities (Table 1) 5.1 Overall Study Design 9 Study Assessments and Procedures Appendix 3 Study Governance Considerations Appendix 11 COVID-19 Protocol Information	Added text and table footnotes to allow for eConsent, telemedicine study-related data collection, collection of visit data as a combination of telemedicine and on-site visits, remote source data verification, and eCRF sign-off flexibility for investigators	To support ongoing study conduct from safety and operational perspectives during the COVID-19 pandemic
Synopsis 3.3.3 Overall Benefit:Risk Conclusion 5.4 Scientific Rationale for Study Design 10.6 Data Monitoring Committee or Other Review Board Appendix 3 Study Governance Considerations	Clarified only internal review teams will monitor study data during the study and that no external data monitoring committee is planned	Text clarification

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities (Table 2) 9.1.2 NAAT Assay	Clarified that any specimens collected for NG NAAT assay at the central laboratory for NG would also be assayed for CT per standard laboratory procedures	Incorporation of Protocol Administration Letter 4 dated 06-MAY-2020, which addressed that CT can cause infection at all 3 body sites (urogenital, rectal, pharyngeal) that are being evaluated in this study. Thus, when NAAT samples are submitted for NG testing, they are also routinely tested for CT and results are reported for both pathogens.
2 Schedule of Activities (Table 2) 9.1.2 NAAT Assay	Clarified text and table footnotes for the NAAT assay at the Follow-up Visit to specify pathogens be tested and to refer to presence of nucleic acid instead of a positive result	Text clarifications
3.2 Background 5.4 Scientific Rationale for Study Design 5.5 Dose Justification	Included text regarding the US CDC current standard of care treatment recommendations for gonococcal infection. Per FDA communications, no changes to the comparator arm are warranted.	Incorporation of the Site Notification Letter dated 26-JAN-2021 (sent to US-only sites), which described the most recent US CDC recommendations for treatment of gonococcal infection
3.3.1 Risk Assessment	Minor text clarifications for gepotidacin (clinical QTc effects, added relevant exposures for nonclinical embryofetal effects, etc.). Note, the risk benefit assessment for the study did not change.	Consistency with currently known safety and PK data for gepotidacin

Section # and Name	Description of Change	Brief Rationale
3.3.1 Risk Assessment 6.2 Exclusion Criteria #15 7.7.2 Prohibited Medications and Nondrug Therapies Appendix 9 Additional Guidance on Permitted and Prohibited Medications and Crediblemeds.org	Removed exclusion for strong P-glycoprotein inhibitors	Consistency with currently known PK data for gepotidacin
6.1 Inclusion Criteria #2 Figure 1 Study Design Schematic	Revised the criterion to further describe what would be considered clinical suspicion of a urogenital gonococcal infection based on investigator feedback	Incorporation of Protocol Administration Letter 2 dated 30-SEP-2019, which provided additional details for expected clinical presentation of urogenital gonococcal infection
6.1 Inclusion Criteria #4b	Revised the criterion to state there was no requirement for contraception use or abstinence within 14 days of study entry in WOCBP who have a negative high sensitivity urine pregnancy test result	Incorporation of Protocol Administration Letter 2 dated 30-SEP-2019, which streamlined the criterion text for clarification and consistency with Appendix 6
6.2 Exclusion Criteria #3 and #5	Edited to include “uncontrolled” before high blood pressure and diabetes	Text clarification
6.2 Exclusion Criteria #17	Added details to the exclusion criterion note for ECG exclusion	To support consistency in ECG measurements
7.7 Concomitant Therapy	Clarified that any antibiotic use within 6 months of the Baseline Visit should be recorded	To support the study analysis
9 Study Assessments and Procedures	Removed the requirement for participants to remain at the site for approximately 30 minutes after dosing at the Baseline Visit; however, retained text indicating that posttreatment assessments still need to be completed	To support site flexibility for study conduct

Section # and Name	Description of Change	Brief Rationale
9.1.1 Bacteriology 6Samples for Culture	Minor text clarifications were added to the defining criteria in the outcome and response Table 5	Clarification to support the planned statistical analyses and programming details
9.1.2 NAAT Assay	Minor text clarifications were added to the defining criteria in the outcome and response Table 6 and Table 7	Clarification to support the planned statistical analyses and programming details
10.2.1 Justification of Sample Size	Clarified the significance level is a 0.025 one-sided significance level rather than a 0.05 two-sided significance level, noted the estimated power was approximate in Table 8, and clarified that no treatment difference is assumed	Text clarifications
10.2.2 Sample Size Sensitivity	Revised the percentage of power in Table 8 for the 92% and 88% success rate rows by a single digit; removed unnecessary text; and clarified that no treatment difference is assumed	Minor text update for consistency in rounding the numbers and text clarifications
10.1 Statistical Hypothesis 10.4.2 Efficacy Analysis	Revised the primary analysis to be performed using the Miettinen and Nurminen method instead of the Cochran-Mantel-Haenszel method and expanded text to state there would be 9 total subgroups based on the randomization stratification variables	Consistency with the reporting and analysis plan
10.3 Populations for Analyses 10.4.2 Efficacy Analysis	Added micro-ITT subpopulations for participants who have NG isolated from the rectal/pharyngeal specimen	To support the planned analysis
10.5 Interim Analysis	Clarification that no interim analysis is planned	Text clarification
Appendix 2 Clinical Laboratory Tests	Added magnesium to the laboratory assessments	Consistency with the chemistry laboratory panel that will be conducted in the study

Section # and Name	Description of Change	Brief Rationale
Appendix 3 Study Governance Considerations	Clarified that study participants should advise their sexual partners of their infection status and that it should be documented in the medical chart per study site staff	Incorporation of Protocol Administration Letter 1 dated 22-JUL-2019, which supports notification of NG infection status to sexual partners of study participants
Appendix 3 Study Governance Considerations	Clarified that, in countries where certain responsibilities reside with the sponsor instead of the investigator, GSK or its designee will be responsible for those activities	To support site feasibility
Throughout	Updated the second dose window for gepotidacin to 10 to 12 hours after the first dose; the original second dose window was 6 to 12 hours	Incorporation of Protocol Administration Letter 3 dated 12-FEB-2020, which narrowed the second dose window for gepotidacin for safety reasons and to support uniformity in study conduct and subsequent data analysis. Note: There is no evidence this impacts efficacy.
Throughout	Updated text to state *Clostridium difficile* and acetylcholinesterase inhibition events are considered adverse events of special interest	To support the planned safety analysis
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized