TITLE PAGE

Protocol Title: A Pharmacokinetic, multi-cohort study in Healthy Adult Subjects to Assess Gepotidacin as Victim and as Perpetrator of Drug-Drug Interactions via CYP450, Renal and Intestinal Transporters, and to Assess Gepotidacin Pharmacokinetics in Japanese Healthy Adults

Protocol Number: 213678

Compound Number or Name: GSK2140944

Brief Title: Drug Interactions between Gepotidacin and Select CYP450, Renal, and Intestinal Transporters, and Gepotidacin Pharmacokinetics in Japanese Healthy Adults

Study Phase: Phase I

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Regulatory Agency Identifying Number(s): IND: 111885

Approval Date: 13-JUL-2020

SPONSOR SIGNATORY:

PPD

PPD

Rajnish Saini, MD, FACC
Disease Area Lead, Specialty (Clinical Sciences)

PPD

Date

Medical Monitor Name and Contact Information: Please refer to the Study Reference Manual

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Pharmacokinetic, multi-cohort Study in Healthy Adult Subjects to Assess Gepotidacin as Victim and as Perpetrator of Drug-Drug Interactions via CYP450, Renal and Intestinal Transporters, and to Assess Gepotidacin Pharmacokinetics in Japanese Healthy Adults.

Brief Title: Drug Interactions between Gepotidacin and Select CYP450, Renal, and Intestinal Transporters, and Gepotidacin Pharmacokinetics in Japanese Healthy Adults

Rationale: The rationale for this study is 2-fold: 1) to determine the magnitude and clinical relevance of potential drug-drug interactions (DDIs) and 2) to generate pharmacokinetic (PK), safety, and tolerability data in a separate Japanese cohort. Clinical PK and safety data generated in Japanese participants will be used to support clinical development (uncomplicated urinary tract infections [uUTI] and gonorrhea) in Japan and provide additional safety data prior to evaluation of gepotidacin in Japanese patients.
.
Comparisons will be made between Japanese and non-Japanese subjects to characterise potential differences in pharmacokinetics across the two groups.

GlaxoSmithKline (GSK) has conducted in vitro studies and used physiologically-based PK (PBPK) modeling to evaluate the DDI potential with gepotidacin. Based on these analyses, GSK conducted a risk assessment for gepotidacin as a DDI victim and perpetrator:

1) Gepotidacin is a substrate of MATE and potentially of OCT transporter: Gepotidacin renal clearance exceeds glomerular filtration rate by greater than 2-fold, which predicts a significant role of tubular secretion in renal elimination. In vitro data suggests that gepotidacin is a substrate of MATE and although it does not suggest that gepotidacin is a substrate of the currently known OCTs, MATE transporters are usually coupled with OCTs. For the uUTI and gonorrhea indications, the DDI risk included the potential increased plasma gepotidacin exposure (may lead to safety implications). For the uUTI indication, there is an added potential risk for reduced gepotidacin urine levels (may translate to a loss of uUTI efficacy);

2) Gepotidacin is a CYP3A4 substrate: Potential cytochrome P450 (CYP)3A4 induction could result in enhanced gepotidacin metabolism, reducing its exposure, which could also lead to lack of efficacy in both gonorrhea and uUTI;

3) Gepotidacin is a P-gp inhibitor: At the high dose (3000 mg, 2 doses given 12 hours apart) for the gonorrhea indication, gepotidacin might inhibit P-glycoprotein (P-gp) at the gut level, potentially increasing the exposure of P-gp substrates that could impact substrate-driven safety.

4) Gepotidacin is a CYP3A4 inhibitor: Potential inhibition of CYP3A4 enzyme by gepotidacin (perpetrator) at both doses for gonorrhea and uUTI may enhance substrate exposure, possibly impacting safety for both indications.

The DDI observations generated from this study will inform the gepotidacin drug label.

Objectives and Endpoints:

A summary of study cohorts 1-4 can be found in Table 14.

Objectives	Endpoints
Primary	
Cohort 1: Gepotidacin is a substrate of MATE and potentially of OCT transporter • To characterize the drug-drug interaction (DDI) effect of repeat oral dosing of cimetidine on the pharmacokinetics (PK) of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Cmax, Tmax, t1/2, AUC(0-t), and AUC(0-∞) of gepotidacin in plasma, as data permit
Cohort 2: Gepotidacin is a CYP3A4 substrate • To characterize the DDI effect of repeat oral dosing of rifampicin on the PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of gepotidacin in plasma, as data permit
Cohort 3: Gepotidacin is a P-gp and CYP3A4 inhibitor • To characterize the DDI effect of two 3000 mg doses of gepotidacin given 12 hours apart given with food on the PK for co-administered drugs digoxin and midazolam in an adult healthy population	• Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of digoxin and midazolam in plasma, as data permit
Cohort 4: Japanese PK • To assess the PK, safety, and tolerability of a single 1500 mg dose of gepotidacin under fed and fasted states, and two 3000 mg doses of gepotidacin given 12 hours apart under fed state in Japanese adult participants	• Cmax, Tmax, AUC(0-24), AUC(0-48), AUC(0-t), and AUC(0-∞) of gepotidacin in plasma following a single 1500 mg dose, as data permit • Cmax, Tmax, and AUC(0-τ) of gepotidacin after the first dose; AUC(0-τ), Cmax, Tmax, RoCmax, and RoAUC of gepotidacin after the second dose; AUC(0-24), AUC(0-48), and AUC(0-t) of gepotidacin using the full profile

Objectives	Endpoints
	(both doses) following two 3000 mg doses, as data permit • Adverse events (AEs), clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead electrocardiogram (ECG) readings
• To evaluate the effect of a Japanese meal on the bioavailability of the gepotidacin tablet formulation	• Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of gepotidacin in plasma, as data permit
Secondary	
Cohort 1	
• To characterize the plasma PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• AUC(0-24), AUC(0-48), Tlag, Vz/F, and CL/F of gepotidacin in plasma after a single 1500 mg dose of gepotidacin, as data permit
• To characterize the DDI effect of repeat oral dosing of cimetidine on the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae total, AUC(0-24), AUC(0-48), and CLr of gepotidacin in urine following a single 1500 mg dose, as data permit
• To characterize the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae(t1-t2) and fe% of gepotidacin in urine following a single 1500 mg dose, as data permit
• To evaluate the safety and tolerability of gepotidacin in adult healthy participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings

Objectives	Endpoints
Cohort 2	
• To characterize the plasma PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• AUC(0-24), AUC(0-48), t1/2, Vz/F, and CL/F of gepotidacin in plasma after a single 1500 mg dose of gepotidacin, as data permit
• To characterize the DDI effect of repeat oral dosing of rifampicin on the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae total, AUC(0-24), AUC(0-48), and CLr of gepotidacin in urine following a single 1500 mg dose, as data permit
• To characterize the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae(t1-t2) and fe% of gepotidacin in urine following a single 1500 mg dose, as data permit
• To evaluate the safety and tolerability of gepotidacin in adult healthy participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings
Cohort 3	
• To characterize the plasma PK of gepotidacin two 3000 mg doses given 12 hours apart with food in an adult healthy population	• Cmax, Tmax, Tlag, AUC(0-τ) of gepotidacin after the first dose; Cmax, Tmax, AUC(0-τ), RoCmax, and RoAUC of gepotidacin after the second dose; AUC(0-24), AUC(0-48), AUC(0-t), Vz/F, CL/F, and t1/2 of gepotidacin using the full profile (both doses), as data permit
• To characterize the DDI effect of two 3000 mg doses of gepotidacin given 12 hours apart with food on the PK of co-administered drugs digoxin and midazolam in an adult healthy population	• Cmin, t1/2, Vz/F, and CL/F of digoxin and midazolam in plasma, as data permit
• To characterize the urine PK of gepotidacin (two 3000 mg doses given 12 hours apart) given with food in an adult healthy population	• Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin in urine following two 3000 mg doses, as data permit
• To evaluate the safety and tolerability of gepotidacin in adult healthy participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings

Objectives	Endpoints
Cohort 4 • To characterize the PK of a single 1500 mg oral dose of gepotidacin given with and without food in Japanese adult healthy participants • To assess the plasma PK of two 3000 mg doses of gepotidacin given 12 hours apart with food in Japanese adult healthy participants • To assess the urine PK of a single 1500 mg dose or two 3000 mg doses of gepotidacin given 12 hours apart with food in Japanese adult healthy participants	• t1/2, Vz/F, and CL/F of gepotidacin in plasma after a single 1500 mg dose of gepotidacin, as data permit • Tlag of gepotidacin after the first dose; Vz/F, CL/F, and t1/2 of gepotidacin using the full profile (both doses) following two 3000 mg doses, as data permit • Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin in urine following a single 1500 mg dose and two 3000 mg doses, as data permit
Exploratory	
Cohort 1 • To characterize the DDI effect of repeat oral dosing of cimetidine on the PK of plasma and urine for N1-methylnicotinamide (1-NMN) biomarker in adult healthy participants • To evaluate concentrations of serum and urine creatinine after administration of gepotidacin with and without cimetidine in adult healthy participants • To evaluate cimetidine PK to assess transporter inhibition in adult healthy participants	• C average, Cmax, Ctrough, AUC(0-24), AUC(0-48), and AUC(0-t) of 1-NMN in plasma, as data permit • Ae total and CLr of 1-NMN in urine, as data permit • 1-NMN plasma and urine PK parameters normalized to creatinine, as data permit • Serum and urine creatinine concentrations, as data permit • 1-NMN plasma and urine PK parameters normalized to creatinine, as data permit • Cimetidine plasma PK concentrations, as data permit

Objectives	Endpoints
Cohort 3 • To evaluate the plasma PK for the metabolite 1'-hydroxymidazolam	• Cmin, Cmax, Tmax, t1/2, AUC(0-t), and AUC(0-∞) of 1'-hydroxymidazolam in plasma, as data permit • Molecular weight normalized parent-to-metabolite AUC(0-∞) ratio, as data permit
• To characterize the DDI effect of two 3000 mg doses of gepotidacin given 12 hours apart given with food on the urine PK of co-administered digoxin in an adult healthy population	• Ae total, fe%, and CLr of digoxin in urine following a single 1500 mg dose, as data permit
Cohort 4 • To compare the plasma and urine PK of gepotidacin 1500 mg single dose (SD) data from the Cohort 4 Japanese versus the gepotidacin-only 1500 mg SD data the DDI Cohorts in adult (non-Japanese) healthy participants	• Plasma and urine concentrations and parameters for gepotidacin, as data permit
• To compare the plasma and urine PK of gepotidacin 3000 mg twice daily data from the Cohort 4 Japanese versus the Cohort 3 gepotidacin 3000 mg twice daily data in adult (non-Japanese) healthy participants	• Plasma and urine concentrations and parameters for gepotidacin, as data permit
Cohorts 1, 2, 3, and 4 • To determine the effect of gepotidacin concentrations on the QT interval corrected with Fridericia's method (QTcF) in adult healthy participants	• Change from Baseline in QTcF versus gepotidacin concentration

Overall Design: This study is a Phase I, DDI, PK, safety, and tolerability study in healthy adult participants, including a Japanese cohort, to be conducted at 1 center in the United States. This study is designed to assess co-administration of probe substrates with gepotidacin in study Cohorts 1 to 3 and establishing PK and safety in a Japanese cohort in Cohort 4.

In all Cohorts, participants will be screened within 28 days before the first dose of study intervention.

Cohort 1: Cohort 1 is an open-label, fixed sequence DDI study to investigate the effect of cimetidine (OCT/MATE inhibitor) on the PK of gepotidacin under fed conditions. Participants will receive the treatments in a fixed sequence: gepotidacin 1500 mg on Day 1 (Treatment A) of Period 1, followed by cimetidine 400 mg 4 times daily on Days 1 through 4 (Treatment B) of Period 2. Gepotidacin 1500 mg will be administered 1 hour after the first dose of cimetidine on Day 2 of Period 2. On Day 4 of Period 2, cimetidine dosing will be discontinued after the last PK sample is collected. There will be a washout of at least 3 days after dosing with gepotidacin in Period 1. A follow-up visit will occur 5 to 7 days after the last dose of cimetidine.

Participants will receive a standard meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until at least 2 hours after gepotidacin dosing.

Pharmacokinetic blood and urine samples for analysis of gepotidacin, creatinine, and the endogenous biomarker N1-methylnicotinamide (1-NMN) will be obtained at pre-specified time points, and sparse blood samples will be collected for cimetidine after dosing at pre-specified time points. Safety and tolerability will be assessed by monitoring and recording of adverse events (AEs), clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Cohort 2: Cohort 2 is an open-label, fixed sequence DDI to investigate the effect of rifampicin (CYP3A4 inducer) on the PK of gepotidacin under fed conditions. Participants will receive the following treatments in a fixed sequence: gepotidacin 1500 mg single dose (SD) on Day 1 of Period 1 (Treatment C); rifampicin 600 mg (administered in the evenings) once daily for 7 days (to elicit maximal enzyme induction) on Days 1 through 7 of Period 2 (Treatment D); and gepotidacin 1500 mg SD administered in the morning on Day 8 of Period 2 with rifampicin 600 mg administered in the evening on Days 8 and 9 of Period 2 (Treatment E). There will be a washout of at least 3 days after gepotidacin dosing in Period 1. A follow-up visit will occur 7 to 10 days after the last dose of rifampicin in Period 2.

The participants will receive a standard meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until at least 2 hours after gepotidacin dosing. Rifampicin will be administered 1 hour before the evening meal.

Pharmacokinetic blood and urine samples of gepotidacin will be obtained at pre-specified time points before and after dosing. Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings.

Cohort 3: Cohort 3 is an open-label, 2-sequence, 2-period crossover randomized DDI study to investigate the effect of gepotidacin on the PK of the 2 probe substrates digoxin (P-gp substrate) and midazolam (CYP3A4 substrate) under fed conditions. Participants will be randomized to 1 of 2 treatment sequences in a 1:1 ratio. In Sequence 1, participants will receive digoxin 0.5 mg and midazolam 2 mg (Treatment F) in Period 1 then two doses of gepotidacin up to 3000 mg (given 12 hours apart) co-administered with digoxin 0.5 mg and midazolam 2 mg in Period 2, with the 2 probe drugs administered with the second daily dose of gepotidacin only (Treatment G). In Sequence 2, these regimens are reversed. There will be a washout of at least 10 days between Period 1 and 2. A follow-up visit will occur 7 to 10 days after the last dose of study intervention (to ensure clearance of digoxin) in Period 2.

The participants will receive a standard meal 30 minutes prior to dosing (similar in calorie content and similar ratios of protein, carbohydrates, and fat as the previous meal). Participants will eat this meal in 30 minutes or less. All dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until at least 2 hours after dosing.

Pharmacokinetic blood samples for analysis of gepotidacin, midazolam, 1'-hydroxymidazolam, and digoxin, and urine samples for gepotidacin and digoxin PK will be obtained at pre-specified time points before and after dosing. Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, pulse oximetry, 12-lead ECG results, Holter monitoring, and physical examination findings.

Cohort 4: Cohort 4 is a double-blind, placebo-controlled, randomized sequence (Periods 1 and 2 only) study to investigate the safety and PK of gepotidacin under fed and fasted conditions in Japanese participants. Participants will be randomly assigned (10 active:2 placebo) to receive gepotidacin or placebo. Within each treatment group, participants will be randomized to each of the 2 sequences in 1:1 ratio: HIJ versus IHJ (to elucidate the food effect). In Sequence 1, participants will receive a SD of gepotidacin 1500 mg or placebo under fed conditions in Period 1 (Treatment H), then a SD of gepotidacin 1500 mg or placebo under fasted conditions in Period 2 (Treatment I), followed by two doses of gepotidacin up to 3000 mg or placebo (given 12 hours apart) under fed conditions in Period 3 (Treatment J). In Sequence 2, the first 2 treatments are reversed (Sequence IHJ). There will be a washout of at least 3 days between each treatment. A follow-up visit will occur 5 to 7 days after the last dose of gepotidacin or placebo.

Participants receiving Treatments H and J will receive a standard meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants receiving

Treatment I will fast overnight for at least 8 hours prior to dosing. Participants will not receive any food until at least 2 hours after dosing.

Pharmacokinetic blood and urine samples for analysis of gepotidacin will be obtained at pre-specified time points before and after dosing. Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, Holter monitoring (Period 3 only), and physical examination findings.

Brief Summary: The purpose of this study to determine potential gepotidacin DDIs and to generate PK, safety, and tolerability data in a Japanese cohort. Study details include:

Study duration: The duration (including screening) for Cohort 1 is up to 42 days, for Cohort 2 up to 50 days, for Cohort 3 up to 50 days, and for Cohort 4 up to 44 days.

Treatment duration: For Cohort 1, two study treatments will be given over 7 days (including a 3-day washout); for Cohort 2, two study treatments will be given over the course of 12 days (including a 3-day washout); for Cohort 3, two study treatments will be given over the course of 11 days (including a 10-day washout), and for Cohort 4, three study treatments will be given over the course of a minimum of 9 days (including a 3-day washout between each treatment).

Visit frequency: Continuous confinement during treatment.

Number of Participants: Approximately 14 participants will be recruited for Cohort 1, 2, and 4 to ensure that each Cohort has at least 12 completers, allowing for up to 20% withdrawal rate. Participants in the Japanese Cohort will be randomly assigned (10 active:2 placebo) to receive gepotidacin or placebo, ensuring at least 10 participants in the gepotidacin Cohort. For Cohort 3, 22 participants will be enrolled to achieve at least 18 completers to accommodate the narrower therapeutic window of digoxin. If participants prematurely discontinue the study, additional participants may be enrolled after consultation with the Sponsor to ensure that the required number of evaluable participants complete each Cohort of the study.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

Cohort 1: Participants in Cohort 1 will receive the following study treatments in a fixed sequence (Sequence AB):

- Treatment A: Gepotidacin 1500 mg SD on Day 1 of Period 1.
- Treatment B: Cimetidine 400 mg 4 times daily Days 1 through 4 of Period 2 and gepotidacin 1500 mg SD. Gepotidacin will be administered 1 hour after the first dose of cimetidine on Day 2 of Period 2 (gepotidacin administration is delayed

for 1 hour due to the changes in gastric pH by cimetidine that could impact gepotidacin dissolution and absorption). On Day 4 of Period 2, cimetidine dosing will be discontinued after the last PK sample is collected.

Including screening, a washout of at least 3 days between Treatment A and Treatment B, and a follow-up visit 5 to 7 days after the last dose of cimetidine, the total duration of Cohort 1 is up to 42 days.

Cohort 2: Participants in Cohort 2 will receive the following study treatments in a fixed sequence (Sequence CDE):

- Treatment C: Gepotidacin 1500 mg SD on Day 1 of Period 1.
- Treatment D: Rifampicin 600 mg (administered in the evenings) once daily for 7 days (Days 1 through 7) in Period 2.
- Treatment E: Gepotidacin 1500 mg SD administered in the morning on Day 8 and rifampicin 600 mg administered in the evening on Days 8 and 9 in Period 2.

Including screening, a washout of at least 3 days between Treatment C and Treatment D, and a follow-up visit 7 to 10 days after the last dose of rifampicin, the total duration of Cohort 2 is up to 50 days.

Cohort 3: Participants in Cohort 3 will receive the following study treatments in a randomized sequence (Sequence FG or Sequence GF):

- Treatment F: Digoxin 0.5 mg and midazolam 2 mg on Day 1.
- Treatment G: Gepotidacin two 3000 mg doses (given 12 hours apart) on Day 1 with digoxin 0.5 mg and midazolam 2 mg given with the second gepotidacin dose on Day 1.

Including screening, a washout of at least 10 days between treatments, and a follow-up visit 7 to 10 days after the last dose of study treatment, the total duration of Cohort 3 is up to 50 days.

Cohort 4: Participants in Cohort 4 will receive the following study treatments in a randomized sequence (Sequence HIJ or Sequence IHJ):

- Treatment H: Gepotidacin 1500 mg or placebo SD under fed conditions on Day 1.
- Treatment I: Gepotidacin 1500 mg or placebo SD under fasted conditions on Day 1.
- Treatment J: Two doses of gepotidacin up to 3000 mg (given 12 hours apart) under fed conditions on Day 1.

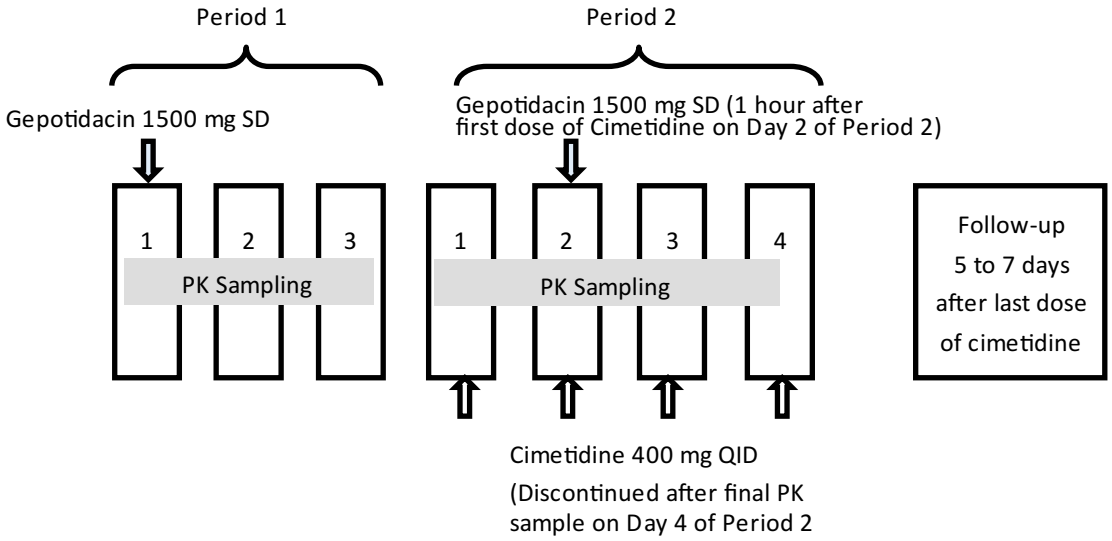
Including screening, a washout of at least 3 days between each treatment, and a follow-up visit 5 to 7 days after the last dose of gepotidacin, the total duration of Cohort 4 is up to 44 days.

Data Monitoring/ Other Committee: No

1.2. Schema

The overall study designs for DDI Cohorts 1, 2, and 3, and for PK and safety in Japanese participants Cohort 4 are summarized in Figure 1, Figure 2, Figure 3, and Figure 4, respectively.

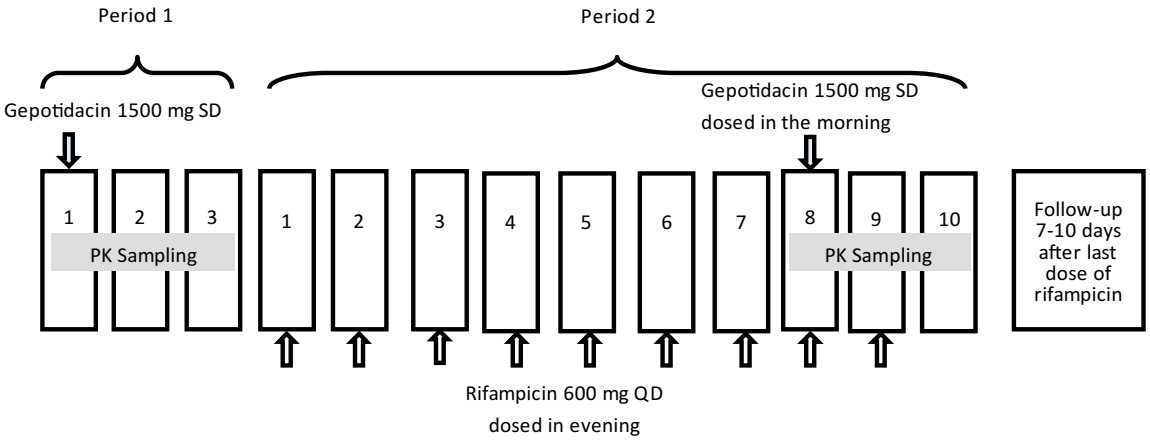
Figure 1 Cohort 1 (Gepotidacin and Cimetidine) Study Design Schematic



PK = pharmacokinetic; QID = 4 times daily; SD = single dose.

There will be a washout of at least 3 days after dosing of gepotidacin in Period 1.

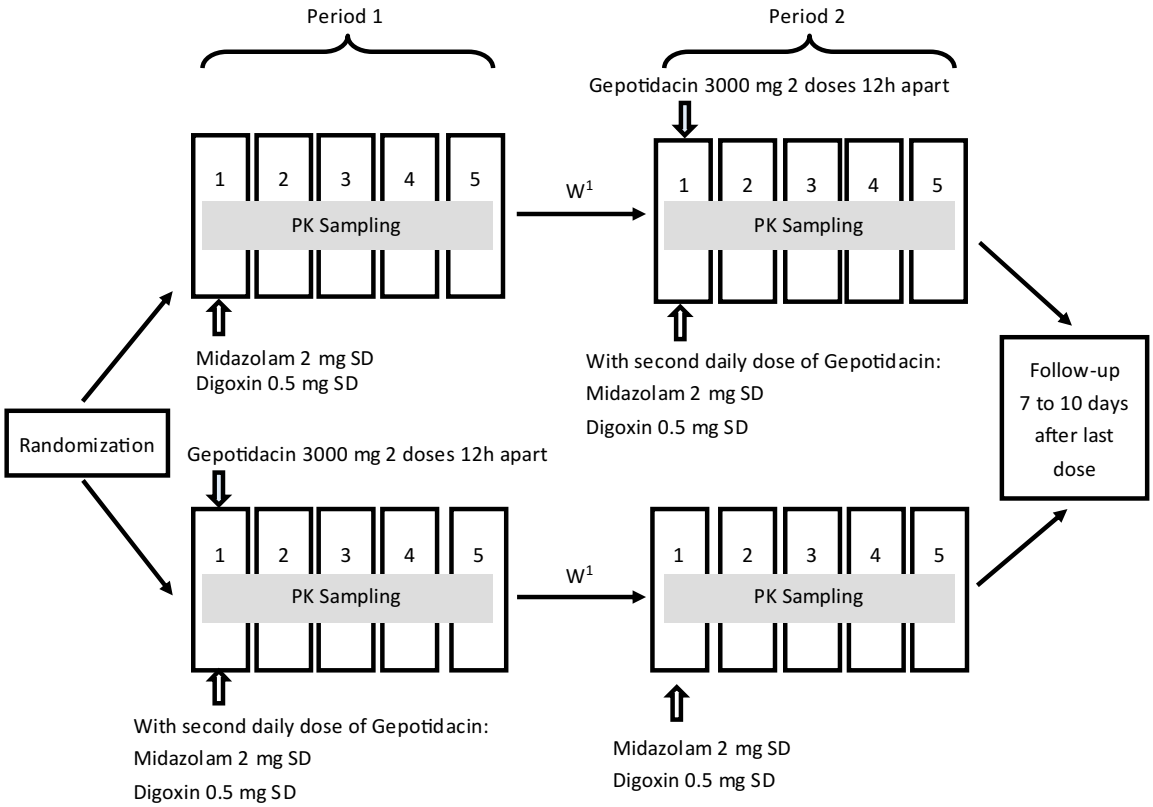
Figure 2 Cohort 2 (Gepotidacin and Rifampicin) Study Design Schematic



PK = pharmacokinetic; QD = once daily; SD = single dose.

There will be a washout of at least 3 days after dosing of gepotidacin in Period 1.

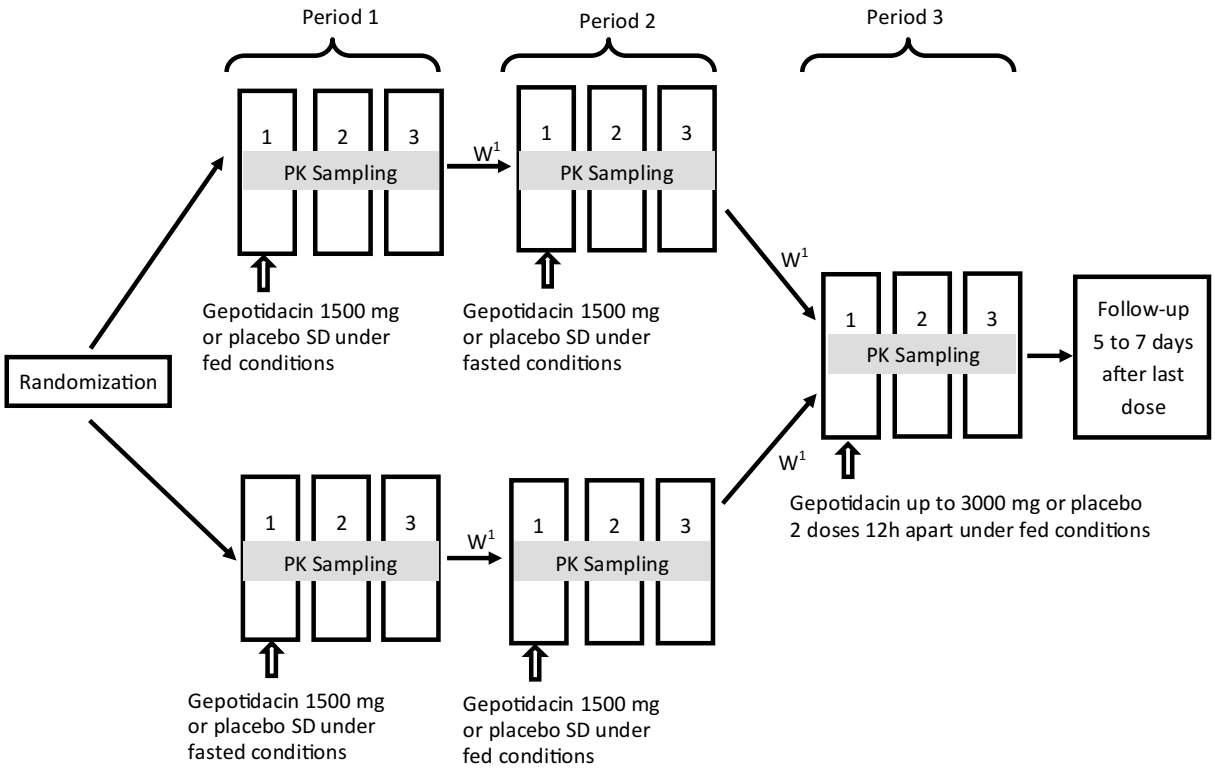
Figure 3 Cohort 3 (Gepotidacin, Digoxin, and Midazolam) Study Design Schematic



h = hour; PK = pharmacokinetic; SD = single dose; W = washout.

1 There will be a washout of at least 10 days between treatments.

Figure 4 Cohort 4 (Japanese Cohort) Study Design Schematic



h = hour; PK = pharmacokinetic; SD = single dose; W = washout.
1.There will be a washout of at least 3 days between each treatment.

1.3. Schedule of Activities (SoA)

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic PK/pharmacodynamic (PD) data from this study must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment.
- The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

Table 1 Screening Visit - All Cohorts

Procedure	Screening (up to 28 days before Day -1)
Outpatient visit	X
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Complete physical examination including height and weight[1]	X
Laboratory assessments (hematology, chemistry, urinalysis)	X
Screening for COVID-19[2]	X
12-lead electrocardiogram[4]	X
Vital sign measurements[3]	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Serum pregnancy test	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status)	X
Drug, alcohol, and cotinine screen	X
HIV, Hepatitis B and C screening	X
Serious adverse event review	X

HIV = human immunodeficiency virus.

1 A full physical examination will include at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal (GI), and neurological systems.

2 COVID 19 Testing will be done according to site procedures.

3 Respiratory rate and temperature collected at Screening only.

4 Single ECG

Table 2 Schedule of Activities - Cohort 1 (Gepotidacin and Cimetidine)

Procedure[1]	Check-in	Period 1 (Days)			Period 2 (Days)				Early Termination	Follow-up	Notes
	–1	1	2	3	1	2	3	4	–	5-7 Days After Last Cimetidine Dose	
In-house stay	X	X	X	X	X	X	X	X			Discharge after last scheduled assessment on Day 4.
Inclusion and exclusion criteria	X										
Brief physical examination[2]	X							X	X	X	
Urine pregnancy test	X									X	Refer to Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X										See Table 16.
Laboratory assessments	X			X				X	X	X	See Table 16.
12-lead ECG[3]	X	X	X	X	X	X	X	X	X	X	See Table 3 and Table 4 for timing of assessments.
Vital signs	X	X	X	X	X	X	X	X	X	X	See Table 3 and Table 4 for timing of assessments.
Gepotidacin administration (victim)		X				X					1500 mg SD. Period 2 Day 2 dose given 1 hour after first cimetidine dose of the day.

Procedure[1]	Check-in	Period 1 (Days)			Period 2 (Days)				Early Termination	Follow-up	Notes
	–1	1	2	3	1	2	3	4	–	5-7 Days After Last Cimetidine Dose	
Cimetidine administration (perpetrator)					X	X	X	X			400 mg 4 times daily. Cimetidine dosing on Day 4 will be discontinued after the last PK sample is collected.
Blood collection for PK		X	X	X		X	X	X			See Table 3 and Table 4 for timing of assessments.
Urine collection for PK		X	X	X		X	X	X			See Table 3 and Table 4 for timing of assessments.
AE review		←==========→							X	X	
SAE review	X	←==========→							X	X	
Concomitant medication review	X	←==========→							X	X	

AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event; SD = Single dose.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

3 Triplicate 12-lead ECGs will be measured on Pre-dose and Single ECGs on Day -1 and at all other timepoints

Table 3 Safety and Pharmacokinetic Assessments - Cohort 1 (Relative to Gepotidacin) Period 1

Procedure[1]		Time point (hours)													
	Predose	0	0.5	1	1.5	2	2.5	3	4	6	8	12	24	36	48
Gepotidacin 1500 mg administration		X													
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X				X	X			X		X	X	X	X	X
Gepotidacin PK blood sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Gepotidacin PK urine sample[3]	X	X				X			X	X	X	X	X	X	
Serum creatinine	X[4]							X					X		X
Urine creatinine[3]	X[4]	X				X			X	X	X	X	X	X	
N1-methylnicotinamide blood sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X
N1-methylnicotinamide urine sample[3]	X	X				X			X	X	X	X	X	X	

ECG = electrocardiogram; PK = pharmacokinetic.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 Triplicate 12-lead ECGs will be measured at pre-dose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours after gepotidacin administration.

4 This pre-dose serum and urine creatinine to be drawn with Day -1 labs

Table 4 Safety and Pharmacokinetic Assessments - Cohort 1 (Relative to Gepotidacin) Period 2

Procedure[1]			Time point (hours)																					
	-1	Gepotidacin Pre-dose	0	0.5	1	1.5	2	2.5	3	4	5	6	8	11	12	17	23	24	29	35	36	41	47	48
Relative to gepotidacin (Period 2/Day 2)																								
Gepotidacin 1500 mg administration			X																					
Cimetidine 400 mg QID administration	X										X			X		X	X		X	X		X	X	
12-lead ECG		X[5]		X	X	X	X	X	X	X		X	X		X			X			X			X
Vital signs		X				X	X			X			X		X			X			X			X
Gepotidacin PK blood sample		X		X	X	X	X	X	X	X		X	X		X			X			X			X
Gepotidacin PK urine sample[2]		X	X				X			X		X	X		X			X			X			
Cimetidine blood PK sample			X															X[3]						X[4]
Serum creatinine		X	X						X									X[3]						X[4]
Urine creatinine[2]		X	X				X			X		X	X		X			X			X			
N1-methylnicotinamide blood sample		X		X	X	X	X	X	X	X		X	X		X			X			X			X
N1-methylnicotinamide urine sample[2]		X	X				X			X		X	X		X			X			X			

ECG = electrocardiogram; PK = pharmacokinetic; QID = 4 times daily.

1 When coinciding with safety and/or PK assessments, Electrocardiograms, vital signs, and PK blood collections should be performed in said order.

2 Urine collection intervals include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours after gepotidacin administration.

3 This PK sample is equivalent to 25 hours after the first dose of cimetidine on Day 2 of Period 2.

4 This PK sample is equivalent to 49 hours after the first dose of cimetidine on Day 2 of Period 2.

5 Triplicate ECGs at pre-dose Period 2

Table 5 Schedule of Activities - Cohort 2 (Gepotidacin and Rifampicin)

Procedure[1]	Check-in	Period 1 (Days)			Period 2 (Days)										Early Termination	Follow-up	Notes
	–1	1	2	3	1	2	3	4	5	6	7	8	9	10		7-10 Days After Last Dose of Rifampicin	
In-house stay	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Inclusion and exclusion criteria	X																
Brief physical examination[2]	X													X	X	X	
Urine pregnancy test	X															X	Refer to Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X																See Table 16.
Laboratory assessments	X			X							X			X	X	X	See Table 16.
12-lead ECG[3]	X	X	X	X								X	X	X	X	X	See Table 6 for timing of assessments.
Vital signs	X	X	X	X								X	X	X	X	X	See Table 6 for timing of assessments.
Gepotidacin administration (victim)		X										X					1500 mg SD in the morning.

Procedure[1]	**Check -in**	**Period 1 (Days)**			**Period 2 (Days)**										**Follow-up**	**Notes**
	–1	**1**	**2**	**3**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**7-10 Days After Last Dose of Rifampicin**	
Rifampicin administration (perpetrator)					X	X	X	X	X	X	X	X	X			600 mg once daily in the evening.
Blood collection for gepotidacin PK		X	X	X								X	X	X		See Table 6 for timing of assessments.
Urine collection for gepotidacin PK		X	X	X								X	X	X		See Table 6 for timing of assessments.
AE review		←==========												==========→	X	
SAE review	X	←==========												==========→	X	
Concomitant medication review	X	←==========												==========→	X	

AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event; SD = single dose.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

3 Triplicate 12-lead ECGs will be measured at pre-dose. Single 12-lead ECGs will be measured at all other time points.

Table 6 Safety and Pharmacokinetic Assessments - Cohort 2 (Gepotidacin and Rifampicin) Period 1 and Period 2

Procedure[1]		Time Point (Hours)													
	Pre-dose	0	0.5	1	1.5	2	2.5	3	4	6	8	12	24	36	48
Gepotidacin 1500 mg administration		X													
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X				X	X			X		X	X	X	X	X
Gepotidacin PK blood sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Gepotidacin PK urine sample[3]	X	X				X			X	X	X	X	X	X	

ECG = electrocardiogram; PK = pharmacokinetic.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 Triplicate 12-lead ECGs will be measured at pre-dose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours after gepotidacin administration.

Table 7 Schedule of Activities - Cohort 3 (Gepotidacin, Digoxin, and Midazolam)

Procedure[1]	Check-in	Period 1 or Period 2[2] (Days)					W	Period 1 or Period 2[2] (Days)					Early Termination	Follow-up	Notes
	–1[3]	1	2	3	4	5	6-10	1	2	3	4	5	–	7-10 Days After Last Dose	
In-house stay	X	X	X	X	X	X	X	X	X	X	X	X			Participants should remain confined during the washout after Period 1. If there is an urgent need to leave the clinic, allowable furlough will be determined on a case-by-case basis with approval from the investigator.
Inclusion and exclusion criteria	X														Recheck clinical status before study intervention if participant is furloughed between periods.
Brief physical examination[4]	X						D10					X	X	X	
Urine pregnancy test	X													X	Refer to Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X														See Table 16.
Laboratory assessments	X						D10					X	X	X	See Table 16.
12-lead ECG[5]	X	X	X	X			D10	X	X	X			X	X	See Table 8 and Table 9 for timing of assessments.
Holter ECG monitoring	X	X					D10	X							See Table 8 and Table 9 for timing of assessments.
Vital signs	X	X	X	X			D10	X	X	X				X	See Table 8 and Table 9 for timing of assessments.

Procedure[1]	**Check -in**	**Period 1 or Period 2**[2] **(Days)**					**W**	**Period 1 or Period 2**[2] **(Days)**					**Early Termination**	**Follow-up**	**Notes**
	–1[3]	**1**	**2**	**3**	**4**	**5**	**6-10**	**1**	**2**	**3**	**4**	**5**	**–**	**7-10 Days After Last Dose**	
Randomization[6]	X														On Day -1 of Period 1 only; day prior to first dose of study intervention.
Pulse oximetry		X						X							See Table 8 for timing of assessments.
Gepotidacin administration (perpetrator)								X							3000 mg twice daily, approximately 12 hours apart.
Probe drug administration - digoxin and midazolam (victims)		X						X							Digoxin 0.5 mg and midazolam 2 mg. Probe drugs are dosed with second daily dose of gepotidacin during the coadministration period.
Blood collection for PK		X	X	X	X	X		X	X	X	X	X			See Table 8 and Table 9 for timing of assessments.
Urine collection for PK		X	X	X	X	X		X	X	X	X	X			
AE review		←==========										==========→	X	X	
SAE review	X	←==========										==========→	X	X	
Concomitant medication review	X	←==========										==========→	X	X	

AE = adverse event; D10 = Day 10; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event; W = washout.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.
2 Actual period depends on which sequence participant is randomized to.
3 Check-in procedures necessary for Period 2 only if participant is furloughed from the clinic between treatment periods.
4 A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
5 Triplicate 12-lead ECGs will be measured on Pre-dose and Single ECGs on Day -1 and at all other timepoints
6 Participants will be randomized to a sequence on Day -1 of Period 1 only.

Table 8 Safety and Pharmacokinetics Assessments - Cohort 3 (Relative to Digoxin and Midazolam) Period 1 and Period 2

Procedure[1]		Time point (hours)																				
	Pre-dose	0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	16	18	20	24	36	48	60	72	96
Digoxin 0.5 mg and midazolam 2 mg administration		X																				
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X					X	X	X	X		
Holter ECG monitoring[3]	←==========→																					
Vital signs	X				X	X			X		X	X					X	X	X	X		
Pulse oximetry	X	X	X	X	X	X	X	X	X													
Digoxin PK blood sample[4]	X		X	X	X	X	X	X	X	X	X						X	X	X		X	X
Digoxin PK urine sample[4, 5]	X	X				X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Midazolam and 1'-hydroxymidazolam PK blood sample	X		X	X	X	X	X	X	X	X	X	X					X	X	X			

ECG = electrocardiogram; PK = pharmacokinetic.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 Triplicate 12-lead ECGs will be measured at pre-dose. Single 12-lead ECGs will be measured at all other time points.

3 When the probe drugs are given alone, Holter ECG monitoring will start 12 hours prior to probe dosing and continue until 10 hours after dosing.

4 Pre-dose blood and urine PK sample for digoxin should be taken no more than 2 hours before the dose.

5 Digoxin urine collection intervals include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 14 hours, 14 to 16 hours, 16 to 18 hours, 18 to 20 hours, 20 to 24 hours, 24 to 36 hours, 36 to 48 hours, 48 to 60 hours, 60 to 72 hours, and 72 to 96 hours after digoxin administration.

Table 9 Safety and Pharmacokinetic Assessments - Cohort 3 (Relative to Gepotidacin) Period 1 or Period 2

Procedure[1]		**Time point (hours)**																							
	Pre-dose	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**	**16**	**18**	**20**	**24**	**36**	**48**	**60**
Gepotidacin 3000 mg administration		X										X													
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Holter ECG monitoring[3]	←==========→																								
Vital signs	X				X	X			X		X	X			X	X				X		X	X	X	X
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sample[4]	X	X				X			X	X	X	X				X			X	X	X	X	X	X	

ECG = electrocardiogram; PK = pharmacokinetic.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 Triplicate 12-lead ECGs will be measured at pre-dose. Single 12-lead ECGs will be measured at all other time points.

3 Holter ECG monitoring will start 12 hours prior to the first dose of gepotidacin and continue until 24 hours after the first dose of gepotidacin.

4 Urine collection intervals include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 14 hours, 14 to 16 hours, 16 to 18 hours, 18 to 20 hours, 20 to 24 hours, 24 to 36 hours, 36 to 48 hours, and 48 to 60 hours after gepotidacin administration.

Table 10 Schedule of Activities - Cohort 4 (Japanese Cohort)

Procedure[1]	Check-in	Period 1 or Period 2[2]			Period 3			Early Termination	Follow-up Visit	Notes
	–1	1	2	3	1	2	3	–	5-7 Days After Last Dose	
In-house stay	X	X	X	X	X	X	X			Washout of at least 3 days between dosing in each period.
Inclusion and exclusion criteria	X									
Brief physical examination[3]	X						X	X	X	
Urine pregnancy test	X								X	Refer to Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X									See Table 16.
Laboratory assessments	X			X			X	X	X	See Table 16.
12-lead ECG[4]	X	X	X	X	X	X	X	X	X	See Table 11 and Table 12 for timing of assessments.
Vital signs	X	X	X	X	X	X	X	X	X	See Table 11 and Table 12 for timing of assessments.
Gepotidacin or placebo administration[5]		X			X					Single dose gepotidacin 1500 mg or placebo in on Day 1 in Periods 1 and 2. Gepotidacin upto 3000 mg or placebo twice daily (approximately 12 hours apart) on Day 1 in Period 3.

Procedure[1]	Check-in	Period 1 or Period 2[2]			Period 3			Early Termination	Follow-up Visit	Notes
	–1	1	2	3	1	2	3	–	5-7 Days After Last Dose	
Randomization[6]		X								On Day 1 of Period 1 only; prior to first dose of study intervention.
Holter ECG monitoring					X	X	X			See Table 12 for timing of assessments.
Blood collection for PK		X	X	X	X	X	X			See Table 11 and Table 12 for timing of assessments.
Urine collection for PK[7]		X	X	X	X	X	X			
AE review		←==========					==========→	X	X	
SAE review	X	←==========					==========→	X	X	
Concomitant medication review	X	←==========					==========→	X	X	

AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.
2 Actual period depends on which sequence participant is randomized to.
3 A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
4 Triplicate 12-lead ECGs will be measured on Day 1 pre-dose only of each period.
5 Gepotidacin will be administered under fasted or fed conditions in Period 1 and Period 2 per randomization sequence, and under fed conditions only in Period 3.
6 Participants will be randomized to gepotidacin or placebo and to a treatment sequence on Day 1 of Period 1 only.
7 Urine PK obtained only when gepotidacin is given under fed conditions.

Table 11 Safety and Pharmacokinetic Assessments - Cohort 4 (Japanese Cohort) Period 1 and Period 2

Procedure[1]		Time point (hours)													
	Pre-dose	0	0.5	1	1.5	2	2.5	3	4	6	8	12	24	36	48
Gepotidacin 1500 mg or placebo administration		X													
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X				X	X			X		X	X	X	X	X
Gepotidacin blood sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Gepotidacin urine sample[3]	X	X				X			X	X	X	X	X	X	

ECG = electrocardiogram; PK = phamacokinetic.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 Triplicate 12-lead ECGs will be measured at pre-dose. Single 12-lead ECGs will be measured at all other time points.

3 Collected only when gepotidacin is administered under fed conditions. Urine collection intervals include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours after gepotidacin administration.

Table 12 Safety and Pharmacokinetic Assessments - Cohort 4 (Japanese Cohort) Period 3

Procedure[1]		**Time point (hours)**																							
	Predose	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**	**16**	**18**	**20**	**24**	**36**	**48**	**60**
Gepotidacin upto 3000 mg or placebo administration		X										X													
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Holter ECG monitoring[3]	←==========→																								
Vital signs	X				X	X			X		X	X			X	X				X		X	X	X	X
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sample[4]	X	X				X			X	X	X	X				X			X	X	X	X	X	X	

ECG = electrocardiogram; PK = pharmacokinetic.

1 When coinciding with safety and/or PK assessments, ECGs, vital signs, and PK blood collections should be performed in said order.

2 Triplicate 12-lead ECGs will be measured at pre-dose. Single 12-lead ECGs will be measured at all other time points.

3 Holter ECG monitoring will start 12 hours prior to the first daily dose of gepotidacin and continue until 24 hours after the first daily dose of gepotidacin.

4 Urine is collected when gepotidacin is given under fed conditions. Urine collection intervals include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 14 hours, 14 to 16 hours, 16 to 18 hours, 18 to 20 hours, 20 to 24 hours, 24 to 36 hours, 36 to 48 hours, and 48 to 60 hours after the first dose of gepotidacin.

2. INTRODUCTION

Gepotidacin (GSK2140944) is a first in class, novel triazaacenaphthylene antibacterial that inhibits bacterial type II topoisomerases. It has activity versus key pathogens, including drug-resistant strains associated with a range of conventional and biothreat infections and is being developed with intravenous (IV) and oral formulations [IB; GlaxoSmithKline Document Number CM2010/00033/06, 2019] for further details on Gepotidacin].

Gepotidacin has demonstrated in vitro activity and in vivo efficacy against conventional and biothreat pathogens, including isolates resistant to existing classes of antimicrobials. Gepotidacin selectively inhibits bacterial deoxyribonucleic acid (DNA) gyrase and topoisomerase IV by a unique mechanism, which is not utilized by any currently approved human therapeutic agent. Structural data with a type II topoisomerase, DNA gyrase, reveals the novel binding mode of the triazaacenaphthylene class and distinguishes it from the binding mode of the quinolone antibacterials [Bax, 2010]. As a consequence of its novel mode of action, gepotidacin is active in vitro against target pathogens carrying resistance determinants to established antibacterials, including fluoroquinolones.

2.1. Study Rationale

The rationale for this study is 2-fold:

1) to determine the magnitude and clinical relevance of potential drug-drug interactions (DDIs) and 2) to generate pharmacokinetic (PK), safety, and tolerability data in a separate Japanese cohort. Clinical PK and safety data generated in Japanese participants will be used to support clinical development (uncomplicated urinary tract infections [uUTIs] and gonorrhea) in Japan and provide additional safety data prior to evaluation of gepotidacin in Japanese patients. Comparisons will be made between Japanese and non-Japanese subjects to characterise potential differences in pharmacokinetics across the two groups.

The rationale for conducting each of the study Cohorts is summarized in Table 13.

Table 13 Rational for Study 213678

Finding	Importance	Study Treatment	Rationale
Gepotidacin is a MATE substrate and potentially an organic cationic transporter (OCT) substrate (Cohort 1)	Gepotidacin plasma concentrations may increase leading to potential safety implications. May also impact gepotidacin efficacy for uUTI due to lower concentration in urine	Cimetidine (perpetrator-inhibitor of MATE and nonspecific OCT inhibitor) Gepotidacin (victim)	Gepotidacin renal clearance exceeds glomerular filtration rate by greater than 2-fold, which predicts a significant role of tubular secretion in renal elimination. Based on in vitro data, MATE likely contributes to the transportation of gepotidacin from the renal cell into the urine, while a non-identified OCT might transport gepotidacin from blood into the renal tubular cell (OCTs are usually coupled with MATEs). Not conducting the study could lead to cautionary language (reduced efficacy and/or safety) when co-

Finding	Importance	Study Treatment	Rationale
			administering with a MATE inhibitor (cimetidine)
Gepotidacin is a CYP3A4 substrate (Cohort 2)	Gepotidacin exposures could decrease when co-administered with a CYP3A4 inducer (lower gepotidacin efficacy)	Rifampicin (perpetrator) Gepotidacin (victim)	There may be some effect from a strong inducer; data could limit risk when used with a moderate or weak inducer and/or inform dose modification recommendations.
Gepotidacin inhibits CYP3A4 and P-gp (Cohort 3)	Victim drug levels increase with potential safety implications	Digoxin and midazolam (victims) Gepotidacin (perpetrator)	Digoxin (P-gp substrate) is a narrow therapeutic index drug commonly used. CYP3A4 substrates (midazolam) are common; data is important for gepotidacin prescribing to improve patient safety. A negative result will decrease risk of interactions at any gepotidacin dose. In vitro data flagged potential interaction via P-gp at the high dose only (gonorrhea) in the gut.
Japanese PK cohort (Cohort 4)	PK, safety, and tolerability to include food effect as advised by GSK Japan based on PMDA guidance	Gepotidacin	Characterisation of the safety and pharmacokinetic profile will support the dose rationale in future studies in Japanese subjects/patients

CYP = cytochrome P450; MATE = multidrug and toxin extrusion; OCT = organic cationic transporter; P-gp = P-glycoprotein, PMDA = Pharmaceuticals and Medical Devices Agency; PK = pharmacokinetic; uUTI = uncomplicated urinary tract infection.

GlaxoSmithKline (GSK) has conducted in vitro studies and used physiologically-based PK (PBPK) modeling to evaluate the DDI potential with gepotidacin. Based on these analyses, GSK conducted a risk assessment for gepotidacin as a DDI victim and perpetrator:

1) Gepotidacin is a substrate of MATE and potentially of OCT transporter: gepotidacin renal clearance exceeds glomerular filtration rate by greater than 2-fold, which predicts a significant role of tubular secretion in renal elimination. In vitro data suggests that gepotidacin is a substrate of MATE and although it does not suggest that gepotidacin is a substrate of the currently known OCTs, MATE transporters are usually coupled with OCTs. For the uUTI and gonorrhea indications, the DDI risk includes the potential increased plasma gepotidacin exposure (may lead to safety implications). For the uUTI indication, there is an added potential risk for reduced gepotidacin urine levels (may translate to a loss of uUTI efficacy);

2) Gepotidacin is a CYP3A4 substrate: Potential cytochrome P450 (CYP)3A4 induction could result in enhanced gepotidacin metabolism, reducing its exposure, which could also lead to lack of efficacy in both gonorrhea and uUTI;

3) Gepotidacin is a P-gp inhibitor: At the high dose (up to 3000 mg, 2 doses given 12 hours apart) for the gonorrhea indication, gepotidacin might inhibit P-glycoprotein (P-gp) at the gut level, potentially increasing the exposure of P-gp substrates that could impact substrate-driven safety;

4) Gepotidacin is a CYP3A4 inhibitor: Potential inhibition of CYP3A4 enzyme by gepotidacin (perpetrator) at both doses for gonorrhea and uUTI may enhance substrate exposure, possibly impacting safety for both indications.

The DDI observations generated from this study will inform the gepotidacin drug label.

2.2. Background

Gepotidacin has demonstrated clinical efficacy in a Phase II study for acute bacterial skin and skin structure infections (ABSSSI), in a Phase II study for uUTI, and in a Phase II study for gonorrhea. A detailed description of the chemistry, pharmacology, efficacy, and safety of gepotidacin is provided in the Investigator's Brochure [IB; GSK Document Number CM2010/00033/06, 2019].

Gepotidacin may act as a perpetrator (may increase levels of the victim drug) when co-administered with midazolam or digoxin and as a victim when co-administered with rifampicin (potential reduction on efficacy) and cimetidine (potential reduction safety and/or on efficacy). A detailed description of the chemistry, pharmacology, efficacy, and safety of the probe drugs can be found in the prescribing information [Cimetidine, 2019; Rifampin, 2019; Midazolam, 2012; Digoxin, 2011].

2.3. Benefit/Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with gepotidacin can be found in the IB. The following section outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) Gepotidacin		
Gastrointestinal (GI) Effects Based on nonclinical data, GI 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 GI effects (soft stools, flatulence, and diarrhea) are among the most common AEs reported in gepotidacin clinical studies.	Gastrointestinal effects observed in gepotidacin clinical studies, both Phase I studies and the Phase II ABSSSI study, included diarrhea (very common, ≥10%) and flatulence (common; ≥1% and <10%); all nonserious and mild in severity (see Section 6 of the IB). In the Phase II urogenital gonorrhea study, the most frequently reported GI AEs overall were diarrhea, flatulence, abdominal pain, and nausea. Comparing the treatment groups, the incidence of diarrhea and nausea was higher in the 3000 mg treatment group and incidence of flatulence was higher in the 1500 mg treatment group. Few occurrences of *Clostridium difficile* (*C. difficile*) have been reported in clinical studies (see Section 6 of the IB). Of the 282 healthy participants in Phase I studies who have received gepotidacin, *C. difficile* was reported in 8 participants, including 2 elderly participants in association with soft stools or diarrhea. In the Phase I renal impairment and hepatic impairment studies and in the Phase II ABSSSI, urogenital gonorrhea, and uUTI studies, no cases of *C. difficile*-associated diarrhea were reported.	Exclusion criterion (Section 5.2) and close monitoring of clinical parameters and AEs will be conducted to mitigate and assess GI effects. Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Appendix 8. Participant evaluation criteria: Participants experiencing Grade 3 or Grade 4 AEs will be followed as appropriate until resolution of the AE (see Section 7.1.3).
Cardiovascular Effects Reversible increase in QT prolongation and a mild increase in heart rate in human participants.	In Study BTZ115775 [GSK Document Number 2015N227098_00], the infusion of gepotidacin at a dose of 1000 mg and 1800 mg over 2 hours (given an oral bioavailability of 50%, these doses would equate to oral doses of 2000 mg and 3600 mg, respectively) caused a mild heart rate effect of approximately 6 bpm to 10 bpm and a QT prolongation, measured as ΔΔQTcF, of 12 msec to 22 msec in healthy volunteers. The QT prolongation evolved during the infusion and was quickly reversed over 2 hours after the end of the infusion. Blood pressure observations were within normal ranges.	Exclusion criteria, close monitoring of clinical parameters, and AEs will be conducted and stopping criteria will be utilized to mitigate and assess cardiovascular effects. Note: Participants with baseline QTcF interval >450 msec will be excluded. Participant monitoring criteria: Participants experiencing a QTcB and/or QTcF >500 msec and/or a change from baseline in QTc >60 msec

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No changes in QRS or corrected QT interval (QTc) of clinical concern have been seen in the clinic (Phase I studies, including renal impairment and hepatic impairment studies, and Phase II ABSSSI and uUTI [acute cystitis] studies) (see Section 6 in the IB). There were electrocardiographic changes noted in a Phase I hepatic impairment study evaluating a single 1500mg oral dose of gepotidacin. The majority of participants with severe hepatic impairment had both predose and maximum postdose ECG parameter corrected QT interval using the Bazett formula (QTcB) and corrected QT interval using the Fridericia formula (QTcF) values of <450 to ≤479 msec throughout the study. Cardiovascular events reported in the Phase II urogenital gonorrhea study were ECG ST segment elevation and palpitations (1 participant each) in the 1500 mg (oral) treatment group and tachycardia (1 participant) in the 3000 mg (oral) treatment group. In the 1500 mg treatment group, cardiovascular AEs consisted of moderate, unrelated ECG ST segment elevation and mild, unrelated palpitations. In the 3000 mg treatment group, cardiovascular AEs consisted of mild, related tachycardia. All cardiovascular AEs resolved. No AEs led to study withdrawal.	(see Section 7.1.2). For cohort 3, subjects will be monitored by holter monitoring during the probe administration with or without gepotidacin
Acetylcholinesterase (AChE) Inhibition In a mass spectrometry model performed with gepotidacin, AChE was inhibited with a concentration of inhibitor where the response (or binding) was reduced by half (inhibitory concentration) of approximately 5 µg/mL (7.5 µg/mL of	At higher doses, some participants have experienced effects consistent with increased cholinergic tone, including central nervous system and GI effects (increased salivation, slurred speech, blurred vision, dizziness, light-headedness, and GI upset). These effects appear to be related to maximum observed concentration (Cmax) and are significantly attenuated when Cmax is below 14 µg/mL.	Coadministration of anticholinergics and administration in participants with certain concomitant conditions will be excluded. Close monitoring of clinical parameters and AEs will be conducted to assess effects potentially related to AChE inhibition.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
total drug concentration).		
Rash/Hypersensitivity	A fine, mild, generalized pruritic macular skin rash was seen in 3 of 6 participants following 10 days of dosing 1500 mg 3 times daily [GSK Document Number 2014N198291_00 , Study ID BTZ115198]. Rash was reported as an AE for 4 of 122 participants (3%) and consisted of mild, related urticaria; moderate, related rash maculopapular; mild, related rash; mild, related urticaria; and mild, not related arthropod bite [GSK Document Number 2015N243789_00 Study ID BTZ116704]. There has been no other evidence of hypersensitivity in human participants to date.	Exclusion criterion: History of sensitivity to any of the study drugs, components thereof, or a history of drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor, contraindicates their participation. Participant monitoring: Participants will be monitored closely for cutaneous effects throughout the study, and specialist advice will be sought as needed to evaluate any clinically significant finding. Participant evaluation criteria**:** Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement (see Section 7.1.4).
Hepatic Effects In preclinical studies, increases in ALT, GLDH, alkaline phosphatase, and total bilirubin were observed in some rat studies of varying exposure. A few healthy volunteer participants experienced isolated ALT/AST increases following repeat oral (up to 14 days) and IV (up to 10 days) dosing. Effects were reversible, asymptomatic, and no changes in bilirubin were observed.	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. In a Phase I hepatic impairment study, a substantial increase in Cmax and AUC and decrease in clearance was observed in severe hepatic impairment.	Participants with severe hepatic impairment are excluded from this trial. See Section 5.2 for excluded medical conditions.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. In a Phase I renal impairment study, a substantial increase in Cmax and AUC and decrease in clearance was observed in severe renal impairment/ESRD participants not on hemodialysis and 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 this trial. See Section 5.2 for excluded medical conditions.
Reproductive System Effects Preclinical studies demonstrated that gepotidacin was not genotoxic and no drug-related malformations were observed. 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.	There are no data on the use of gepotidacin in pregnant women.	Gepotidacin is contraindicated in pregnant or nursing mothers and women of childbearing potential (WOCBP) who are not employing adequate contraceptive measures. See Appendix 5 for contraceptive measures.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cimetidine		
Cardiovascular and GI Effects; Serum Chemistry/Hematology Abnormalities	Cimetidine can cause the following AEs: diarrhoea, headache, gynecomastia, rare cases of leukocytopenia and agranulocytosis, dose-related increases in transaminases, rare cases of bradycardia, tachycardia, and atrioventricular block.	Inclusion or exclusion criteria: Only healthy participants will be allowed to participate in the proposed study. Any condition or symptom contraindicated for administration of cimetidine as per the patient information leaflet will be excluded from this study. Participant monitoring: Liver function tests, hematology parameters, and 12-lead ECGs will be assessed periodically.
Rifampicin		
Various Systemic Effects	The following considerations before use of rifampicin are documented in the patient information leaflet: Individuals with the following conditions should not take rifampicin: Individuals who are allergic (hypersensitive) to rifampicin or any of the other ingredients, or who are jaundiced. Special care with rifampicin should be taken for individuals in the following situations: Individuals with porphyria, individuals using contact lenses (taking rifampicin may permanently stain soft contact lenses), and individuals taking other medicines because rifampicin can affect the way some other medicines work and some medicines can affect the way rifampicin works. During treatment with rifampicin and for a period of 2 weeks after the last dose of rifampicin, drugs administered that are victim to induction may be impacted; resulting in reduced victim drug levels when co-administered with rifampicin followed by an increase in victim drug when induction has stopped. The following side effects are documented in the patient information leaflet:	Inclusion or exclusion criteria: Only healthy participants will be allowed to participate in the proposed study. Any condition or symptom contraindicated for administration of rifampicin as per the patient information leaflet or any history of porphyria, elevated liver function tests, or concomitant administration of protease inhibitors will exclude a participant from this study. Participant monitoring: Close monitoring of clinical parameters and AEs will be conducted. Stopping criteria will be utilized to mitigate and assess cardiovascular and liver effects. Participants who normally wear contact lenses should wear glasses for the duration of the study and for 5 half-lives thereafter.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Allergic reaction including a rash, swallowing or breathing problems, wheezing, and swelling of the lips, face, throat, or tongue • Liver effects including fever, jaundice, feeling tired, weak or generally unwell, anorexia, nausea, and vomiting • Skin effects including blistering, peeling, bleeding, scaling, or fluid filled patches on any part of the skin • Bruising more easily than usual or purpura • Chills, tiredness, unusually pale skin color, shortness of breath, fast heartbeat, or dark colored urine • Kidney effects including hematuria or an increase or decrease in amount of urine produced • Sudden severe headache • Shock • Leukopenia • Bleeding from the nose, ear, gums, throat, skin, or stomach • Pseudomembranous colitis, symptoms include severe watery diarrhea that will not stop, feeling of weakness, and fever • Water retention (edema), which may cause swollen face, stomach, Cohorts or legs • Muscle weakness or pain or loss of muscle reflexes • Dizziness, feel lightheaded and faint especially on standing or sitting up quickly • Hair loss • Being unable to concentrate, feeling nervous • Irritability or depression; short-term memory loss, anxiety, being less alert or responsive • Insomnia • Wasting of muscles or other body tissues • Eosinophilia	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Midazolam		
Cardiac, Respiratory, Neurologic, and GI Effects	Midazolam is contraindicated in patients with a known hypersensitivity to the drug or allergies to formulation excipients. Potential AEs may include transient drowsiness, nausea and emesis, dizziness and confusion, respiratory depression, decreased systolic and diastolic blood pressure, and increased heart rate.	Inclusion or exclusion criteria: Only healthy participants will be allowed to participate in the proposed study. Any condition or symptom contraindicated for administration of midazolam as per the patient information leaflet or any participant with narrow angle glaucoma will be excluded from this study. Participant monitoring: Continuous cardiac monitoring and pulse oximetry will be performed following dosing with midazolam to monitor participant safety. In addition, flumazenil, which selectively blocks the binding of benzodiazepines to the central nervous system and acts to reverse the clinical effects of toxicity, will be available at the bedside in case of emergency in this study.
Digoxin		
Cardiovascular and Electrolyte Effects	Digoxin should not be used in participants with Wolff-Parkinson-White Syndrome. It has been shown that after IV digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory atrioventricular pathway (Wolff-Parkinson-White Syndrome) have developed increased antegrade conduction across the accessory pathway bypassing the atrioventricular node, leading to a very rapid ventricular response or ventricular fibrillation. Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic	Inclusion or exclusion criteria: Only healthy participants will be allowed to participate in the proposed study. Any condition or symptom contraindicated for administration of digoxin as per the patient information leaflet, any participant with a history of ventricular fibrillation, or a known hypersensitivity to other digitalis compounds will be excluded from the study. Participant monitoring: Serum electrolytes, renal function (serum creatinine concentrations), and 12-lead ECGs will be assessed periodically.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin. Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin. In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2 ng/mL, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Calcium, particularly when administered rapidly by the IV route, may produce serious arrhythmias in digitalized patients. Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically. Because digoxin slows sinoatrial and atrioventricular conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete atrioventricular block. Potential side effects from digoxin are not common, and include, but are not limited to the following: • Loss of appetite, nausea and vomiting, drowsiness, dizziness, headache, confusion, depression, apathy, anxiety, fatigue and muscle weakness • Visual disturbances, such as flashes or flickering of light, sensitivity to light, seeing things larger or smaller than they are, blurring, color changes (yellow or green), and seeing halos or borders on objects	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Symptoms caused by rhythm disturbances, such as palpitation, light-headedness, presyncope and syncope	

ABSSSI = acute bacterial skin and skin structure infection; AChE = Acetylcholinesterase; AE = adverse event; bpm = beats per minute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the concentration-time curve; Cmax = maximum observed concentration; ECG = electrocardiogram; ESRD = end-stage renal disease; GI = gastrointestinal; GLDH = glutamate dehydrogenase; IB = Investigator's Brochure; IV = intravenous; msec = millisecond; 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 formula; QTcF = interval corrected for heart rate according to Fridericia formula; uUTI = uncomplicated urinary tract infection.

2.3.2. Benefit Assessment

Since this Phase I study is being conducted in healthy adult participants, there is no direct clinical benefit to study participants. Participation in this study will contribute to the process of developing new antibiotic therapies in areas of growing unmet need.

2.3.3. Overall Benefit: Risk Conclusion

The risk of adverse events (AEs) is minimized for the population being investigated in the proposed study by careful selection of dose and participants for the study, the relatively short duration of study drug exposure, and the extent of safety monitoring incorporated into the study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Cohort 1: Gepotidacin is a substrate of MATE and potentially of OCT transporter • To characterize the drug-drug interaction (DDI) effect of repeat oral dosing of cimetidine on the pharmacokinetics (PK) of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Cmax, Tmax, t1/2, AUC(0-t), and AUC(0-∞) of gepotidacin in plasma, as data permit
Cohort 2: Gepotidacin is a CYP3A4 substrate • To characterize the DDI effect of repeat oral dosing of rifampicin on the PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of gepotidacin in plasma, as data permit
Cohort 3: Gepotidacin is a P-gp and CYP3A4 inhibitor • To characterize the DDI effect of two 3000 mg doses of gepotidacin given 12 hours apart given with food on the PK for co-administered drugs digoxin and midazolam in an adult healthy population	• Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of digoxin and midazolam in plasma, as data permit
Cohort 4: Japanese PK • To assess the PK, safety, and tolerability of a single 1500 mg dose of gepotidacin under fed and fasted states, and two 3000 mg doses of gepotidacin given 12 hours apart under fed state in Japanese adult participants	• Cmax, Tmax, AUC(0-24), AUC(0-48), AUC(0-t), and AUC(0-∞) of gepotidacin in plasma following a single 1500 mg dose, as data permit • Cmax, Tmax, and AUC(0-τ) of gepotidacin after the first dose; AUC(0-τ), Cmax, Tmax, RoCmax, and RoAUC of gepotidacin after the

Objectives	Endpoints
	second dose; AUC(0-24), AUC(0-48), and AUC(0-t) of gepotidacin using the full profile (both doses) following two 3000 mg doses, as data permit • Adverse events (AEs), clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead electrocardiogram (ECG) readings
• To evaluate the effect of a Japanese meal on the bioavailability of the gepotidacin tablet formulation	• Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of gepotidacin in plasma, as data permit
Secondary	
Cohort 1	
• To characterize the plasma PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• AUC(0-24), AUC(0-48), Tlag, Vz/F, and CL/F of gepotidacin in plasma after a single 1500 mg dose of gepotidacin, as data permit
• To characterize the DDI effect of repeat oral dosing of cimetidine on the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae total, AUC(0-24), AUC(0-48), and CLr of gepotidacin in urine following a single 1500 mg dose, as data permit
• To characterize the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae(t1-t2) and fe% of gepotidacin in urine following a single 1500 mg dose, as data permit
• To evaluate the safety and tolerability of gepotidacin in adult healthy participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings

Objectives	Endpoints
Cohort 2	
• To characterize the plasma PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• AUC(0-24), AUC(0-48), t1/2, Vz/F, and CL/F of gepotidacin in plasma after a single 1500 mg dose of gepotidacin, as data permit
• To characterize the DDI effect of repeat oral dosing of rifampicin on the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae total, AUC(0-24), AUC(0-48), and CLr of gepotidacin in urine following a single 1500 mg dose, as data permit
• To characterize the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population	• Ae(t1-t2) and fe% of gepotidacin in urine following a single 1500 mg dose, as data permit
• To evaluate the safety and tolerability of gepotidacin in adult healthy participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings
Cohort 3	
• To characterize the plasma PK of gepotidacin two 3000 mg doses given 12 hours apart with food in an adult healthy population	• Cmax, Tmax, Tlag, AUC(0-τ) of gepotidacin after the first dose; Cmax, Tmax, AUC(0-τ), RoCmax, and RoAUC of gepotidacin after the second dose; AUC(0-24), AUC(0-48), AUC(0-t), Vz/F, CL/F, and t1/2 of gepotidacin using the full profile (both doses), as data permit
• To characterize the DDI effect of two 3000 mg doses of gepotidacin given 12 hours apart with food on the PK of co-administered drugs digoxin and midazolam in an adult healthy population	• Cmin, t1/2, Vz/F, and CL/F of digoxin and midazolam in plasma, as data permit
• To characterize the urine PK of gepotidacin (two 3000 mg doses given 12 hours apart) given with food in an adult healthy population	• Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin in urine following two 3000 mg doses, as data permit
• To evaluate the safety and tolerability of gepotidacin in adult healthy participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings

Objectives	Endpoints
Cohort 4 • To characterize the PK of a single 1500 mg oral dose of gepotidacin given with and without food in Japanese adult healthy participants • To assess the plasma PK of two 3000 mg doses of gepotidacin given 12 hours apart with food in Japanese adult healthy participants • To assess the urine PK of a single 1500 mg dose or two 3000 mg doses of gepotidacin given 12 hours apart with food in Japanese adult healthy participants	• t1/2, Vz/F, and CL/F of gepotidacin in plasma after a single 1500 mg dose of gepotidacin, as data permit • Tlag of gepotidacin after the first dose; Vz/F, CL/F, and t1/2 of gepotidacin using the full profile (both doses) following two 3000 mg doses, as data permit • Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin in urine following a single 1500 mg dose and two 3000 mg doses, as data permit
Exploratory	
Cohort 1 • To characterize the DDI effect of repeat oral dosing of cimetidine on the PK of plasma and urine for N1-methylnicotinamide (1-NMN) biomarker in adult healthy participants • To evaluate concentrations of serum and urine creatinine after administration of gepotidacin with and without cimetidine in adult healthy participants • To evaluate cimetidine PK to assess transporter inhibition in adult healthy participants	• C average, Cmax, Ctrough, AUC(0-24), AUC(0-48), and AUC(0-t) of 1-NMN in plasma, as data permit • Ae total and CLr of 1-NMN in urine, as data permit • 1-NMN plasma and urine PK parameters normalized to creatinine, as data permit • Serum and urine creatinine concentrations, as data permit • 1-NMN plasma and urine PK parameters normalized to creatinine, as data permit • Cimetidine plasma PK concentrations, as data permit

Objectives	Endpoints
Cohort 3 • To evaluate the plasma PK for the metabolite 1'-hydroxymidazolam	• Cmin, Cmax, Tmax, t1/2, AUC(0-t), and AUC(0-∞) of 1'-hydroxymidazolam in plasma, as data permit • Molecular weight normalized parent-to-metabolite AUC(0-∞) ratio, as data permit
• To characterize the DDI effect of two 3000 mg doses of gepotidacin given 12 hours apart given with food on the urine PK of co-administered digoxin in an adult healthy population	• Ae total, fe%, and CLr of digoxin in urine following a single 1500 mg dose, as data permit
Cohort 4 • To compare the plasma and urine PK of gepotidacin 1500 mg single dose (SD) data from the Cohort 4 Japanese versus the gepotidacin-only 1500 mg SD data the DDI Cohorts in adult (non-Japanese) healthy participants	• Plasma and urine concentrations and parameters for gepotidacin, as data permit
• To compare the plasma and urine PK of gepotidacin 3000 mg twice daily data from the Cohort 4 Japanese versus the Cohort 3 gepotidacin 3000 mg twice daily data in adult (non-Japanese) healthy participants	• Plasma and urine concentrations and parameters for gepotidacin, as data permit
Cohorts 1, 2, 3, and 4 • To determine the effect of gepotidacin concentrations on the QT interval corrected with Fridericia's method (QTcF) in adult healthy participants	• Change from Baseline in QTcF versus gepotidacin concentration

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase I, DDI, PK, safety, and tolerability study in adult healthy participants, including a Japanese cohort, to be conducted at 1 center in the United States. Further phase 1 units may be used to perform this study should the need arise, due to interruptions around recruitment of participants during the Covid-19 pandemic. This study is designed to assess co-administration of probe substrates with gepotidacin in study Cohorts 1 to 3 and establishing PK and safety in a Japanese cohort in Cohort 4.

The study Cohorts are summarized in Table 14.

Table 14 Summary of Study Cohorts

Study Cohort	Co-administered Drug Probe	Gepotidacin	Design
Cohort 1	Cimetidine 400 mg 4 times daily for 4 days (perpetrator)	Gepotidacin 1500 mg × 1 (victim)	Fixed sequence
Cohort 2	Rifampicin 600 mg once daily for 9 days (perpetrator)	Gepotidacin 1500 mg × 1 (victim)	Fixed sequence
Cohort 3	Midazolam 2 mg SD Digoxin 0.5 mg SD (victims)	Gepotidacin 3000 mg × 2 12 hours apart (perpetrator)	Randomized sequence
Cohort 4 (Japanese cohort)	N/A	Gepotidacin 1500 mg × 1 Gepotidacin upto 3000 mg × 2	Randomized sequence for Periods 1 and 2; fixed sequence for Period 3

SD = single dose; N/A= not applicable

In all Cohorts, participants will be screened within 28 days before the first dose of study treatment.

Cohort 1: Cohort 1 is an open-label, fixed sequence DDI study to investigate the effect of cimetidine on the PK of gepotidacin under fed conditions. Participants will receive the following treatments in a fixed sequence (Sequence AB). A follow-up visit will occur 5 to 7 days after the last dose of cimetidine.

- Treatment A: Gepotidacin 1500 mg single dose (SD) on Day 1 of Period 1.
- Treatment B: Cimetidine 400 mg 4 times daily on Days 1 through 4 of Period 2 and gepotidacin 1500 mg SD. Gepotidacin will be administered 1 hour after the first dose of cimetidine on Day 2 of Period 2 (gepotidacin administration is delayed for 1 hour due to the changes in gastric pH by cimetidine that could impact gepotidacin dissolution and absorption). On Day 4 of Period 2, cimetidine dosing will be discontinued after the last PK sample is collected.

There will be a washout of at least 3 days after dosing with gepotidacin in Period 1. Cimetidine will be administered in the fasted condition. Prior to dosing with gepotidacin, participants will receive a standard meal 30 minutes prior to dosing. Participants will eat

this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until at least 2 hours after gepotidacin dosing.

Pharmacokinetic blood and urine samples for analysis of gepotidacin, creatinine, and the endogenous biomarker N1-methylnicotinamide (1-NMN) will be obtained at pre-specified time points, and sparse blood samples will be collected for cimetidine after dosing as indicated in the schedule of activities (SoA) (Table 2, Table 3, and Table 4). Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Including screening, a washout of at least 3 days between Treatment A and Treatment B, and a follow-up visit 5 to 7 days after the last dose of cimetidine, the total duration of Cohort 1 is up to 42 days.

Cohort 2: Cohort 2 is an open-label, fixed sequence DDI to investigate the effect of rifampicin on the PK of gepotidacin under fed conditions. Participants will receive the following treatments in a fixed sequence (Sequence CDE). A follow-up visit will occur 7 to 10 days after the last dose of rifampicin.

- Treatment C: Gepotidacin 1500 mg SD on Day 1 of Period 1.
- Treatment D: Rifampicin 600 mg (administered in the evenings) once daily for 7 days (Days 1 through 7 of Period 2, to elicit maximal enzyme induction).
- Treatment E: Gepotidacin 1500 mg SD administered in the morning on Day 8 and rifampicin 600 mg administered in the evening on Days 8 and 9 of Period 2.

There will be a washout of at least 3 days after dosing of gepotidacin in Period 1. The participants will receive a standard meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until at least 2 hours after gepotidacin dosing. Rifampicin will be administered 1 hour before the evening meal.

Pharmacokinetic blood and urine samples of gepotidacin will be obtained at pre-specified time points before and after dosing as indicated in the SoA (Table 5 and Table 6). Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings.

Including screening, a washout of at least 3 days between Treatment C and Treatment D, and a follow-up visit 7 to 10 days after the last dose of rifampicin, the total duration of Cohort 2 is up to 50 days.

Cohort 3: Cohort 3 is an open-label, 2-sequence, 2-period crossover randomized DDI study to investigate the effect of gepotidacin on the PK of 2 probe drugs (digoxin and midazolam) under fed conditions. Participants will be randomized to 1 of 2 treatment sequences in a 1:1 ratio. In Sequence 1, participants will receive digoxin 0.5 mg and

midazolam 2 mg (Treatment F) in Period 1 on Day 1 then gepotidacin two 3000 mg doses (given 12 hours apart) co-administered with digoxin 0.5 mg and midazolam 2 mg in Period 2 on Day 1, with the 2 probe drugs administered with the second daily dose of gepotidacin only (Treatment G). In Sequence 2, these regimens are reversed. A follow-up visit will occur 7 to 10 days after the last dose of study intervention in Period 2 (to ensure clearance of digoxin). The 2 treatments are as follows:

- Treatment F: Digoxin 0.5 mg and midazolam 2 mg on Day 1.
- Treatment G: Gepotidacin two 3000 mg doses (given 12 hours apart) on Day 1 with digoxin 0.5 mg and midazolam 2 mg given with the second gepotidacin dose on Day 1.

There will be a washout of at least 10 days between treatments. The participants will receive a standard meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. All dose administrations will occur within 5 minutes of completion of meal consumption. Another standard meal (similar in calorie content and similar ratios of protein, carbohydrates, and fat as the previous meal) will be provided prior to the second gepotidacin dose (Treatment G). Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until at least 2 hours after dosing.

Blood samples for analysis of gepotidacin, midazolam, 1'-hydroxymidazolam, and digoxin PK; and urine samples for gepotidacin and digoxin PK will be obtained at pre-specified time points before and after dosing as indicated in the SoA (Table 7, Table 8, and Table 9). Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, pulse oximetry, 12-lead ECG results, Holter monitoring, and physical examination findings.

Including screening, a washout of at least 10 days between treatments, and a follow-up visit 7 to 10 days after the last dose of study treatment, the total duration of Cohort 3 is up to 50 days.

Cohort 4: Cohort 4 is a double-blind, placebo-controlled, randomized sequence (Periods 1 and 2 only) study to investigate the safety and PK of gepotidacin under fed and fasted conditions in Japanese participants. Participants will be randomly assigned (10 active:2 placebo) to receive gepotidacin or placebo. Within each treatment group, participants will be randomized to each of the 2 sequences in 1:1 ratio: HIJ versus IHJ (to elucidate the food effect). In Sequence 1, participants will receive a SD of gepotidacin 1500 mg or placebo under fed conditions in Period 1 (Treatment H), then a SD of gepotidacin 1500 mg or placebo under fasted conditions in Period 2 (Treatment I), followed by two doses of gepotidacin up to 3000 mg or placebo (given 12 hours apart) under fed conditions in Period 3 (Treatment J). In Sequence 2, the first 2 treatments are reversed (Sequence IHJ). A follow-up visit will occur 5 to 7 days after the last dose of gepotidacin or placebo.

- Treatment H: Gepotidacin 1500 mg or placebo SD under fed conditions on Day 1.

- Treatment I: Gepotidacin 1500 mg or placebo SD under fasted conditions on Day 1.
- Treatment J: Two doses of gepotidacin up to 3000 mg or placebo (given 12 hours apart) under fed conditions on Day 1.

There will be a washout of at least 3 days between each treatment. Participants receiving Treatments H and J will receive a standard meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants receiving Treatment I will fast overnight for at least 8 hours prior to dosing. Participants will not receive any further food until at least 2 hours after dosing.

Pharmacokinetic blood and urine samples for analysis of gepotidacin will be obtained at pre-specified time points before and after dosing, as indicated in the SoA (Table 10, Table 11, and Table 12). Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, Holter monitoring (Period 3 only), and physical examination findings.

Including screening, a washout of at least 3 days between each treatment, and a follow-up visit 5 to 7 days after the last dose of gepotidacin, the total duration of Cohort 4 is up to 44 days.

4.2. Scientific Rationale for Study Design

Following a single oral administration of [^{14}C]-gepotidacin to humans (study BTZ115774), approximately 50% of the dose was absorbed, consistent with the oral bioavailability of 44%. After oral administration, gepotidacin was eliminated mainly as parent in urine, accounting for approximately 20% of the administered dose. Elimination via metabolism (urine plus feces) accounted for a total of 13% to 19% of the dose. The oxidative metabolism of gepotidacin in vitro is mediated primarily by CYP3A4. In addition, gepotidacin is a substrate of the human P-gp and breast cancer resistance protein (BCRP) transporters in vitro. Gepotidacin exposure may, therefore, be affected by any co-medications that are CYP3A4 and/or P-gp and BCRP inhibitors. Gepotidacin renal clearance exceeds glomerular filtration rate by greater than 2-fold, suggesting that renal transporters are involved in gepotidacin renal elimination. Based on in vitro data, MATE likely contributes to gepotidacin urine levels. Therefore, concomitant administration with a MATE inhibitor may lead to increased plasma levels and decreased gepotidacin levels in the urine, and thus, potentially less safety for both indications and/or efficacy for uUTIs.

Gepotidacin may act as an inhibitor for CYP3A4 and P-gp. Concomitant use of gepotidacin with sensitive CYP3A4 or P-gp substrates (e.g., midazolam, digoxin) may increase the area under the concentration-time curve (AUC) and maximum observed concentration (Cmax) of the substrate drug. This may increase the risk of toxicities when these drugs are taken together.

Cohort 1: Cimetidine is an H2 antagonist used to reduce the acid in the stomach with a half-life of approximately 2 hours. Cimetidine tablets are rapidly absorbed after oral

administration and peak levels occur in 45 to 90 minutes. After oral administration, the drug is extensively metabolized in which the sulfoxide is the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound.

Cimetidine as a nonspecific inhibitor of organic cationic transporter (OCT) and an inhibitor of MATE: Cimetidine will be employed to assess the impact on gepotidacin (victim) plasma and urine levels via inhibition of MATE and potentially via inhibition of OCTs in the basolateral membrane of the renal tubular cells. While none of the in vitro testing pointed to currently known OCTs as responsible for the transportation of gepotidacin, MATE transporters are usually coupled with OCTs. MATE is responsible for transporting gepotidacin at the apical membrane from the tubular renal cell into the urine. These data will inform on gepotidacin safety regarding potential enhanced plasma exposure and efficacy specific to the uUTI indication (inhibition of MATE and possibly unknown OCTs might reduce gepotidacin urine exposure, potentially also reducing its efficacy in uUTI). Therefore, cimetidine will be administered 400 mg 4 times daily aligned to the prescribing information [Cimetidine, 2019] before and during gepotidacin administration together with PK sampling to ensure adequate systemic exposure.

Cimetidine PK samples will be collected at 1, 25, and 49 hours after the first dose of cimetidine to assess if the MATE transporter is fully inhibited based on clinical exposure and in vitro data (compared to half maximal inhibitory concentration).

The endogenous biomarker 1-NMN is taken up by OCT2 and secreted by MATEs. Levels of 1-NMN will help assess OCT2 inhibition, and a reduction in clearance to MATE inhibition. Given the unknown mechanism for transportation of gepotidacin from blood to the renal tubular cell, the endogenous biomarker 1-NMN will be assessed to provide direct confirmation if renal organic cationic transport systems are inhibited, and therefore involved in the transportation of gepotidacin on the basolateral membrane (not demonstrated in vitro). Serum and urine creatinine will also provide data on renal inhibition.

Cohort 2: Rifampicin is a semisynthetic antibiotic derivative of rifamycin indicated for the treatment of tuberculosis and meningococcal carrier state. Rifampicin is usually administered on a daily basis at doses not exceeding 600 mg/day. Protein binding is approximately 80% and the terminal half-life is approximately 3 hours. Although some enzyme induction is noted with the first dose of rifampicin, repeat dose administration (daily for approximately 9 days) is required to achieve maximal induction [Nassr, 2009].

Rifampicin as a CYP3A4 inducer: Rifampicin is a potent inducer of CYP3A4, CYP2C9, CYP2C19, and a potent inducer of P-gp transporter. It strongly induces the expression of CYP3A4 in both the liver and intestine; thereby reducing the plasma concentrations and effects of several CYP3A4 substrates. In most cases, rifampicin reduces the plasma concentrations of a drug which itself is active and has no important active metabolites, the result being a reduction in its pharmacodynamic (PD) effects [Niemi, 2003]. As gepotidacin is a CYP3A4 substrate, this Cohort will identify potential for reduced gepotidacin exposure that may impact efficacy. These findings will be appropriate for both uUTI and gonorrhea indications.

Cohort 3: A 2-probe (digoxin and midazolam) approach will be used to assess gepotidacin as the perpetrator of CYP3A4 and P-gp inhibition. These observations will be appropriate for both the uUTI (CYP3A4 inhibition only) and gonorrhea (both CYP3A4 and P-gp inhibition) indications.

Digoxin: Digoxin is indicated for the treatment of mild to moderate heart failure and for rate control in chronic atrial fibrillation. Following oral administration, Cmax of digoxin occurs between 1 and 3 hours. Oral absorption of digoxin tablets is between 60% and 80%. In healthy participants with normal renal function, t1/2 is 1.5 to 2 days; therefore, steady-state concentrations are not achieved until approximately 10 days. When given after a meal, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin; thus participants with a known hypersensitivity to digoxin or other digitalis preparations will be excluded from this study.

Digoxin as P-gp substrate: In vitro experiments suggest that gepotidacin is a P-gp inhibitor at the gut level at the gonorrhea dose (2 × 3000 mg). Since digoxin is a substrate for P-gp, co-administration of gepotidacin gonorrhea dose with digoxin may change the PK profile of digoxin. In addition, digoxin has a narrow therapeutic range, a low safety margin, and has been shown to interact with many other drugs that are substrates, inhibitors (e.g., fostamatinib), or inducers (e.g., rifampicin) of P-gp in several clinical studies [Fuhr, 2007]. Thus, digoxin has been used as a probe for potential drug interactions with other drugs that affect P-gp. A low dose of digoxin 0.5 mg has been selected to minimize the risk of AEs.

Midazolam: Midazolam, a short-acting benzodiazepine used for pre-operative sedation, is a well characterized probe drug for CYP3A4/5 [Huang, 2007; Fuhr, 2007]. Midazolam is well absorbed after oral dosing, has a terminal half-life of approximately 2 hours and is almost exclusively metabolized by CYP3A enzymes to its primary metabolite, 1'-hydroxymidazolam, as well as to the minor metabolites 4-hydroxymidazolam and 1', 4-hydroxymidazolam [Heizmann, 1983].

Midazolam as CYP3A probe: IV midazolam is used to probe the metabolic activity of hepatic CYP3A enzymes, while oral administration allows simultaneous assessment of both intestinal and hepatic CYP3A activity [Thummel, 1996]. More than 200 drug interaction studies involving midazolam have been reported. The US Food and Drug Administration has developed a CYP3A inhibitor classification system based on the magnitude of inhibitory effect on midazolam plasma AUC that serves to benchmark the risk of clinically significant CYP3A-mediated DDIs.

Oral midazolam doses in drug interaction studies have ranged from 1.75 to 15 mg, with the majority of studies using a dose ≥5 mg [University of Washington School of Pharmacy, 2020]. The midazolam dose (as one of the probe drugs) will be 2 mg orally. A lower dose was chosen to reduce the chance of excessive sedation in the presence of an interaction causing increasing levels of midazolam. As an added precaution, flumazenil, a

benzodiazepine antagonist, will be readily available if any participant experiences excessive sedation.

Cohort 4: A Japanese (healthy participant) cohort will be recruited to evaluate a single 1500 mg gepotidacin oral dose (fed and fasted) to cover uUTI indication. The data for the 1500 mg dose will be compared to gepotidacin PK profiles generated in the DDI Cohorts 1 and 2 (periods without co-administration of DDI drugs). This cohort may also be used to evaluate a 2-dose regimen to cover the gonorrhea indication. Dose selection for gonorrhea is subject to ongoing PK modeling but will be a maximum 3000 mg dose given twice daily 12 hours apart. A 3000mg dose given twice daily has previously been studied (209611 in IB) in adult and adolescent healthy participants and was generally well tolerated. Completed PK modelling will inform on the final 2-dose regimen to cover the gonorrhea indication in healthy Japanese participants. The final 2-dose regimen will be communicated to the site before dosing cohort 4 in period 3. The gepotidacin PK data in Japanese for the gonorrhea indication will be compared to 2 × 3000 mg doses in the population from the 2-probe Cohort (Cohort 3).

This study (Cohorts 1 to 4) will collect gepotidacin PK data in plasma and urine (where applicable) following dosing of gepotidacin. For the 2-probe (Cohort 3) administration, plasma PK for midazolam, and digoxin will be collected, including intensive gepotidacin PK sampling at specific timepoints, to serve as a control (ensure adequate gepotidacin exposure and for comparison with the Japanese PK data).

4.3. Justification for Dose

The 1500 mg dose was tested in the recently completed Phase I study in healthy adult and adolescent participants [GSK Document Number 2019N422403_00, 209611], and no new safety issues were identified. The majority of AEs were mild in intensity and involved gastrointestinal (GI) events, a known risk with gepotidacin as indicated in Section 2.3.1. The 1500 mg dose is also being studied in 2 ongoing Phase 3 studies in uUTIs [GSK Document Number 2017N318043_01 and GSK Document Number 2019N407320_01, study number 204989 and 212390].

Based on PK modeling, gepotidacin will be administered for gonorrhea as 2 single oral 3000 mg doses, given either 10 or 12 hours apart with a minimum body weight of 40 kg. This will provide higher daily systemic exposures that allow coverage of *Neisseria gonorrhoeae* isolates with higher gepotidacin minimum inhibitory concentration values, which are likely to be observed in the global Phase III study and reduce the risk of resistance emergence. The 2 single oral 3000 mg doses given 12 hours apart was one of the dosing regimens tested in the recently completed Phase I study in healthy adult and adolescent participants [GSK Document Number 2019N422403_00], and, as indicated above, no new safety issues were identified. The 2 single oral 3000 mg doses, given either 10 or 12 hours apart, is also being studied in an ongoing Phase III study in gonorrhea [GSK Document Number 2017N317989_01, BTZ116577]. An oral dose of up to 6g has been administered to healthy volunteers in completed studies [IB; GSK Document Number CM2010/00033/06, 2019] for further details on Gepotidacin].

In the current study, gepotidacin will be administered as either a single 1500 mg oral dose or as two 3000 mg oral doses. The single 1500 mg dose is expected to provide additional PK and safety data for the uUTI indication. The two 3000 mg doses, given 12 hours apart, are expected to provide valuable PK and safety data to guide Phase III studies and the prescribing information for the gepotidacin tablet for the *N. gonorrhoeae* indication. The doses of the substrate drugs are typical doses for this type of study as indicated in Section 4.2.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled visit shown in the SoA (Section 1.3) for the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit shown in the SoA (Section 1.3).

5. STUDY POPULATION

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

Healthy participants will be recruited to this study meeting the inclusion and exclusion criteria. The Japanese cohort aims to enroll at least 30% females with a target of 50% (depending on feasibility). The inclusion of females in the Japanese cohort is especially associated with the uUTI indication being pursued.

5.1. Inclusion Criteria

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

Age

1. Participant must be ≥18 to ≤50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by the investigator or medically qualified designee based on medical evaluation including medical history, physical examination, clinical laboratory tests, vital sign measurements, and 12-lead ECG results. A participant with clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the investigator feels and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
3. Additional inclusion criteria for Japanese participants (Cohort 4):

- The participant is a non-naturalized Japanese citizen and holds a Japanese passport (current or expired).
- The participant has/had 2 Japanese parents and 4 Japanese grandparents who are/were all non-naturalized Japanese citizens, as confirmed by interview.
- The participant has been living outside of Japan for up to 10 years as confirmed by interview.

Weight

4. Participants have a body weight ≥40 kg and body mass index within the range 18.5 to 32.0 kg/m^2 (inclusive).

Sex

Sex and Contraceptive/Barrier Requirements

5. Male and/or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
  - Is a woman of non-childbearing potential as defined in Appendix 5

    OR

  - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 5 for at least 30 days prior to dosing until completion of the follow-up Visit. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention and for women not on effective contraception at least 14 days prior to baseline visit. See Section 8.2.5 Pregnancy Testing.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Clinically significant abnormality in the past medical history or at the screening physical examination that in the investigator's opinion may place the participant at risk or interfere with the outcome variables of the study. This includes, but is not limited to, history or current cardiac, hepatic, renal, neurologic, GI, respiratory, hematologic, or immunologic disease.
2. Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study intervention, or any other condition that may place the participant at risk, in the opinion of the investigator.
3. Female participant has a positive pregnancy test result or is lactating at Screening or upon admission to the clinic.
4. Positive test for SARS-CoV-2. Note: Testing will be performed according to site procedures.
5. Within 2 months before Screening, either a confirmed history of *Clostridium difficile* (*C. difficile*) diarrhea infection or a past positive of *C. difficile* toxin test.
6. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
7. History of drug and/or alcohol abuse within 6 months before Screening, as determined by the investigator, or has a positive drug screen at Screening or upon admission to the clinic.
8. History of sensitivity/hypersensitivity to any of the study drugs, components thereof, or a history of drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor contraindicates their participation.
9. Cohort 2 Only: Participant is a contact lens wearer who is unable or unwilling to wear glasses for the duration of the study and for 5 half-lives after the last dose of rifampicin.

Prior/Concomitant Therapy

10. Use of any systemic antibiotic within 30 days of screening.
11. Participants must abstain from taking prescription or non-prescription drugs (except for hormonal contraceptives and/or acetaminophen at doses of ≤2 grams/day), vitamins, and dietary or herbal supplements, unless specified in Section 6.8, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives

(whichever is longer) prior to study intervention until completion of the follow-up Visit, unless, in the opinion of the investigator and Sponsor, the medication will not interfere with the study. Any exceptions will be discussed with the Sponsor or Medical Monitor on a case-by-case basis and the reasons will be documented.

Prior/Concurrent Clinical Study Experience

12. Previous exposure to gepotidacin.
13. Participant has participated in a clinical trial and has received an investigational product (IP) prior to gepotidacin administration within 30 days, 5 half-lives, or twice the duration of the biological effect of IP (whichever is longer).
14. Past participation in this clinical study.

Diagnostic assessments

15. Baseline corrected QT interval using the Fridericia formula (QTcF) of >450 milliseconds (msec) at Screening or Check-in.
16. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention.
17. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN) at Screening or Check-in.
18. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at Screening or Check-in.
19. History of any kidney disease or current or chronic history of mild impaired renal function as indicated by an estimated creatinine clearance ≤90 mL/min.
20. A positive test for human immunodeficiency virus (HIV) antibody.
21. History of regular alcohol consumption within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full strength beer, 470 mL of light beer, 30 mL of spirits, or 100 mL of wine.
22. Cohort 3 Only: Digoxin-related exclusions include the following at Screening:
    - Serum potassium >5.5 mEq/L or < 3.6 mEq/L
    - Serum magnesium <1.6 mg/dL
    - Serum calcium (total) <8.5 mg/dL
    - History of hypersensitivity to digoxin or other digitalis glycosides
    - Any clinically relevant abnormality on 12-lead ECG at Screening or Check-in.

Other Exclusions

23. Participant has donated blood in excess of 500 mL within 12 weeks prior to dosing or participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
24. Participant is unable to comply with all study procedures, in the opinion of the investigator.
25. Participant should not participate in the study, in the opinion of the investigator or Sponsor.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Participants receiving study intervention under fed conditions will receive a standard meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Approximately 240 mL of water will be provided for swallowing the dose. Up to 480 mL of water is allowed if needed to swallow the entire dose. Participants will not receive any further food until at least 2 hours after dosing.
- Participants receiving study intervention under fasted conditions will fast overnight for at least 8 hours prior to dosing. Approximately 240 mL of water will be provided for swallowing the dose. Up to 480 mL of water is allowed if needed to swallow the entire dose. Participants will not receive any food until at least 2 hours after dosing.
- For doses scheduled to occur 12 hours after the initial dose, participants will have the standard meal in the morning and will receive another standard meal (similar in calorie content and similar ratios of protein, carbohydrates, and fat as the previous meal) prior to the second dose. Participants should consume this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 2 hours after dosing.
- Standard meals will be provided during the study intervention period at times that do not interfere with study procedures.
- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of dosing until after collection of the final PK sample.
- No water is allowed until 2 hours after dosing, unless administered under the investigator's direct order for treatment of an AE. Water is allowed ad libitum at all other times.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from 3 months before Screening until after the final follow-up visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- After dosing gepotidacin, the participants will remain in semi-supine position where possible up to 4 hours post dose.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations, and any serious AEs (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened (for the same Cohort or another Cohort of the study, subject to meeting eligibility criteria). Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention Administration

Not applicable for this study.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Cohort Name	All Cohorts	Cohort 1	Cohort 2	Cohort 3		Cohort 4
Intervention Name	Gepotidacin	Cimetidine	Rifampicin	Midazolam	Digoxin	Placebo (matched to gepotidacin)
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Tablet containing gepotidacin mesylate (GSK2140944E)	Tablet	Capsule	Oral syrup	Tablet	Tablet
Unit Dose Strengths	750 mg	400 mg	300 mg	2 mg/mL	0.25 mg	Not applicable
Dosage Levels	1500 mg (2 × 750 mg) SD (Cohorts 1, 2, and 4) or 3000 mg (4 × 750 mg) 2 doses 12 hours apart (Cohorts 3 and 4).	400 mg 4 times per day	600 mg once per day	2 mg (1.0 mL) SD	0.5 mg SD	Not applicable
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided locally by the trial site	Provided locally by the trial site	Provided locally by the trial site	Provided locally by the trial site	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in amber glass bottles of 118 mL of syrup. Each bottle will be labeled as per country requirement.	Study Intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.

HDPE = high-density polyethylene; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; SD = single dose.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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 site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention 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 intervention are provided in the Study Reference Manual (SRM).
    - Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
    - A Material Safety Data Sheet/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.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will act as their own controls in all Cohorts of the study (with the exception of Cohort 4, Period 3). Treatment sequences in Cohorts 3 and 4 are randomized. Cohort 4 contains blinded treatment of gepotidacin and placebo. An unblinded pharmacist will dispense study intervention in Cohort 4; neither the participant nor immediate study personnel (i.e., investigators, PPD staff) will know which study intervention the participant is receiving. Participants who are randomly assigned to receive placebo will receive a matching placebo form of the active treatment. The matching placebo will look identical to the active form.

6.4. Study Intervention 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.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention 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 intervention. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Dose modification is not applicable in this study.

6.6. Continued Access to Study Intervention after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy participants are eligible for study participation.

6.7. Treatment of Overdose

For this study, any dose of gepotidacin or the substrate drugs greater than the planned dose within a 24-hour time period (± 2 hours) will be considered an overdose. All study interventions will be administered at the clinic, thus limiting the risk of overdose. In the unlikely event that an overdose should occur, the investigator must notify the Sponsor promptly. There is no specific antidote for overdose with a bacterial topoisomerase inhibitor such as gepotidacin. 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 clinic status.

GlaxoSmithKline does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until gepotidacin or any of the probe drugs can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the electronic case report form (eCRF).
5. For midazolam (Cohort 3), flumazenil, a benzodiazepine antagonist, will be readily available if any participant experiences excessive sedation.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- 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.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up Visit, unless, in the opinion of the investigator and Sponsor, the medication will not interfere with the study.

For Cohort 2, participants should be advised that taking medications within 14 days of the last dose of rifampicin that are victim to induction may be impacted; resulting in reduced victim drug levels when co-administered with rifampicin followed by an increase in victim drug when induction has stopped.

Since gepotidacin is known to have some prolongation of the corrected QTc interval (QTc), any drugs known to increase QTc interval should be avoided when treating an AE.

Due to the potential for acetylcholinesterase (AChE) inhibition with gepotidacin, the following medications are prohibited:

- Succinylcholine or other depolarizing muscle relaxants
- AChE inhibitors as required for myasthenia gravis including edrophonium, pyridostigmine, neostigmine, etc

Hormonal contraceptives and acetaminophen at doses of ≤2 grams/day are permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

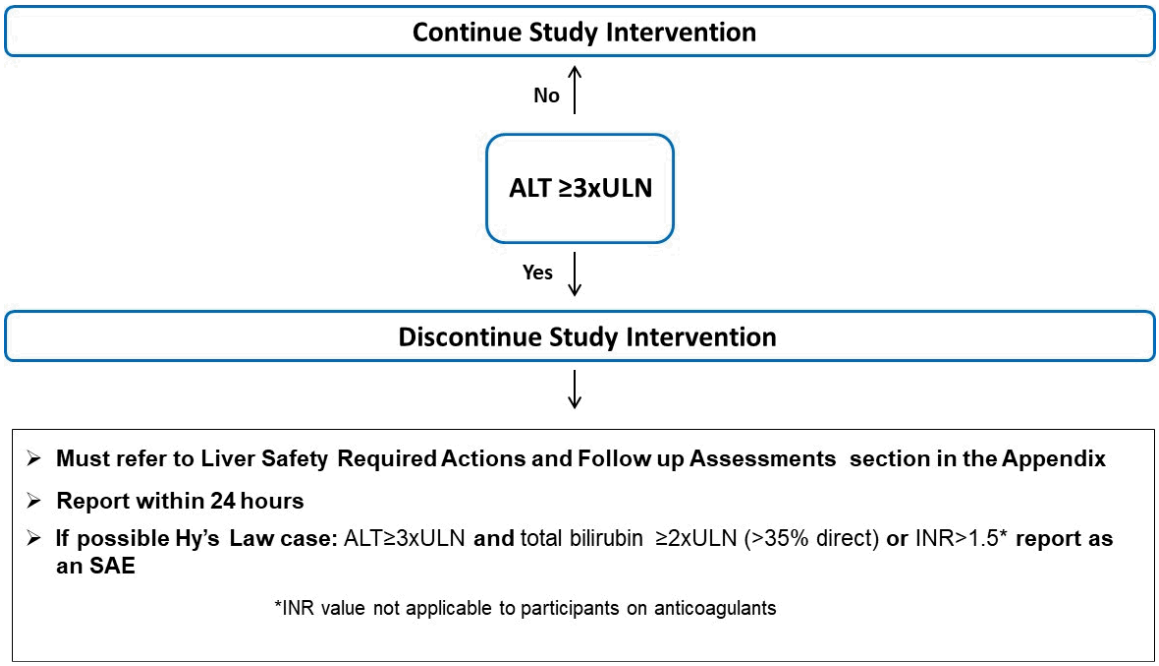
In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA (Section 1.3) for data to be

collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met:

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Appendix 6 for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping Criteria

- A participant who meets the following bulleted criteria based on triplicate ECG readings will be withdrawn from study intervention:
- QTc >500 msec
- Change from baseline of QTc >60 msec
- For participants with underlying bundle-branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle-Branch Block	Discontinuation 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 and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on corrected QT interval using the Fridericia formula (QTcF), then QTcF 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 non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of ECG readings obtained over a brief (e.g., 5 to 10 minute) recording period.
- If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed

7.1.3. Gastrointestinal Evaluation Criteria

If a participant meets the criteria in Appendix 8, *C. difficile* toxin testing should be conducted.

7.1.4. Rash/Hypersensitivity Evaluation Criteria

A participant presenting with a Grade 3 AE or higher rash (diffuse macular, maculopapular, OR morbilliform rash with vesicles or limited number of bullae; OR superficial ulcerations of mucous membrane limited to 1 site) or a Grade 2 rash (diffuse macular, maculopapular, or morbilliform rash; OR target lesions) with evidence of systemic involvement will be followed as appropriate until resolution of the AE(s).

7.1.5. Temporary Discontinuation

Temporary discontinuation is not allowed during this study.

7.1.6. Rechallenge

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. 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 clinic for a required study visit:

- The 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/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 3.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All 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.
- 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 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy and/or Immunogenicity Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure and heart rate. Temperature and respiratory rate will be collected at Screening only. Each measurement will be recorded in the eCRF. Pulse oximetry will be measured in Cohort 3 only, during administration of midazolam.

8.2.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

- Twelve-lead ECGs will be performed with the participant in a semi-supine position after a rest of at least 10 minutes.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession but no more than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5 to 10 minutes) recording period.
- ECG Holter (telemetry) monitoring will be obtained as outlined in the SoA (Section 1.3). The Holter monitoring data will be sent to GSK and may be analyzed at a later date.

8.2.4. Clinical Safety Laboratory Assessments

- See Table 16 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study and until completion of the follow-up Visit 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 clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Table 16, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.
- Additional considerations around Covid-19 can be found in Appendix 7.

8.2.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted the time points indicated in the SoA (Section 1.3) during the study intervention period.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs or SAEs can be found in Appendix 4.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the start of intervention until the the follow-up Visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of study intervention until the follow-up Visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions sections of the eCRF, not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance 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 information on AEs or SAEs after the conclusion of the study participation. 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/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. 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 non-serious AEs of special interest (as defined in Section 2.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4. 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 intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent EC (IEC), and investigators.
- 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.
- 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.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the follow-up Visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for this study are cardiovascular and GI events (including *C. difficile* infection), and AchE inhibition.

8.4. Pharmacokinetics

- Plasma and urine samples will be collected for PK assessment. Time points for PK collection are indicated in the SoA (Section 1.3). All volumes for PK assessment will be provided in the SRM.
- There are samples in storage that GSK may retrieve for analysis at a later date if unexpected results are observed.
- Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Processing, storage, and shipping procedures for blood and urine samples are provided in the SRM and/or laboratory manual.
- Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6. Biomarkers

Plasma and urine samples will be collected to evaluate 1-NMN and creatinine in Cohort 1 only. Samples will be collected according to the schedule described in the SoA (Section 1.3). Details of sample collection will be provided in the SRM.

GSK may store samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with participants consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of infections or other diseases, the development of related or new treatments or research methods.

8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no formal research hypothesis that will be statistically tested in this study.

9.2. Sample Size Determination

Approximately 14 participants will be recruited for Cohort 1, 2, and 4 to ensure that each Cohort has at least 12 completers, allowing for up to a 20% withdrawal rate. Participants in the Japanese Cohort will be randomly assigned (11 active:3 placebo) to receive gepotidacin or placebo, ensuring at least 10 completers in the gepotidacin arm. For Cohort 3, 22 participants will be enrolled to achieve at least 18 completers to accommodate the narrower therapeutic window of digoxin.

The precision, measured by the relative distance of the upper 90% confidence interval (CI) to the geometric mean (GM) of the victim drug PK parameters, is determined using the reported intrasubject coefficient of variability (CV_w%) for each of the PK parameters in each Cohort under the current planned sample size. The CV_w% values are obtained from either previous GSK studies for gepotidacin (Study BTZ117349 [GSK Document Number 2014N199850_00]; for digoxin and midazolam (Study AI468063 [Bristol-Myers Squibb Document Control Number 930102301]); or from the literature for 1'-hydroxymidazolam [Paulson, 2017]. Results are presented in Table 15 below. The precision ranges from 4.8% to 12.8%. Taking the AUC(0-∞) for the gepotidacin in Cohort 1 under sample size 12 as an example, this means that the upper bound of the 90% CI for the GM ratio of gepotidacin + cimetidine: gepotidacin would be within approximately 4.8% of the observed GM ratio for AUC(0-∞). Example CIs based on GM=1 are also included in Table 15.

Based on the previous gepotidacin Study 209611 [GSK Document Number 2019N422403_00], the GM of Cmax of gepotidacin 2 × 3000 mg dose after the second dose was 11.02 µg/mL with a standard deviation on the log scale of 0.2753. For the Japanese cohort (Cohort 4), with 10 participants in the active Cohort, the 95% CI for Cmax assuming the same GM is (9.05, 13.41). The upper limit of this CI is below 14 µg/mL which has been associated with mild transient AEs in previous studies.

Table 15 Sample Size Precision

Cohort	Active Arm Sample Size	Victims	PK Parameter	CV_w%	Precision[1]	90% CI if GM Ratio=1
Cohorts 1 and 2	12	Gepotidacin	AUC(0-∞)	9.01%	4.8%	(0.954, 1.048)
			Cmax	20.6%	11.4%	(0.898, 1.114)

Cohort	Active Arm Sample Size	Victims	PK Parameter	CV_w%	Precision[1]	90% CI if GM Ratio=1
Cohort 3	18	Midazolam	AUC(0-∞)	21.93%	9.29%	(0.915, 1.093)
			Cmax	23.23%	9.86%	(0.91, 1.099)
		1'-hydroxy-midazolam	AUC(0-∞)	14.06%	5.9%	(0.944, 1.059)
			Cmax	25.23%	10.7%	(0.903 1.107)
		Digoxin	AUC(0-∞)	13.84%	5.81%	(0.945, 1.058)
			Cmax	20.04%	8.48%	(0.922, 1.085)
Cohort 4	10	Gepotidacin	AUC(0-∞)	9.01%	5.3%	(0.950, 1.053)
			Cmax	20.6%	12.8%	(0.886, 1.128)

AUC(0-∞) = area under the concentration-time curve from time 0 (predose) extrapolated to infinite time; Cmax = maximum observed concentration; CI = confidence interval; CV_w% = intrasubject coefficient of variability; GM = geometric mean; PK = pharmacokinetic.

1 Precision: (Upper Limit-GM)/GM or (GM-Lower Limit)/Lower Limit.

If participants prematurely discontinue the study, additional participants may be enrolled after consultation with the Sponsor to ensure that the required number of evaluable participants complete each Cohort of the study.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

9.3. Analysis Sets

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

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who are randomized.
Safety	All participants who receive at least 1 dose of study intervention. This population will be used for all demographic and safety summaries.
PK	Participants who receive at least 1 dose of study intervention and have at least 1 non-missing plasma or urine PK concentration. This primary analysis population will be used in the assessment and characterization of PK concentrations (summary tables and figures).
PK Parameter	All participants in the PK population who received study intervention for whom valid and evaluable plasma or urine PK parameters are derived. This primary analysis population will be used in the assessment and characterization of PK parameters (summary and analysis tables and figures).

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and key secondary endpoints.

9.4.1. Pharmacokinetic and Biomarker Analyses

Plasma and urine gepotidacin, 1-NMN, creatinine, and digoxin; and plasma cimetidine, midazolam, and 1'-hydroxymidazolam concentration-time data will be analyzed by PPD, under the oversight of the Department of Bioanalysis, Immunogenicity and Biomarkers within GSK. Pharmacokinetic and biomarker analysis will be performed by PPD using noncompartmental methods with Phoenix WinNonlin Version 8.0 or higher and SAS Version 9.4 or higher under the oversight of Clinical Pharmacology Modeling & Simulation within GSK. Statistical analysis will be performed by PPD, under the oversight of Biostatistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

The underlying distributional assumptions involved in the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the assumptions are violated, then alternative statistical methods will be considered. Within- and between-subject coefficient of variation (CV) will also be displayed for all analyses.

Endpoint	Statistical Analysis Methods
Primary	The primary endpoints of this study are PK related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. **Cohort 1** Analysis will be performed to compare the PK exposure of gepotidacin with and without cimetidine. Analysis will be performed on the natural logarithms of plasma gepotidacin AUC(0-t), AUC(0-∞), Cmax and t1/2 using a linear mixed-effect model with treatment as a fixed effect and participant as a random effect. Effects will be estimated, and 90% CIs will be constructed for the following treatment comparison: • Gepotidacin + cimetidine versus gepotidacin alone Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean (GM) ratios and CIs on the original scale. Within and between-subject CV will be calculated as well. **Cohort 2** Analysis will be performed to compare the PK exposure of gepotidacin with and without rifampicin as described above for the Cohort 1. Analysis will be performed on plasma gepotidacin AUCs and Cmax for the following treatment comparison: • Gepotidacin + rifampicin versus gepotidacin alone

Endpoint	Statistical Analysis Methods
	Cohort 3 Analysis will be performed to compare the PK exposure of digoxin, and midazolam with and without gepotidacin. Analyses will be performed on the natural logarithms of plasma digoxin and midazolam AUC(0-t), AUC(0-∞), and Cmax using linear mixed-effect models with treatment and period, as fixed effects and participant as a random effect. Effects will be estimated, and CIs will be constructed for the following treatment comparison: • Gepotidacin + digoxin and midazolam versus digoxin and midazolam alone Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for GM ratios and CIs on the original scale. Within and between-subject CV will be calculated as well. **Cohort 4** The effect of food on the PK exposure of gepotidacin in Japanese participants will be similarly analyzed as described above for Cohort 3. Analysis will be performed on plasma gepotidacin AUC(0-24), AUC(0-48), AUC(0-t), AUC(0-∞), and Cmax for the following treatment comparison: • Gepotidacin under fed conditions versus gepotidacin under fasted conditions **All Cohorts** Summary statistics (arithmetic mean, GM, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) for plasma gepotidacin, and plasma digoxin and midazolam PK parameters, will be summarized by treatment for each Cohort, as applicable. Time variables, including Tmax, and Tlag, may be analysed. Nonparametric analysis using the Wilcoxon signed-rank test will be used to compute the point estimate. 90% CIs for the median difference for each comparison of interest will also be computed.
Secondary	The analysis for the secondary PK endpoints will be performed for the PK Parameter Population. **Cohorts 1, 2, 3 and 4** DDI endpoints will be analyzed using the same statistical model as described for primary endpoints. Summary statistics (arithmetic mean, GM, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) for plasma and urine gepotidacin PK parameters, will be summarized by treatment. Time variables, including Tmax, Tlag, and t1/2, may be analyzed as described above for the primary endpoints.
Exploratory	The analysis for the exploratory biomarker endpoints will be performed for the PK Parameter Population. The analysis for the exploratory biomarker endpoints will be performed for the PK or PK Parameter Population, as appropriate. **Cohort 1** Summary statistics (arithmetic mean, GM, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) for plasma and urine 1-NMN parameters will be summarized by treatment. Summary statistics (arithmetic mean, median, standard deviation, minimum, maximum, and CV) for plasma cimetidine concentrations and serum and urine creatinine concentrations will be summarized by treatment.

Endpoint	Statistical Analysis Methods
	Cohort 3 Analysis will be performed to compare the PK exposure of 1'-hydroxymidazolam with and without gepotidacin as described above for midazolam under the primary statistical analysis method for Cohort 3. Analysis will be performed on plasma 1'-hydroxymidazolam AUC(0-t), AUC(0-∞), and Cmax for the following treatment comparison: • Gepotidacin + digoxin and midazolam versus digoxin and midazolam alone Summary statistics (arithmetic mean, GM, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) for plasma 1'-hydroxymidazolam PK parameters, will be summarized by treatment. **Cohort 4** Summary statistics (arithmetic mean, GM, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) will be used to compare the plasma and urine gepotidacin PK parameters for Japanese and non-Japanese subjects for the following: Single dose: • Japanese subject data (Cohort 4, fed only) versus non-Japanese subject data (Cohorts 1 and 2, gepotidacin alone only) Multi-dose: • Japanese subject data (Cohort 4, fed only) versus non-Japanese subject data (Cohort 3)

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library standards. No formal statistical analysis of the safety data will be conducted.

The details of the statistical analyses of safety and PK data will be provided in the reporting and analysis plan.

9.4.3. Other Analysis

Not applicable.

9.5. Interim Analysis

No formal interim analysis is planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

1-NMN	N1-methylnicotinamide
ABSSSI	acute bacterial skin and skin structure infection
AChE	acetylcholinesterase
AE	adverse event
Ae total	total unchanged drug
Ae(t1-t2)	amount of drug excreted in urine in a time interval
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-∞)	area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
AUC(0-24)	area under the concentration-time curve from time 0 (predose) to 24 hours post dose administration following the first dose
AUC(0-48)	area under the concentration-time curve from time 0 (predose) to 48 hours post dose administration following the first dose
AUC(0-t)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC(0-τ)	area under the concentration-time curve from time 0 (predose) to time tau
BCRP	breast cancer resistance protein
bpm	beats per minute
CA	Competent Authorities
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent oral clearance
CI	confidence interval
CLr	renal clearance of drug
Cmax	maximum observed concentration
Cmin	trough concentration
CV	coefficient of variation
CV_w%	intrasubject coefficient of variability
CYP	cytochrome P450
DDI	drug-drug interaction
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
ESRD	end-stage renal disease
fe%	percentage of the given dose of drug excreted in urine
FSH	follicle-stimulating hormone

GCP	Good Clinical Practice
GI	gastrointestinal
GM	geometric mean
GSK	GlaxoSmithKline
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
MATE	multidrug and toxin extrusion
mm Hg	millimeters of mercury
msec	millisecond
NIAID	National Institute of Allergy and Infectious Disease
OCT	organic cationic transporter
P-gp	P-glycoprotein
PBPK	Physiologically-based pharmacokinetics
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QID	four times daily
QTc	corrected QT interval; the measure of time between the start of the Q wave and the end of the T wave
QTcB	corrected QT interval using the Bazett formula
QTcF	corrected QT interval using the Fridericia formula
QTL	quality tolerance limit
RoAUC	accumulation ratio for AUC
RoCmax	accumulation ratio for Cmax
SAE	serious adverse event
SoA	schedule of activities
SD	single dose
SRM	Study Reference Manual
t1/2	terminal phase half-life
tlag	lag time before observation of drug concentrations
Tmax	time to reach maximum observed plasma concentration
ULN	upper limit of normal
uUTI	uncomplicated urinary tract infection
Vz/F	apparent volume of distribution
WOCPB	Wome(a)n of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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NONE

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing should be conducted at the time points indicated in the SoA (Section 1.3).
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 16 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters		
Hematology	Platelet Count Red Blood Cell Count Hemoglobin Hematocrit	Red Blood Cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	Blood urea nitrogen Creatinine Glucose (fasting) Potassium Sodium Magnesium	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Total and direct bilirubin Creatine phosphokinase Calcium	Chloride Carbon dioxide Total protein Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood, leukocyte esterase, or protein is abnormal)		

Laboratory Assessments	**Parameters**
Other Screening Tests	• Serology: HIV-1 and -2 antigen/antibody immunoassay, hepatitis B surface antigen, hepatitis C antibody) • Alcohol, cotinine, and drug screen (to include at minimum amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Pregnancy • Follicle-stimulating hormone • Fecal occult blood test and stool cultures as appropriate for gastrointestinal (GI) adverse events (8).

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6. All events of ALT ≥3 ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × 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).

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. 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 for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an 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 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/EC
    - Notifying the IRB/IEC of SAE 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, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.3.2. 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.

10.3.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.

- 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 that meets the requirements of 21 Code of Federal Regulations Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written 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) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative
- Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about gepotidacin or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have gepotidacin approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box. There are samples in storage that GSK may retrieve for analysis at a later date if unexpected results are observed.

10.3.4. 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.
- 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. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.3.5. Committees Structure

Not applicable.

10.3.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding.

10.3.7. Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF 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.
- Guidance on completion of eCRFs will be provided in the eCRF guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

- 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.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, 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.

10.3.8. 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 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 and its origin can be found in the SRM.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification 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.

10.3.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or 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.

10.3.10. 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 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.

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

10.4.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • 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 intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, 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 intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected DDI interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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.

10.4.2. Definition of SAE

An SAE is defined as any serious adverse event 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 admitted (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 AEs. 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.

d. Results in persistent or significant 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:

- Possible Hy's Law case: ALT ≥3 × ULN AND total bilirubin ≥2 × ULN (>35% direct bilirubin) or INR >1.5 must be reported as an SAE.
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as

significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.4.3. Cardiovascular and Gastrointestinal Events of Special Interest

Investigators will be required to fill out the specific cardiovascular or GI event page of the eCRF for the following AEs and SAEs:

Cardiovascular Events:	**Gastrointestinal 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	• Nausea • Vomiting • Dysphagia • Abdominal pain • Diarrhea • Flatulence • Feces soft • Constipation

10.4.4. Recording and Follow-Up of AE and SAE

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.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- 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 investigator will make an assessment of intensity for each AE and SAE reported during the study according to the US National Institute of Allergy and Infectious Disease (NIAID) Division of Microbiology and Infectious Diseases (DMID) criteria for adult toxicity assessment (Appendix 9).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention 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 intervention administration will be considered and investigated.
- The investigator will also consult the IB 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. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- 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 post-mortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.4.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given 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 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 site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical Monitor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- 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 hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women of Non-childbearing Potential

Women in the following categories are considered women of non-childbearing potential:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS) [b]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) • Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's

review of the participant's medical records, medical examination, or medical history interview.)
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationc • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulationc • oral • injectable
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 intervention. 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.*
• **Effective Methods[d] That Are Not Considered Highly Effective** *Failure rate of ≥1% per year when used consistently and correctly.*
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
Male or female condom with or without spermicidee
Cervical cap, diaphragm, or sponge with spermicide
A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)c
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. e. Male condom and female condom should not be used together (due to risk of failure from friction).

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

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

Phase 1 Liver Chemistry Stopping Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3 × ULN
If ALT ≥3 × ULN AND total bilirubin ≥2 × ULN (>35% direct bilirubin) or INR >1.5, report to GSK as an SAE.[1,2]</td></tr>
<tr><th colspan="3">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column.
• Do not restart or rechallenge participant with study intervention
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING)

MONITORING:
If ALT≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferase values show downward trend
• Obtain blood sample for PK analysis within 24 hours after the most recent dose[4]
• Obtain serum creatine phosphokinase, lactate dehydrogenase, gamma-glutamyl transferase, glutamate dehydrogenase, and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥2 × 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 liver event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over the counter medications.</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT ≥3 × ULN AND total bilirubin <2 × ULN and INR ≤1.5: • Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	• **If ALT ≥3 x ULN AND total bilirubin ≥2 × ULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins. • Serum acetaminophen adduct assay should be done (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g. where the participant has been resident in the clinical • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialists if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable**, record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, which may indicate severe liver injury (possible "Hy's Law"), must be reported **to GSK** as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A immunoglobulin (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody.
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw. 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 SRM.

10.7. Appendix 7: Covid-19

10.7.1. Overall Rationale for this Appendix

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, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any 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 will remain in place until study completion.

10.7.2. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you 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 trial participants.

As outlined in Section 8, Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants:

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and 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 participant notes and recorded as a COVID-19 protocol deviation.

10.7.3. Protocol Defined Procedures/Visits:

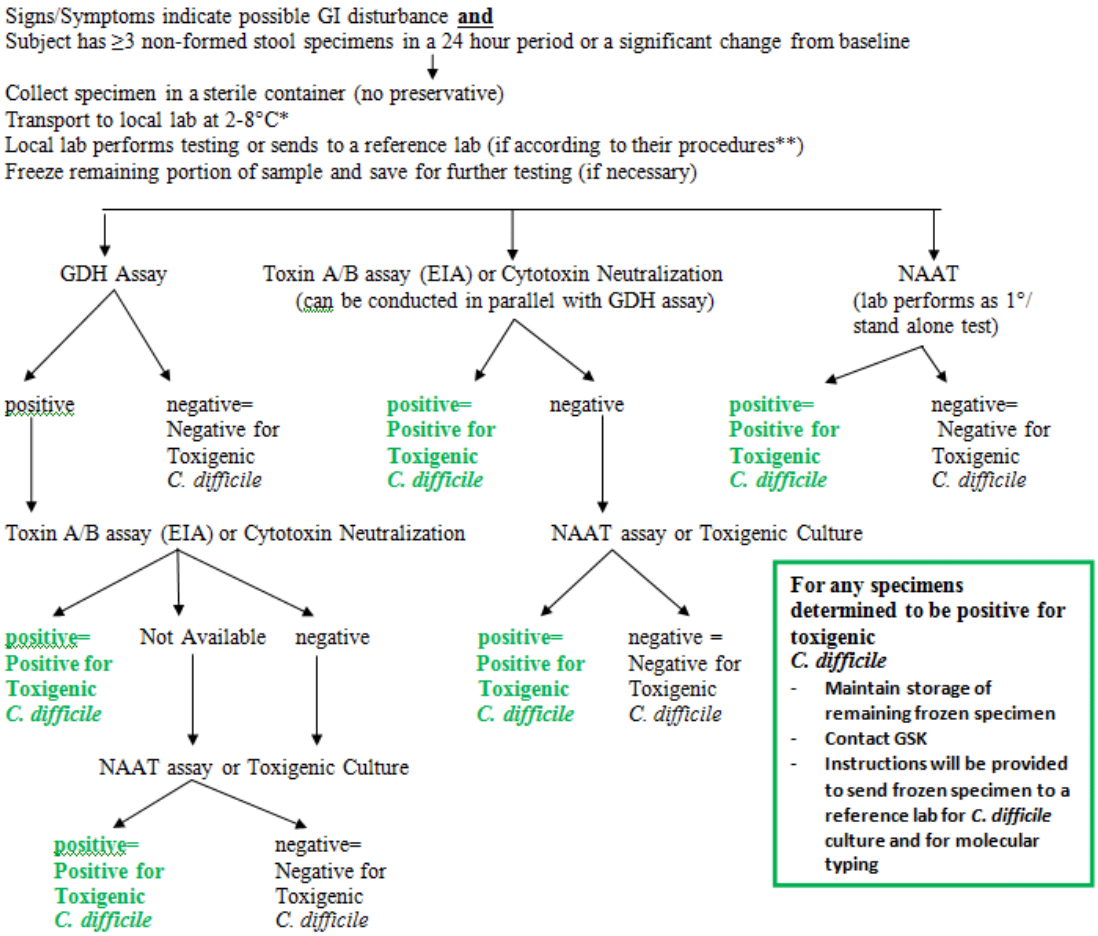
- The protocol defined interval for the collection of samples during the Follow-up visit (see Section 1.3 Schedule of Activities), may be extended up to a maximum length of 14 days.

10.7.4. Data Management/Monitoring:

- If a situation arises where on-site monitoring is no longer permitted, GSK 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 will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) 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 PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.

Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.8. Appendix 8: *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

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.

10.9. Appendix 9: 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 (DMID) and modified to better meet the needs of participants in 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.

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/mL	>60 mcg/mL
Prothrombin Time (PT)	1.01 to 1.25 × ULN	1.26 to 1.5 × ULN	1.51 to 3.0 × ULN	>3 × ULN
Activated Partial Thromboplastin (APTT)	1.01 to 1.66 × ULN	1.67 to 2.33 × ULN	2.34 to 3 × ULN	>3 × 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 or 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

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 × ULN	1.25 to <1.5 × ULN	1.5 to 1.75 × ULN	>1.75 × ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 to <1.5 × ULN	1.5 to <2.0 × ULN	2.0 to 3.0 × ULN	>3.0 × ULN
Blood urea nitrogen	1.25 to 2.5 × ULN	2.6 to 5 × ULN	5.1 to 10 × ULN	>10 × 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 × ULN	1.6 to 3.0 × ULN	3.1 to 6.0 × ULN	>6 × 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 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alanine aminotransferase (ALT)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Gamma to glutamyl transferase (GGT)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alkaline Phosphatase	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Amylase	1.1 to 1.5 × ULN	1.6 to 2.0 × ULN	2.1 to 5.0 × ULN	>5.1 × ULN
Lipase	1.1 to 1.5 × ULN	1.6 to 2.0 × ULN	2.1 to 5.0 × ULN	>5.1 × 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 mm Hg systolic BP. No treatment required	Symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	Requires IV fluids; no hospitalization required	Mean arterial pressure <60 mm Hg 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; mm Hg = millimeters of mercury; 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 change in taste, smell, vision, and/or hearing	Moderate impairment (moderately decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	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
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 pain; 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

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