Reporting and Analysis Plan

Study ID: 213678

Official Title of Study: Reporting and Analysis Plan for A Pharmacokinetic, multicohort 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

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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for 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
Compound Number	:	GSK2140944
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Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol GSK213678.
- This RAP is intended to describe the safety, tolerability, and pharmacokinetic (PK) analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) and Interim Analysis (IA) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the CSR for Protocol GSK213678

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The protocol states both within- and between-subject coefficient of variation (CV) will be calculated during statistical analysis of the PK data using linear mixed-effect models. It was subsequently determined that only within-subject CV is necessary.

2.2. Study Objective(s) and Endpoint(s)

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 3000mg 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	• 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

Objectives	Endpoints
adult participants	the second dose; AUC(0-24), AUC(0-48), and AUC(0-t) of gepotidacin using the full profileb(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
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	• Ae total, AUC(0-24), AUC(0-48), and CLr of gepotidacin in urine following a single 1500 mg dose, as data permit

Objectives	Endpoints
population • To characterize the urine PK of a single 1500 mg oral dose of gepotidacin given with food in an adult healthy population • To evaluate the safety and tolerability of gepotidacin in adult healthy participants	• Ae(t1-t2) and fe% of gepotidacin in urine following a single 1500 mg dose, as data permit • 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
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	• 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

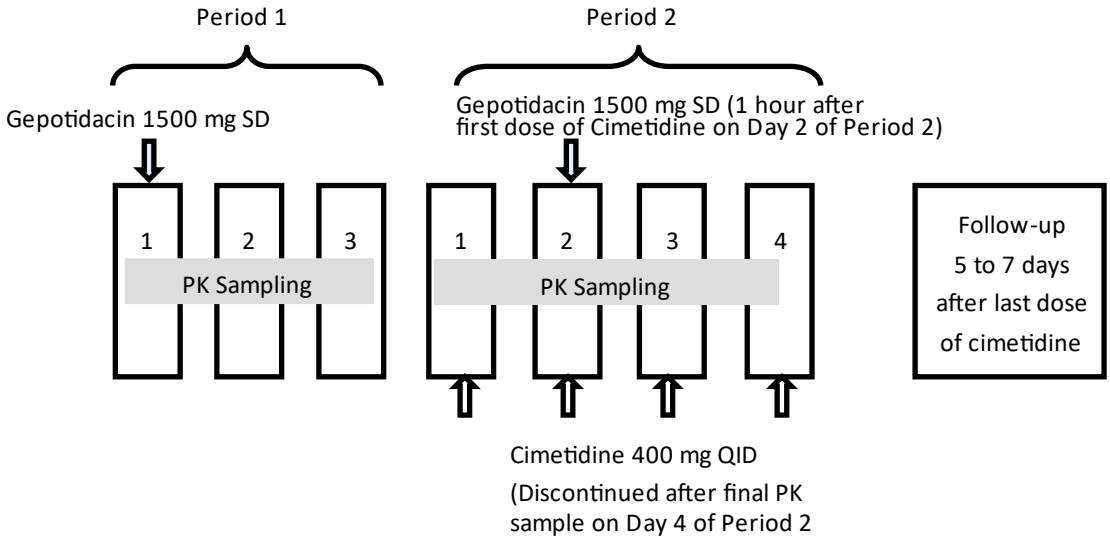
Objectives	Endpoints
participants	3000 mg doses, as data permit
• To assess the urine PK of a single 1500 mg dose or two 3000 mg doses of gepotidacin given 12 hours apart with food in Japanese adult healthy participants	• Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin 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	• 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
• To evaluate concentrations of serum and urine creatinine after administration of gepotidacin with and without cimetidine in adult healthy participants	• Serum and urine creatinine concentrations, as data permit • 1-NMN plasma and urine PK parameters normalized to creatinine, as data permit
• To evaluate cimetidine PK to assess transporter inhibition in adult healthy participants	• Cimetidine plasma PK concentrations, as data permit
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 coadministered 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	• Plasma and urine concentrations and parameters for gepotidacin, as data permit

Objectives	Endpoints
DDI Cohorts in adult (non-Japanese) healthy participants • 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

2.3. Study Design

Overview of Study Design and Key Features

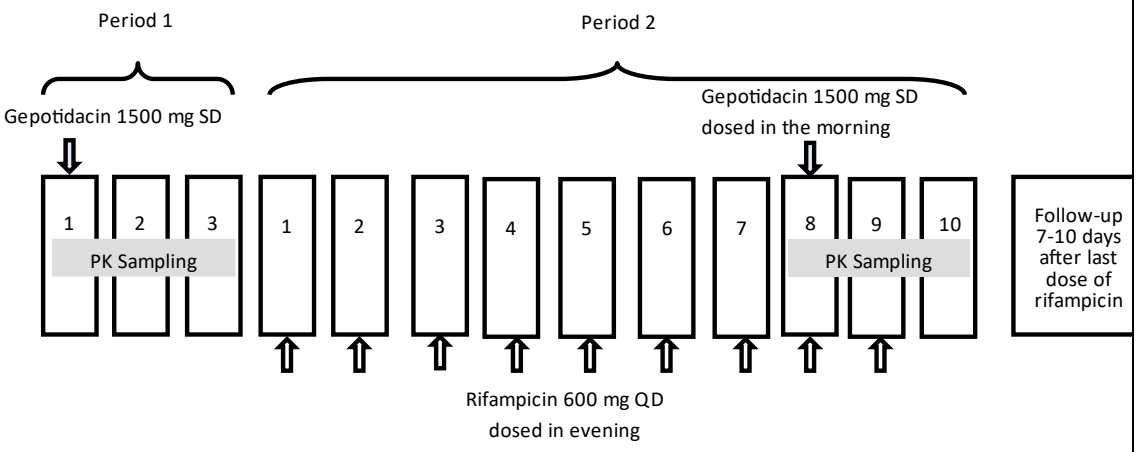
Cohort 1 (Gepotidacin and Cimetidine) Study Design Schematic



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.

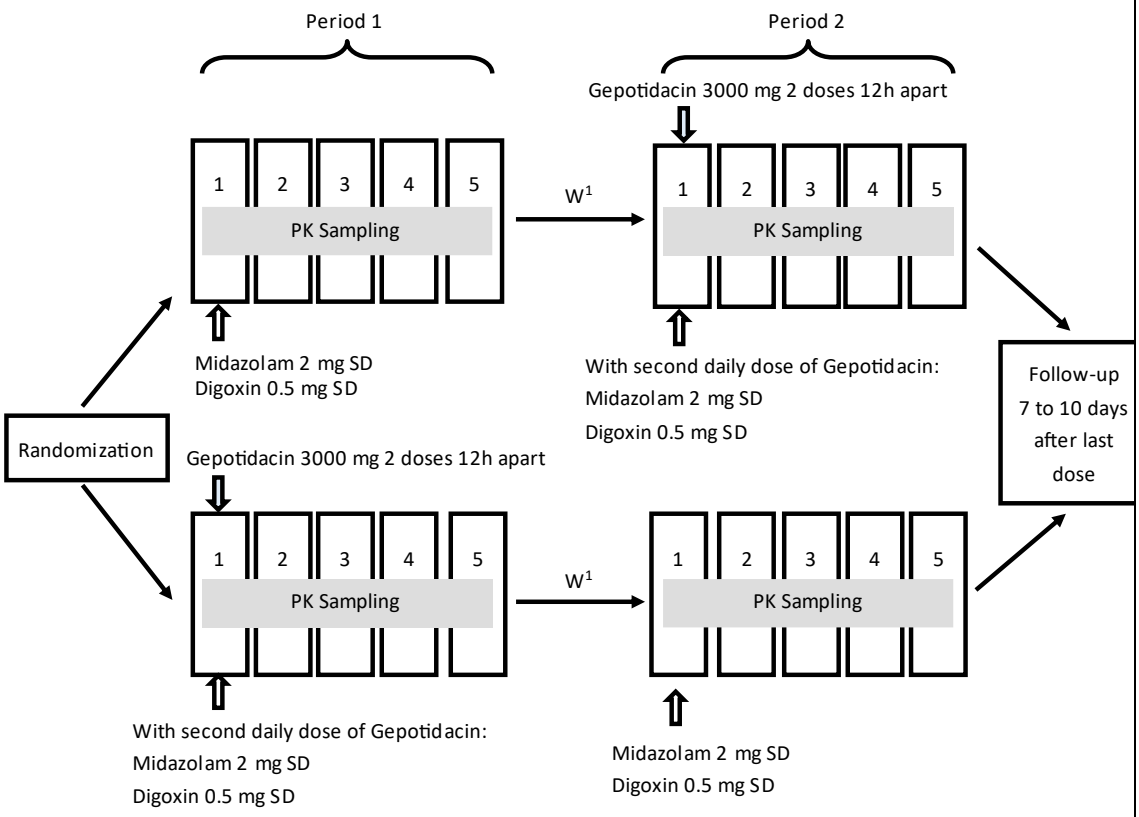
Cohort 2 (Gepotidacin and Rifampicin) Study Design Schematic



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.

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

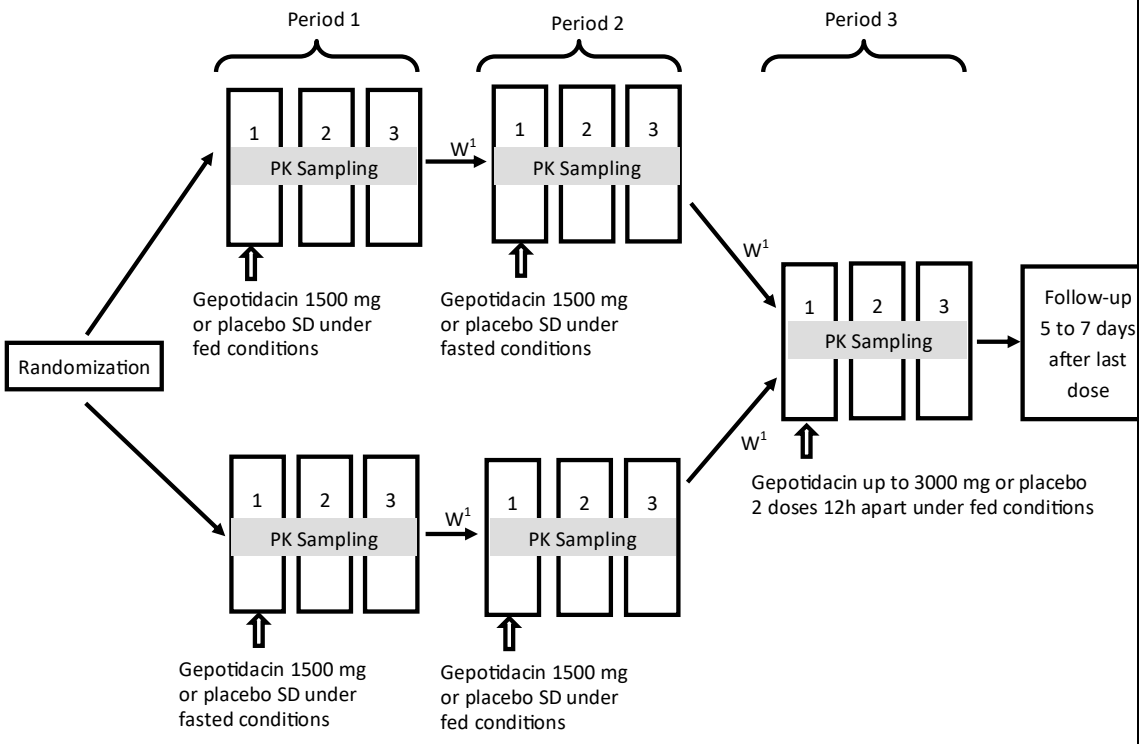


h = hour; PK = pharmacokinetic; SD = single dose; W = washout.

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

Overview of Study Design and Key Features

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.

Design Features	• Phase I, DDI, PK, safety, and tolerability, 4-cohort study in adult healthy participants. • **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. • **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 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. • **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. **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. a participant who is randomized to gepotidacin receives gepotidacin in all periods and a participant randomized to placebo receives placebo in all periods. 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

Overview of Study Design and Key Features	
	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.

Dosing	**Cohort 1:** • Treatment A: Gepotidacin 1500 mg 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 1 hour after the first dose of cimetidine on Day 2 of Period 2.. **Cohort 2:** • 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. **Cohort 3:** • 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. **Cohort 4:** • 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.
Time and Events	• See Appendix 1: Schedule of Activities (SoA)
Treatment Assignment	• **Cohort 1**: Participants will receive the treatments in a fixed sequence (Sequence AB) • **Cohort 2:** Participants will receive the treatments in a fixed sequence (Sequence CDE)

	• **Cohort 3**: Participants will be randomly assigned to receive 1 of 2 treatment sequences in a 1:1 ratio (Sequence FG or Sequence GF) • **Cohort 4**: Participants will be randomly assigned (11 active:3 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
Interim Analysis	No formal interim analysis is planned for this study.

2.4. Statistical Analyses

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

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analysis is planned for this study.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met (for Cohort 4).
4. Randomization codes have been distributed as per PPD procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who sign the informed consent form (ICF).	• Study Population
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Randomized	• All participants who are randomized. (Cohorts 3 and 4)	• Study Population
Safety	• All participants who take at least 1 dose of study intervention.	• Study Population • Safety
PK	• Participants who receive at least 1 dose of study intervention and have at least 1 non-missing plasma or urine PK concentration.	• PK and Biomarker Concentration
PK Parameter	• All participants in the PK population who received study intervention for whom valid and evaluable plasma or urine PK parameters are derived.	• PK and Biomarker parameter • PK and Biomarker statistical analysis

NOTES:

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

Important (significant) protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorized on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Baseline Definitions

Both study baseline and period baseline will be used for this study.

For 12-lead ECG and vital signs, period baseline will be used. The baseline for 12-lead ECG will be the mean of pre-dose assessments for each period. The baseline for vitals will be the pre-dose assessment for each period. If the pre-dose assessment for a period will be missing, then the baseline for the last period will be used. If Period 1 pre-dose are missing, the last available assessment prior to time of first study drug administration, including unscheduled and repeated measurements will be used. If period 1 baseline data are missing no derivation will be performed and baseline will be set to missing, unless otherwise stated.

For all other safety assessment, study baseline will be used. The baseline value will be the last available assessment prior to time of first study drug administration, including unscheduled and repeated measurements, unless noted otherwise. If study baseline data are missing no derivation will be performed and baseline will be set to missing, unless otherwise stated.

5.2. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
11.1	Appendix 1: Schedule of Activities
11.2	Appendix 2: Assessment Windows
11.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Reporting Standards for Missing Data
11.7	Appendix 7: Values of Potential Clinical Importance
11.8	Appendix 8: Adverse Event Assessment Criteria
11.9	Appendix 9: Multiple Comparisons and Multiplicity
11.10	Appendix 10: Abbreviations & Trade Marks
11.11	Appendix 11: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Screened, Enrolled, Randomized, or Safety population, unless otherwise specified.

Study population analyses including analyses of subjects enrolled by Country and Site ID, subject's disposition, screening failures, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 11: List of Data Displays.

7. PHARMACOKINETIC ANALYSES

7.1. Primary Pharmacokinetic Analyses

7.1.1. Endpoint / Variables

7.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic).

7.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin (8.0 or higher) or using the currently supported version of SAS (9.4 or higher). All calculations of non-compartmental parameters will be based on actual sampling times. Primary pharmacokinetic parameters listed below will be determined from the plasma concentration-time data for gepotidacin, digoxin, and midazolam, as appropriate and as data permit.

Parameter	Parameter Description
AUC(0-t)	Area under the plasma concentration-time curve from time 0 (predose) to the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (calculated for Cohorts 1 and 2: gepotidacin; Cohort 3: digoxin and midazolam; Cohort 4 (all periods): gepotidacin (using the full profile (both doses) in Period 3)).
AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (calculated for Cohorts 1 and 2: gepotidacin; Cohort 3: digoxin and midazolam; Cohort 4 (periods 1 and 2 only): gepotidacin).
AUC(0-24)	Area under the plasma concentration-time curve from time 0 (predose) to the concentration at 24 hours postdose to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (calculated for gepotidacin for Cohort 4 (all periods); the full profile (both doses) will be used for Period 3).
AUC(0-48)	Area under the plasma concentration-time curve from time 0 (predose) to the concentration at 48 hours postdose, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. (calculated for gepotidacin for Cohort 4 (all periods); the full profile (both doses) will be used for Period 3).
AUC(0-τ)	Area under the plasma concentration-time curve from time 0 (predose) to time tau (tau = 12 h) (calculated for gepotidacin for Cohort 4, Period 3; separate estimates for each dose).
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data (calculated for Cohorts 1 and 2: gepotidacin; Cohort 3: digoxin and midazolam; Cohort 4 (all periods): gepotidacin (separate estimates for each dose in Period 3)).
Tmax	Time to reach maximum observed plasma concentration (calculated for Cohorts 1 and 2: gepotidacin; Cohort 3: digoxin and midazolam; Cohort 4 (all periods): gepotidacin (separate estimates for each dose in Period 3)).
Tlag	Lag time before observation of drug concentration in plasma (calculated for Cohort 2: gepotidacin; Cohort 3: digoxin and midazolam; Cohort 4 (periods 1 and 2 only): gepotidacin).

Parameter	Parameter Description
t1/2	Apparent plasma terminal phase half-life (plasma) (calculated for gepotidacin in Cohort 1 only).
RoAUC	Accumulation ratio calculated as AUC(0-τ) after the second dose, where 0 is the timepoint prior to second dose, divided by AUC(0-τ) after the first dose, where 0 is the predose timepoint prior to the first dose (calculated for geptodacin in Cohort 4, Period 3 only).
RoCmax	Accumulation ratio calculated as Cmax after the second dose divided by Cmax after the first dose (calculated for geptodacin in Cohort 4, Period 3 only).

NOTES:

- Additional parameters may be included as required.

7.1.2. Summary Measure

Cohort 1

Plasma PK parameters Cmax, Tmax, t1/2, AUC(0-t), and AUC(0-∞) of gepotidacin following a single 1500 mg dose of gepotidacin alone (Period 1) and in the presence of cimetidine 400 mg QID (Period 2) in healthy adult participants will be summarized by treatment. Gepotidacin PK parameter estimates will be listed by participant and treatment.

Cohort 2

Plasma PK parameters Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of gepotidacin following a single 1500 mg dose of gepotidacin alone (Period 1) and in the presence of rifampin 600 mg QD (Period 2) in healthy adult participants will be summarized by treatment. Gepotidacin PK parameter estimates will be listed by participant and treatment.

Cohort 3

Plasma PK parameters Cmax, Tlag, Tmax, AUC(0-t), and AUC(0-∞) of digoxin and midazolam following a single dose (0.5 mg of digoxin and 2 mg of midazolam) alone and in the presence of gepotidacin (co-administered with the second dose of a two 3000 mg dose gepotidacin treatment) in healthy adult participants will be summarized by treatment. Digoxin and midazolam PK parameter estimates will be listed by participant and treatment.

Cohort 4, Periods 1 and 2

Plasma PK parameters Cmax, Tlag, Tmax, AUC(0-24), AUC(0-48), AUC(0-t), and AUC(0-∞) of gepotidacin following a single 1500 mg dose of gepotidacin under fasted or fed conditions in healthy adult Japanese participants will be summarized by treatment. Gepotidacin PK parameter estimates will be listed by participant and treatment.

Cohort 4, Period 3

The following gepotidacin PK parameters will be summarized following a two 3000 mg dose treatment in healthy adult Japanese participants: Cmax, Tmax, and AUC(0-τ)

(separately for dose 1 and dose 2); RoAUC and RoCmax (dose 2); AUC(0-24), AUC(0-48), and AUC(0-t) using the full profile (both doses). Gepotidacin PK parameter estimates will be listed by participant.

7.1.3. Population of Interest

The primary PK analyses will be based on the PK population for plasma PK concentrations and the PK parameter population for plasma PK parameters.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent events identified are:

- Treatment Discontinuation
- Not consuming 100% food (Only for Cohort 4)

The "while on treatment" strategy will be used to handle the intercurrent event "treatment discontinuation". For this strategy, responses to treatment until the occurrence of the intercurrent event will be considered. PK parameters will not be derived once the subject discontinues the treatment so change to the protocol planned statistical model is not anticipated.

The intercurrent event "not consuming 100% food" will handled by "Treatment Policy" strategy. Data will be considered regardless of whether or not the intercurrent event occurs so change to the protocol planned statistical model is not anticipated.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Primary plasma PK parameters as described in Section 7.1.1 will be estimated for gepotidacin, digoxin, and midazolam. For each of these parameters the following summary statistics will be calculated by cohort and treatment: median, maximum, minimum, arithmetic mean, standard deviation, 95% confidence interval (CI) for the arithmetic mean, geometric mean, CV on geometric mean, 95% CI for the geometric mean, and SD of logarithmically transformed data. Parameters that are not logarithmically transformed are listed in Section 11.4.3.

7.1.5.1. Statistical Methodology Specification

The following PK statistical analyses will only be performed if sufficient data are available (i.e. if participants have well defined plasma profiles).

For the linear mixed model analyses described below, the Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Endpoint / Variables

- Plasma primary PK endpoints include plasma PK parameters for gepotidacin (Cohorts 1, 2, and 4) and plasma PK parameters for digoxin and midazolam (Cohort 3), as data permit.

Model Specification

Cohort 1

- Analysis will be performed to compare the plasma 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-subject CV will be calculated as well.
- The effect of cimetidine on gepotidacin Tmax will also be assessed. Nonparametric analysis using the Wilcoxon signed-rank test will be used to compute the point estimate for the above treatment comparison. 90% CIs for the median difference will also be computed.

Cohort 2

- A linear mixed model analysis will be performed to compare the plasma PK exposure of gepotidacin with and without rifampicin as described above for the Cohort 1. Analysis will be performed on the natural logarithms of plasma gepotidacin AUC(0-t), AUC(0-∞), and Cmax for the following treatment comparison:
  Gepotidacin + rifampicin versus gepotidacin alone
- Wilcoxon signed-ranked test will be performed to compare the plasma Tmax and Tlag of gepotidacin with and without rifampicin as described above for the Cohort 1.

Cohort 3

- Analysis will be performed to compare the plasma 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-subject CV will be calculated as well.
- A Wilcoxon signed-rank test will be performed to compare the plasma Tmax and Tlag of digoxin and midazolam with and without gepotidacin as described above for the Cohorts 1 and 2.

Cohort 4

- The effect of food on the plasma PK exposure of gepotidacin in Japanese participants (Periods 1 and 2) will be similarly analyzed using a linear mixed-effect model as described above for Cohort 3.

Analysis will be performed on the natural logarithms of plasma gepotidacin AUC(0-t), AUC(0-∞), and Cmax for the following treatment comparison:
Gepotidacin under fed conditions versus gepotidacin under fasted conditions

- Wilcoxon signed-rank test will be performed to compare the plasma Tmax and Tlag of gepotidacin with and without food as described above for the Cohorts 1-3.

All Cohorts

- Summary statistics (arithmetic mean, geometric mean, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) for primary plasma gepotidacin, and primary plasma digoxin and midazolam PK parameters will be summarized by treatment for each cohort, as applicable.
- Should emesis occur the impact on PK will be assessed. If emesis causes differences on the PK exposure statistical analyses may be performed with and without data from participants that experience emesis, otherwise all data will be analyzed together, as appropriate.

Model Checking & Diagnostics

- Model assumptions will be checked before analysis.
- 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 seriously violated, then alternative data transformations will be explored. If no suitable transformation can be found, equivalent nonparametric analyses (ex. Wilcoxon signed-rank test) will be performed.

Model Results Presentation

- Statistical analysis by linear mixed-effect models and Wilcoxon signed-rank test will be presented in tabular format for the following comparisons:
  Cohort 1: Gepotidacin + cimetidine versus gepotidacin alone
  Cohort 2: Gepotidacin + rifampicin versus gepotidacin alone
  Cohort 3: Gepotidacin + digoxin and midazolam versus digoxin and midazolam alone
  Cohort 4: Gepotidacin under fed conditions versus gepotidacin under fasted conditions in Japanese participants
- For linear mixed-effect model tables, N, n, least squares GM values, GM ratios and associated 90% CIs, and within-subject CV will be presented.
- For Wilcoxon signed-rank test the N, n, median values, median difference of the median values and associated 90% CIs will be presented (median difference and 90% CI of the median difference are from the Hodges-Lehmann estimate).
- The gepotidacin geometric mean ratios and associated 90% CIs will also be presented in a forest plot for the DDI comparisons (Cohorts 1 and 2, Gepotidacin as a victim). PK data from BTZ117349 (Gepotidacin + itraconazole versus gepotidacin alone) may be incorporated. In addition, a forest plot for Gepotidacin as a perpetrator, showing midazolam (potentially also with 1-hidroxymidazolam) and digoxin geometric mean ratios and associated 90% CIs might be included.

7.2. Secondary Pharmacokinetic Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Derived Pharmacokinetic Parameters

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic)

7.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin (8.0 or higher) or using the currently supported version of SAS (9.4 or higher). All calculations of non-compartmental parameters will be based on actual sampling times. Secondary pharmacokinetic parameters listed below will be determined from the plasma or urine concentration-time data for gepotidacin and the plasma concentration-time data for digoxin and midazolam, as appropriate and as data permit.

Parameter	Parameter Description
Ae total	Total amount excreted in urine (total amount of drug excreted in urine; concentration x volume), calculated by adding all the fractions of drug collected over all the allotted time intervals (calculated for gepotidacin for Cohort 1-4).
Ae(t1-t2)	Amount excreted in urine in a time interval (concentration x volume; calculated for gepotidacin for Cohort 1-4).
AUC(0-t)	Area under the plasma concentration-time curve from time 0 (predose) to the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (calculated for gepotidacin for Cohort 3 using the full profile (both doses)).
AUC(0-24)	Area under the plasma or urine concentration-time curve from time 0 (predose) to the concentration at 24 hours, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (calculated for gepotidacin for Cohorts 1-3 (plasma and urine) and Cohort 4 (urine only) (using the full profile when 2 doses are administered)).
AUC(0-48)	Area under the plasma or urine concentration-time curve from time 0 (predose) to the concentration at 48 hours postdose, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (calculated for gepotidacin for Cohorts 1-3 (plasma and urine) and Cohort 4 (urine only) (using the full profile when 2 doses are administered)).
AUC(0-τ)	Area under the plasma or urine concentration-time curve from time 0 (predose) to time tau (tau = 12 h) (calculated for gepotidacin for Cohort 3 (plasma and urine) and Cohort 4, Period 3 (urine); separate estimates for each dose for plasma).
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data (calculated for gepotidacin for Cohort 3; separate estimates for each dose).
Cmin	Minimum observed plasma concentration, determined directly from the concentration-time data (calculated for digoxin and midazolam for Cohort 3).
Tmax	Time to reach maximum observed plasma concentration (calculated for gepotidacin for Cohort 3; separate estimates for each dose).
Tlag	Lag time before observation of drug concentrations in plasma (calculated for gepotidacin for Cohort 1, Cohorts 3 (first dose only), and 4 (first dose only)).

Parameter	Parameter Description
Vz/F	Apparent plasma volume of distribution (calculated for Cohorts 1 and 2: gepotidacin; Cohort 3: digoxin, midazolam, and gepotidacin; Cohort 4 (all periods): gepotidacin; calculated using the full profile when 2 doses are given).
CL/F	Apparent plasma oral clearance (calculated for Cohorts 1 and 2: gepotidacin; Cohort 3: digoxin, midazolam, and gepotidacin; Cohort 4 (all periods): gepotidacin; calculated using the full profile when 2 doses are given).
t1/2	Apparent plasma terminal phase half-life (calculated for Cohort 2: gepotidacin; Cohort 3: digoxin, midazolam, and gepotidacin; Cohort 4 (all periods): gepotidacin; calculated using the full profile when 2 doses are given).
RoAUC	Accumulation ratio calculated as AUC(0-τ) after the second dose, where 0 is the timepoint prior to second dose, divided by AUC(0-τ) after the first dose, where 0 is the predose timepoint prior to the first dose (calculated for gepotidacin for Cohort 3).
RoCmax	Accumulation ratio calculated as Cmax after the second dose divided by Cmax after the first dose (calculated for gepotidacin for Cohort 3).
fe%	Percentage of the given dose of drug excreted in urine, calculated as: fe% = (Ae total/Dose) × 100% (calculated for gepotidacin for Cohorts 1-4).
CLr	Renal clearance (of drug), calculated as: Ae total/AUC(0-t) (calculated for gepotidacin for Cohorts 1-4).

NOTES:

- Additional parameters may be included as required.

7.2.2. Summary Measure

Cohort 1

Plasma PK parameters AUC(0-24), AUC(0-48), Tlag, Vz/F, and CL/F and urine PK parameters Ae total, Ae(t1-t2), fe%, AUC(0-24), AUC(0-48), and CLr of gepotidacin following a single 1500 mg dose of gepotidacin alone (Period 1) and in the presence of cimeditine 400 mg QID (Period 2) in healthy adult participants will be summarized by treatment. Gepotidacin PK parameter estimates will be listed by participant and treatment.

Cohort 2

Plasma PK parameters AUC(0-24), AUC(0-48), t1/2, Vz/F, and CL/F and urine pharmacokinetic parameters Ae total, Ae(t1-t2), fe%, AUC(0-24), AUC(0-48), and CLr of gepotidacin following a single 1500 mg dose of gepotidacin alone (Period 1) and in the presence of rifampin 600 mg QD (Period 2) in healthy adult participants will be summarized by treatment. Gepotidacin PK parameter estimates will be listed by participant and treatment.

Cohort 3

Plasma PK parameters Cmin, t1/2, Vz/F, and CL/F of digoxin and midazolam following a single dose (0.5 mg and 2 mg, respectively) alone and in the presence of gepotidacin (co-administered with the second dose of a two 3000 mg dose gepotidacin treatment) in healthy adult participants will be summarized by treatment. Digoxin and midazolam PK parameter estimates will be listed by participant and treatment.

The following gepotidacin plasma PK parameters will be summarized following two 3000 mg doses of gepotidacin in healthy adult participants in the presence of digoxin and midazolam following a single dose (0.5 mg and 2 mg, respectively): Tlag (dose 1 only); Cmax, Tmax, and AUC(0-τ) (separately for dose 1 and dose 2); RoAUC and RoCmax (dose 2); AUC(0-24), AUC(0-48), AUC(0- t), Vz/F, CL/F, and t1/2 using the full profile (both doses). Gepotidacin urine pharmacokinetic parameters Ae total, Ae(t1-t2), fe%, AUC(0-24), AUC(0-48), and CLr will be calculated using the full profile and summarized. Gepotidacin urine AUC(0-τ) will be calculated for the first dose and summarized. Gepotidacin PK parameter estimates will be listed by participant.

Cohort 4, Periods 1 and 2

Plasma pharmacokinetic parameters t1/2, Vz/F, and CL/F and urine pharmacokinetic parameters Ae total, Ae(t1-t2), fe%, AUC(0-24), AUC(0-48), and CLr of gepotidacin following a single 1500 mg dose of gepotidacin under fasted or fed conditions in healthy adult Japanese participants will be summarized by treatment. Gepotidacin PK parameter estimates will be listed by participant and treatment.

Cohort 4, Period 3

The following plasma gepotidacin PK parameters will be summarized following a two 3000 mg dose gepotidacin treatment in healthy adult Japanese participants: Tlag (dose 1 only); t1/2, Vz/F, and CL/F using the full profile (both doses). Gepotidacin urine pharmacokinetic parameters Ae total, Ae(t1-t2), fe%, AUC(0-24), AUC(0-48), and CLr will be calculated using the full profile and summarized. Gepotidacin urine AUC(0-τ) will be calculated for the first dose and summarized. Gepotidacin PK parameter estimates will be listed by participant

7.2.3. Population of Interest

The secondary PK analyses will be based on the PK population for plasma and urine PK concentrations and the PK parameter population for plasma PK parameters.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

For intercurrent events, see Section 7.1.4.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Secondary plasma and urine PK parameters as described in Section 7.2.1 will be estimated for gepotidacin, digoxin, and midazolam. For each of these parameters the following summary statistics will be calculated by cohort and treatment: median, maximum, minimum, arithmetic mean, standard deviation, 95% confidence interval (CI) for the arithmetic mean, geometric mean, CV on geometric mean, 95% CI for the geometric mean, and standard deviation of logarithmically transformed data. Parameters that are not logarithmically transformed are listed in Section 11.4.3.

7.2.5.1. Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data are available (i.e. if participants have well defined plasma profiles).

For the linear mixed model analyses described below, the Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Endpoint / Variables
• Plasma and urine secondary PK endpoints include plasma and urine PK parameters for gepotidacin (Cohorts 1, 2, 3, and 4) and plasma PK parameters for digoxin and midazolam (Cohort 3), as data permit.
Model Specification
Cohort 1 • Analysis will be performed to compare the urine PK exposure of gepotidacin with and without cimetidine. Analysis will be performed on the natural logarithms of urine gepotidacin Ae total, AUC(0-24), AUC(0-48), and CLr 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-subject CV will be calculated as well. **Cohort 2** • A linear mixed-effect model will be performed to compare the urine PK exposure of gepotidacin with and without rifampicin as described above for the Cohort 1. Analysis will be performed on the natural logarithms of urine gepotidacin Ae total, AUC(0-24), AUC(0-48), and CLr for the following treatment comparison: Gepotidacin + rifampicin versus gepotidacin alone **Cohort 3** • Analysis will be performed to compare the plasma PK exposure of digoxin and midazolam with and without gepotidacin. Analyses will be performed on the natural logarithms of plasma digoxin and midazolam Cmin, t1/2, Vz/F, and CL/F 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-subject CV will be calculated as well.

No Specific secondary analyses for Cohort 4 **All Cohorts** • Summary statistics (arithmetic mean, geometric mean, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) for secondary plasma and urine gepotidacin, and secondary plasma digoxin and midazolam PK parameters will be summarized by treatment for each cohort, as applicable.
Model Checking & Diagnostics
• Model assumptions will be checked before analysis. • 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 seriously violated, then alternative data transformations will be explored. If no suitable transformation can be found, equivalent nonparametric analyses (ex. Wilcoxon signed-rank test) will be performed.
Model Results Presentation
• Linear mixed-effect model results will be presented in tabular format for the following comparisons: Cohort 1: Gepotidacin + cimetidine versus gepotidacin alone Cohort 2: Gepotidacin + rifampicin versus gepotidacin alone Cohort 3: Gepotidacin + digoxin and midazolam versus digoxin and midazolam alone • The N, n, least squares GM values, GM ratios and associated 90% CIs, and within-subject CV will be presented.

7.3. Exploratory Pharmacokinetic Analyses

7.3.1. Endpoint / Variables

7.3.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic)

7.3.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin (8.0 or higher) or using the currently supported version of SAS (9.4 or higher). All calculations of non-compartmental parameters will be based on actual sampling times. Exploratory plasma pharmacokinetic parameters listed below will be determined from the plasma concentration-time data for 1'-hydroxymidazolam for Cohort 3, as data permit. Exploratory urine pharmacokinetic parameters listed below will be determined from the urine concentration-time data for digoxin for Cohort 3, as data permit. Only Cohort 3 contains exploratory PK parameters.

Parameter	Parameter Description
Ae total	Total amount excreted in urine (total amount of drug excreted in urine; concentration x volume), calculated by adding all the fractions of drug collected over all the allotted time intervals.
AUC(0-t)	Area under the plasma concentration-time curve from time 0 (predose) to the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the plasma concentration-time curve from time 0 (predose) extrapolated to infinite time, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data.
Cmin	Minimum observed plasma concentration, determined directly from the concentration-time data.
Tmax	Time to reach maximum observed plasma concentration
t1/2	Apparent plasma terminal phase half-life
AUC m/p[1]	Metabolite-to-parent ratio based on AUC(0-∞) with correction for molecular weight. If data for AUC(0-∞) are insufficient then AUC(0-t) may be used.
fe%	Percentage of the given dose of drug excreted in urine, calculated as: fe% = (Ae total/Dose) × 100%.
CLr	Renal clearance (of drug), calculated as: Ae total/AUC(0-t).

[1]Molecular weights by analyte: midazolam: 325.78, 1-hydroxymidazolam: 341.77.

NOTES:

- Additional parameters may be included as required.

7.3.2. Summary Measure

Cohort 3

Plasma pharmacokinetic parameters Cmin, Cmax, Tmax, t1/2, AUC(0-t), AUC(0-∞) and AUC m/p for 1'-hydroxymidazolam and urine pharmacokinetic parameters Ae total, fe% and CLr for digoxin following a single dose (0.5 mg of digoxin and 2 mg of midazolam) alone and in the presence of gepotidacin (co-administered with the second dose of a two 3000 mg dose gepotidacin treatment) in healthy adult participants will be summarized by treatment. PK parameter estimates will be listed by participant and treatment.

7.3.3. Population of Interest

The exploratory PK analyses will be based on the PK population for plasma and urine PK concentrations and the PK parameter population for plasma and urine PK parameters.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

For intercurrent events, see Section 7.1.4.

7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Exploratory plasma and urine PK parameters as described in Section 7.3.1 will be estimated for 1'-hydroxylmidazolam and digoxin. For each of these parameters the following summary statistics will be calculated by cohort and treatment: median, maximum, minimum, arithmetic mean, standard deviation, 95% confidence interval (CI) for the arithmetic mean, geometric mean, CV on geometric mean, 95% CI for the geometric mean, and standard deviation of logarithmically transformed data. Parameters that are not logarithmically transformed are listed in Section 11.4.3.

7.3.5.1. Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data are available (i.e. if participants have well defined plasma profiles).

For the linear mixed model analyses described below, the Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Endpoint / Variables
• Plasma exploratory PK endpoints include plasma PK parameters for 1'-hydroxymidazolam (Cohort 3) and urine PK parameters for digoxin (Cohort 3), as data permit.
Model Specification
Cohort 3 • Upon review of the PK data, analysis may be performed to compare the plasma PK exposure of 1'-hydroxymidazolam and urine PK exposure of digoxin with and without gepotidacin. Analyses will be performed on the natural logarithms of plasma 1'-hydroxymidazolam AUC(0-t), AUC(0-∞), Cmax, and AUC m/p and urine digoxin Ae total and CLr 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-subject CV will be calculated as well. • 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 and urine digoxin 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 Western (non-Japanese) participants (all-comers and Caucasians only) for the following:

Single dose:
- Japanese participant data (Cohort 4, fed only) versus Western (non-Japanese) participant (all-comers and Caucasians only) data (Cohorts 1 and 2, Period 1 only)

Multi-dose:
- Japanese participant data (Cohort 4, Period 3 only) versus Western (non-Japanese) participant (all-comers and Caucasians only) data (Cohort 3).

- Should emesis occur, Japanese and Western (non-Japanese) comparisons may be repeated with and without data from participants that experience emesis to evaluate the impact of emesis on PK exposure.

- Japanese and Western (non-Japanese) participant data from BTZ117351 may be incorporated into summary outputs

All Cohorts

- Change from baseline in QTcF versus PK plasma concentrations of gepotidacin will be plotted separately by treatment.

Model Checking & Diagnostics

- Model assumptions will checked before analysis.
- 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 seriously violated, then alternative data transformations will be explored. If no suitable transformation can be found, equivalent nonparametric analyses (ex. Wilcoxon signed-rank test) will be performed.

Model Results Presentation

- Linear mixed-effect model results will be presented in tabular format for the following comparison:
  Cohort 3: Gepotidacin + digoxin and midazolam versus digoxin and midazolam alone
- The N, n, least squares GM values, GM ratios and associated 90% CIs, and within-subject CV will be presented.

8. BIOMARKER ANALYSES

8.1. Exploratory Biomarker Analyses

8.1.1. Endpoint / Variables

8.1.1.1. Biomarker Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic).

8.1.1.2. Derived Biomarker Parameters

Biomarker parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin (8.0 or higher) or using the currently supported version of SAS (9.4 or higher). All calculations of non-compartmental parameters will be based on actual sampling times. Exploratory biomarker parameters listed below will be determined from the baseline-corrected plasma or urine concentration-time data for N1-methylnicotinamide (1-NMN) and serum or urine concentration-time data for creatinine for Cohort 1, as appropriate and as data permit.

Parameter	Parameter Description
Ae total	Total amount excreted in urine (total amount of biomarker excreted in urine), calculated by adding all the amounts excreted collected over all the allotted time intervals (1-NMN and creatinine).
AUC(0-t)	Area under the plasma or serum concentration-time curve from time 0 (predose) to the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (1-NMN and creatinine).
AUC(0-24)	Area under the plasma concentration-time curve from time 0 (predose) to the concentration at 24 hours postdose, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (1-NMN only).
AUC(0-48)	Area under the plasma concentration-time curve from time 0 (predose) to the concentration at 48 hours postdose, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid (1-NMN only).
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data (1-NMN only).
Tmax	Time to reach maximum observed plasma concentration (1-NMN only).
C average	Average concentration, calculated as AUC(0-48)/48 (1'-NMN only).
Ctrough	Trough plasma concentration (1-NMN only; 48 h post gepotidacin dose).
CLr	Renal clearance (of biomarker), calculated as: Ae total/AUC(0-t). (1-NMN and creatinine; CLr will also be reported for 1-NMN after normalization to creatinine CLr)

NOTES:

- Additional parameters may be included as required.

8.1.2. Summary Measure

Cohort 1

Plasma biomarker parameters C average, Cmax, Ctrough, Tmax, AUC(0-24), AUC(0-48) and AUC(0- t) of 1-NMN and urine biomarker parameters Ae total and CLr of 1-NMN following a single 1500 mg dose of gepotidacin alone (Period 1) and in the presence of cimeditine 400 mg QID (Period 2) in healthy adult participants will be summarized by treatment. Biomarker parameter estimates will be listed by participant and treatment. Creatinine Ae total, AUC(0-t) (serum), and CLr will similarly be summarized and listed. Estimated glomerular filtration rate (eGFR) will be summarized and listed for the predose time point. The Modification of Diet in Renal Disease formula will be used to derive eGFR:

$$\mathbf{eGFR}\ ([\mathbf{mL/min}]/\mathbf{1.73\ m^2}) = 175 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ if female} \times 1.212 \text{ if African American}$$

8.1.3. Population of Interest

The exploratory biomarker analyses will be based on the PK population for plasma, serum, and urine biomarker concentrations and the PK parameter population for plasma, serum, and urine biomarker parameters.

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

For intercurrent events, see Section 7.1.4.

8.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Exploratory biomarker parameters as described in Section 8.1.1 will be estimated for 1-NMN and creatinine. For each of these parameters the following summary statistics will be calculated by treatment: median, maximum, minimum, arithmetic mean, standard deviation, 95% confidence interval (CI) for the arithmetic mean, geometric mean, CV on geometric mean, 95% CI for the geometric mean, and standard deviation of logarithmically transformed data.

8.1.5.1. Statistical Methodology Specification

The following biomarker statistical analyses will only be performed if sufficient data are available (i.e. if participants have well defined plasma profiles).

Endpoint / Variables
• Biomarker exploratory endpoints include biomarker parameters for plasma and urine 1-NMN and serum and urine creatinine (Cohort 1), as data permit.
Model Specification
Cohort 1 • Upon review of the biomaker data, analysis may be performed to compare the plasma and urine exposure of 1-NMN and the serum and urine exposure of creatinine with and without cimetidine. Analysis will be performed on the natural logarithms of plasma 1-NMN AUC(0-t), AUC(0-24), and Cmax, serum creatinine AUC(0-t), and urine 1-NMN and creatinine Ae total and CLr 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-subject CV will be calculated as well. • Summary statistics (arithmetic mean, geometric mean, median, 95% CI (arithmetic and geometric), standard deviation (arithmetic and geometric), minimum, maximum, and geometric CV) for exploratory biomarker plasma and urine 1-NMN (including those normalized to creatinine) and serum and urine creatinine parameters will be summarized by treatment.
Model Checking & Diagnostics
• Model assumptions will be checked before analysis. • 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 seriously violated, then alternative data transformations will be explored. If no suitable transformation can be found, equivalent nonparametric analyses (ex. Wilcoxon signed-rank test) will be performed.
Model Results Presentation
• Linear mixed-effect model results will be presented in tabular format with geometric mean ratios for the following comparison: Cohort 1: Gepotidacin + cimetidine versus gepotidacin alone • The N, n, least squares GM values, GM ratios and associated 90% CIs, and within-subject CV will be presented.

9. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

9.1. Adverse Events Analyses

The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) criteria for adult toxicity assessment. All reported AEs will be coded using MedDRA and summarized by system organ class (SOC) and preferred term (PT) and treatment. In Cohort 4, all the placebo arms will be summarized together, whether in the fed or fasted state.

Adverse event severity is classified as mild (grade = 1), moderate (grade = 2), and severe (grade = 3), and Potentially Life-Threatening (grade = 4). Adverse events starting after the first dose of study treatment with a missing severity will be classified as severe. If a participant reports an AE more than once within an SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

Relationship to study treatment, as indicated by the investigator, is classified as “No” (not related) or “Yes” (related). Adverse events with a missing relationship to study treatment will be regarded as “Yes” to study treatment. If a participant reports the same AE more than once within an SOC/PT, the AE with the worst-case relationship to study treatment will be used in the corresponding relationship summaries.

Adverse events analyses including the analysis of AEs, SAEs and other significant AEs will be based on GSK Core Data Standards. All AEs, study drug related AEs, SAEs, and AEs leading to discontinuation of study treatment or withdrawal from study will be provided in separate listings. The relationship between SOC and PT will be listed. Summary tables will be provided by SOC, PT, and maximum severity.

In summary tables where AEs are presented by SOC, PT, and maximum severity, SOCs will be sorted in descending order of the total incidence then alphabetically, PTs will be sorted in descending order of the total incidence then alphabetically within the SOC.

For completely missing or partial missing AE start date or end date, imputation rules will be applied following Section 11.6.2.

In addition, a summary of the number and percentage of participants with common AEs, defined as AEs occurring more than two times irrespective of treatment by cohort, will be presented in descending order of total incidence by PT. The details of the planned displays are provided in Appendix 11: List of Data Displays.

9.1.1. Adverse Events of Special Interest Analyses

Gastrointestinal AEs, Cardiovascular AEs, potential events related to Acetylcholinesterase inhibition as determined by algorithm, and Clostridium difficile infection events will be considered AEs of Special Interest (AESIs). AESIs except those for Acetylcholinesterase inhibition, are flagged in the eCRF and details of events are

collected on special eCRF pages. Potential acetylcholinesterase-Inhibition AESIs will be programmatically matched with the list of AEs specified in Section 9.1.2 In addition, there will be a manual review of AE listings to ensure accuracy and completeness of AESI reporting.

9.1.2. Potential Acetylcholinesterase-Inhibition AESIs

Any reported AE listed in the Section 11.8.2 with a start time after first dose of study treatment administered and no later than 12 hours after the last dose of the study treatment administered in each period, as evaluated by the investigator as per the DMID grading criteria provided in protocol Section 11.8.1: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment, will be programmatically identified as potential Acetylcholinesterase inhibition related AESI in Section 11.8.2 .

AESIs will be listed and tabulated.

The details of the planned displays are provided in Appendix 11: List of Data Displays.

9.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests, urinalysis, and liver function tests will be based on GSK Core Data Standards. Division of Microbiology and Infectious Diseases (DMID) grading for all parameters as specified in the protocol will be assigned programmatically by PPD in the Laboratory Analysis Dataset. Summary of worst case of assessment results relative to normal range for clinical laboratory will be included. The details of the planned displays are in Appendix 11: List of Data Displays.

9.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, including summary of worst case of assessment results relative to normal range for vital signs, unless otherwise specified. The details of the planned displays are presented in Appendix 11: List of Data Displays.

9.4. Strategy for Intercurrent (Post-Randomization) Events

The only intercurrent event identified for safety analyses is treatment discontinuation. A “while on treatment” strategy will be used . which attempts to estimate safety effects more likely to be attributable to the drug.

10. REFERENCES

GlaxoSmithKline Document Numbers 2020N434866_00 (Original – 13-JUL-2020): 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 (13-JUL-2020).

11. APPENDICES

11.1. Appendix 1: Schedule of Activities

11.1.1. Protocol Defined Time and Events Table

Table 1 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 Protocol Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X										See Protocol Table 16.
Laboratory assessments	X			X				X	X	X	See Protocol Table 16.

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	
12-lead ECG[3]	X	X	X	X	X	X	X	X	X	X	See Triplicate 12-lead ECGs will be measured on Pre-dose and Single ECGs on Day -1 and at all other timepoints Table 6 and Table 7 for timing of assessments.
Vital signs	X	X	X	X	X	X	X	X	X	X	See Triplicate 12-lead ECGs will be measured on Pre-dose and Single ECGs on Day -1 and at all other timepoints Table 6 and Table 7 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.
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.

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	
Blood collection for PK		X	X	X		X	X	X			See Triplicate 12-lead ECGs will be measured on Pre-dose and Single ECGs on Day -1 and at all other timepoints Table 6 and Table 7 for timing of assessments.
Urine collection for PK		X	X	X		X	X	X			See Triplicate 12-lead ECGs will be measured on Pre-dose and Single ECGs on Day -1 and at all other timepoints Table 6 and Table 7 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 2 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 Protocol Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X																See Protocol Table 16.
Laboratory assessments	X			X							X			X	X	X	See Protocol Table 16.
12-lead ECG[3]	X	X	X	X								X	X	X	X	X	See Table 8 for timing of assessments.
Vital signs	X	X	X	X								X	X	X	X	X	See Table 8 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)										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	
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 8 for timing of assessments.
Urine collection for gepotidacin PK		X	X	X								X	X	X			See Table 8 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 3 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 Protocol Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X														See Protocol Table 16.
Laboratory assessments	X						D10					X	X	X	See Protocol Table 16.
12-lead ECG[5]	X	X	X	X			D10	X	X	X			X	X	See Table 9 and Table 10 for timing of assessments.
Holter ECG monitoring	X	X					D10	X							See Table 9 and Table 10 for timing of assessments.
Vital signs	X	X	X	X			D10	X	X	X			X	X	See Table 9 and Table 10 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 9 and Table 10 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 4 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 Protocol Section 8.2.5 – pregnancy testing for instruction on time points.
Drug, alcohol, and cotinine screen	X									See Protocol Table 16.
Laboratory assessments	X			X			X	X	X	See Protocol Table 16.
12-lead ECG[4]	X	X	X	X	X	X	X	X	X	See Protocol Table 11 and Table 12 for timing of assessments.
Vital signs	X	X	X	X	X	X	X	X	X	See Protocol Table 11 and Table 12 for timing of assessments.

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	
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.
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.

11.1.2. Protocol Defined Safety and PK Assessments

Table 5 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 6 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 7 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 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	
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 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[4]	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[4,5]	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.

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 24 hours, 24 to 36 hours, 36 to 48 hours, and 48 to 60 hours after digoxin administration.

Table 10 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 11 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.

11.2. Appendix 2: Assessment Windows

- Actual times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots

- PK concentration listings shall have both the planned and actual times

- Planned time will be used for all other analysis

11.3. Appendix 3: Study Phases and Periods

11.3.1. Treatment States

Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date/Time < Study Treatment Start Date/Time
Treatment	AE Start Date/Time ≥ Study Treatment Start Date/Time In summaries of AEs by treatment, AEs will be summarized according to the most recent treatment received prior to the AE.
Onset Time Since First Dose (Days)	If Treatment Start Date/Time > AE Onset Date/Time = AE Onset Date - Treatment Start Date If Treatment Start Date/Time ≤ AE Onset Date/Time = AE Onset Date - Treatment Start Date +1 Missing otherwise
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF OR value is missing

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

11.3.2. Treatment Period for Safety Summaries by Treatment Cohort

The originally periods could refer to Section 11.1.1. The strategy for subject discontinuation is in Section 9.4.

For AEs and Concomitant medications, the treatment period will be defined as the last treatment prior to the event. And event start datetime will be used instead of date (date will be used if datetime is missing) in below definition and table.

For safety assessments other than AEs and Concomitant medications, the nominal periods are taken from Section 11.1.1. Time window will be used to determine period, and within each period, nominal visit will be used for summary purpose. The full definition of periods for safety summary are defined in below table.

Treatment Cohort	Period	Start	End
Cohort 1	1	Date of first dose in nominal period 1 (inclusive)	Date of first dose in nominal period 2 (not inclusive) if not missing Last Visit of Study if start date of period 2 is missing
	2	Date of first dose of nominal period 2 (inclusive)	Last Visit of Study if start date of period 2 is not missing
Cohort 2	1	Date of first dose in nominal period 1 (inclusive)	Date of first dose in nominal period 2 (not inclusive) if not missing

Treatment Cohort	Period	Start	End
			Last Visit of Study if start date of period 2 is missing
	2	Date of first dose in nominal period 2 administration (inclusive)	Last Visit of Study if start date of period 2 is not missing
Cohort 3	1	Date of dose in nominal period 1 (inclusive)	Date of first dose in nominal period 2 (not inclusive) if not missing Last Visit of Study if start date of period 2 is missing
	2	Date of first dose in nominal period 2 (inclusive)	Last Visit of Study if start date of period 2 is not missing
Cohort 4	1	Date of dose in nominal period 1 (inclusive)	Date of first dose in nominal period 2 (not inclusive) if not missing Last Visit of Study if start date of period 2 is missing
	2	Date of first dose in nominal period 2 administration (inclusive)	Date of first dose in nominal period 3 (not inclusive) if not missing Last Visit of Study if start date of period 3 is missing
	3	Date of first dose in nominal period 3 administration (inclusive)	Last Visit of Study if start date of period 3 is not missing

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
Study Cohort	Treatment Group		Data Displays for Reporting	
	Code	Description	Description	Order [1]
1	A	Gepotidacin 1500 mg SD on Day 1 of Period 1	Gepotidacin 1500 mg	1
1	B	Cimetidine 400 mg 4 times daily Days 1 through 4 of Period 2 and gepotidacin 1500 mg SD.	Cimetidine 400 mg + Gepotidacin 1500 mg	2
2	C	Gepotidacin 1500 mg SD on Day 1 of Period 1	Gepotidacin 1500 mg	3
2	D	Rifampicin 600 mg (administered in the evenings) once daily for 7 days (Days 1 through 7) in Period 2.	Rifampicin 600 mg	4
2	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.	Gepotidacin 1500 mg + Rifampicin 600 mg	5
3	F	Digoxin 0.5 mg and midazolam 2 mg on Day 1.	Midazolam and Digoxin	6
3	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.	Gepotidacin two 3000 mg + Midazolam and Digoxin	7
4	H	Gepotidacin 1500 mg SD under fed conditions on Day 1.	Gepotidacin 1500 mg Fed	9
4	I	Gepotidacin 1500 mg SD under fasted conditions on Day 1.	Gepotidacin 1500 mg Fasted	10
4	J	Two doses of gepotidacin up to 3000 mg (given 12 hours apart) under fed conditions on Day 1.	Gepotidacin 3000 mg Fed	11
4	H/I/J	Matching Placebo for H/I/J	Placebo	8

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

11.4.2. Reporting Process & Standards

Reporting Process
Software
• The currently supported versions of SAS and WinNonlin software will be used.
Analysis Datasets
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1]. • For creation of ADaM datasets (ADCM/ADC1/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.
Generation of RTF Files
• RTF files will be generated for all reporting efforts described in the RAP.

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: Principles for all displays o 5.01 to 5.09: Principles for Data Listings o 6.01 to 6.11: Principles for Summary Tables o 7.01 to 7.13: Principles for Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (4.23 & 6.9) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : o Planned time relative to dosing will be used in figures (with the exception of individual PK concentration-time figures, where actual relative time will be used), summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. o The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings.
Unscheduled Visits
• Unscheduled visits will be considered when calculating baseline and in Table 2.8, Table 2.10, Table 2.11, Table 2.12, Table 2.14, Table 2.15, and Table 2.18 but will not be included in any other summary tables. • Unscheduled visits will not be included in figures.

Reporting Standards	
• All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (xpt format) for the non-compartmental analysis will be created according to SOP 314000(2.0). Note: Concentration values will be imputed as per GUI_51487

Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.
	Refer to IDSL Statistical Principle 6.06.1.
	For continuous data:
	• NQs at the beginning of a participant profile (i.e. before the first incidence of a measurable concentration) are deemed to be zero as it is assumed that in this circumstance no drug is yet measurable in the blood.
	• For NQs at the end of the participant profile (i.e. after the last incidence of a measurable concentration);
	  • for individual plots and pharmacokinetic analyses these are dropped (set to missing) as they do not provide any useful information (and can erroneously indicate that absolutely no drug is present)
	  • for summary statistics, these are set to 0 (to avoid skewing of the summary statistics)
	• Individual NQs which fall between two measurable concentrations are set to missing (individual values of this nature are assumed to be an anomaly)
	If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual participant plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).
	Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.

Pharmacokinetic Parameter Data	
PK Parameter to be Derived by Programmer	The following plasma PK and biomarker parameters will be derived by the Programmer: RoCmax, RoAUC, AUC m/p, Ctrough, C average The following urine PK and biomarker parameters will be derived by the Programmer: Ae total, Ae(t1-t2), fe%, CLr Note: Parameter definitions are found in Section 7.1.1.2, Section 7.2.1.2, Section 7.3.1.2, and Section 8.1.1.2.
Descriptive Summary Statistics, Graphical Displays and Listings	N, n, arithmetic mean, 95% CI of arithmetic mean, geometric mean, 95% CI of geometric mean, standard deviation, standard deviation of logged data, CV (%), and between-subject geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(standard deviation^2) - 1) * 100 (standard deviation = between-subject SD of Ln-$_e$Transformed data)
Within-subject CV for Statistical Analysis Tables	Within-subject coefficient of variation (%CVw) will be reported. CVw (%) = $\sqrt{}$ (exp(σw2) - 1) * 100 (σw2 is the mean squares estimate (MSE) from the statistical linear mixed model)
Parameters Not Being Ln-Transformed	Tlag, Tmax, AUC%extrap. (percentage of the extrapolated area to infinity in ratio to the total area under the curve, calculated as: ((AUC0-∞ - AUC0-t) / AUC0-∞) × 100), λz (apparent terminal elimination rate constant, estimated by linear regression of the terminal portion of the log-concentration by time curve), λz lower (lower limit on time for values to be included in the calculation of λz), λz upper (upper limit on time for values to be included in the calculation of λz), and λz no. of points (number of time points used in the calculation of λz).
Parameters Not Being Summarized	AUC%extrap., λz, λz lower, λz upper, and λz no. of points.
Listings	Include the first point, last point and number of points used in the determination of λz for listings.

11.5. Appendix 5: Derived and Transformed Data

11.5.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented • For maximum grade increase summary and PCI summaries, each of the multiple measurements will be used to derive the subject worst case.
Study Day

• Calculated as the number of days from date of first study drug administration (Dose Date) for each cohort:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Dose Date → Study Day = Ref Date – Dose Date
  • Ref Data ≥ Dose Date → Study Day = Ref Date – (Dose Date) + 1

Period Day

• Calculated as the number of days from treatment start date for the respective period for each cohort:
  • Ref Date = Missing → Period Day = Missing
  • Ref Date < Treatment Date → Period Day = Ref Date – Treatment Date
  • Ref Data ≥ Treatment Date → Period Day = Ref Date – (Treatment Date) + 1

11.5.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Only the year of birth will be collected. The date and month will be imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)²]**
eGFR
See Section 8.1.2.
estimated creatine clearance (CLcr)
The Cockcroft-Gault equation will be used to derive estimated creatine clearance (CLcr): CLcr (mL/min) = $\frac{[140-\text{age (years)}]*\text{weight(kg)}}{72*\textbf{serum creatine } (mg/dl)}$ $[*\ 0.85\ for\ female\ subjects]$

11.5.3. Safety

Adverse Events

AE'S of Special Interest

- Cardiovascular (CV) events
- Gastrointestinal events
- Potential Acetylcholinesterase inhibition events

Adverse Events with Missing Relationship or Missing Serious Indicator

- If the relationship to study treatment is missing for a treatment-emergent AE, it'll be considered as related to the study treatment.
- If the serious indicator "Was event serious?" is missing, the AE will be considered as SAE.
- Adverse events with missing relationship or missing serious indicator will be presented as it is in listings but will be treated as related AEs or SAEs in summary tables.

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

ECG Parameters

RR Interval

- IF RR interval (millisecond [msec]) is not provided directly, then RR can be derived as:
  [1] If QTcB is machine read & QTcF is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
- Machine read values of RR should not be replaced with derived values.

Corrected QT Intervals

- When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fridericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements.
- IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as:

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

11.6. Appendix 6: Reporting Standards for Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as completing all phases of the study including the follow-up visit. • Withdrawn participants may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Early termination visits will be summarized as early termination visits.

11.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the CSR.

11.6.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day: First of the month will be used unless this is before the date of first study treatment of the cohort; in this case the date of first study treatment date will be used. o Missing Stop Day: Last day of the month will be used, unless this is after the date of last visit of the cohort; in this case the last visit date of the cohort will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings. If only the start date is completely missing, we assume that the medication has been taken from the beginning of the study for the participant.

Element	Reporting Detail
	If only the stop date is missing, assume that the medication has been taken till the end of the compete study for the participant. • If both start and end date is missing, we assume that the medication has been taken for the duration of the study for the participant.

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	Upper
Absolute			
Absolute QTc Interval[3]	msec	> 450[1]	
		> 450[2]	≤ 480[2]
		> 480[2]	≤ 500[2]
		> 500[2]	
Absolute PR Interval	msec	< 110[1]	> 220[1]
Absolute QRS Interval	msec	< 75[1]	> 110[1]
Change from Baseline			
Increase from Baseline QTc[3]	msec	≤ 30[2]	
	msec	> 30[2]	≤ 60[2]
	msec	> 60[1]	

NOTES:

1. Represent standard ECG values of PCI for HV studies.
2. Represent further subdivisions of ECG values for analysis.
3. Qualifying QTc events, regardless whether QTcB or QTcF, will be captured.

11.7.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Potential Clinically Important Range	
		Lower	Upper
Systolic Blood Pressure	millimeters of mercury (mmHg)	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

11.7.2.1. Normal Range for Vital Signs

		Predose	Postdose
	Temperature	96.0-101.0 °F / 35.6-38.3 °C	96.0-101.0 °F / 35.6-38.3 °C
	Respiratory Rate	8-22	8-22
Supine	Heart Rate	40-110 (per GSK PCI Slides)	40-110 (per GSK PCI Slides)
	BP	<85 and >160 / <45 and >100 (per GSK PCI Slides)	<85 and >160 / <45 and >100 (per GSK PCI Slide)
	Pulse Oximetry	94-99	94-99

11.8. Appendix 8: Adverse Event Assessement Criteria

11.8.1. Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Events Assessments (2007) - Laboratory Values

Parameter values are converted to use SI units.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 to 10.5 gm/dL	8.0 to 9.4 gm/dL	6.5 to 7.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count	1000 to 1500 /mm^3	750 to 999 /mm^3	500 to 749 /mm^3	<500 /mm^3
Platelets	75,000 to 99,999 /mm^3	50,000 to 74,999 /mm^3	20,000 to 49,999 /mm^3	<20,000 /mm^3
White Blood Cells	11,000 to 13,000 /mm^3	13,000 to 15,000 /mm^3	15,000 to 30,000 /mm^3	>30,000 or <1000 /mm^3
% Polymorphonuclear Leukocytes + Band Cells	>80%	90 to 95%	>95%	N/A
Abnormal Fibrinogen	Low: 100 to 200 mg/dL High: 400 to 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL High: N/A	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 to 40 mcg/mL	41 to 50 mcg/mL	51 to 60 mcg/dL	>60 mcg/dL
Prothrombin Time (PT)	1.01 to 1.25 × 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 of hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6 to 6.0 mEq/L	6.1 to 6.5 mEq/L	6.6 to 7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55 to 64 mg/dL	40 to 54 mg/dL	30 to 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma

Hyperglycemia (nonfasting and no prior diabetes)	116 to 160 mg/dL	161 to 250 mg/dL	251 to 500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 to 7.8 mg/dL	7.7 to 7.0 mg/dL	6.9 to 6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 to 1.2 mEq/L	1.1 to 0.9 mEq/L	0.8 to 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 to 2.4 mg/dL	1.5 to 1.9 mg/dL or replacement Rx required	1.0 to 1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 to <1.25 × 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.

11.8.2. List of Potential AEs for programming to be considered due to Acetylcholinesterase-Inhibition

Abdominal discomfort
Abdominal pain
Abdominal pain lower
Abdominal pain upper
Abdominal symptom
Abdominal tenderness
Asthma
Atonic seizures
Atypical benign partial epilepsy
Autonomic seizure
Bradyarrhythmia
Bradycardia
Bronchial hyperreactivity
Bronchospasm
Clonic convulsion
Cold sweat
Convulsions local
Convulsive threshold lowered
Defaecation urgency
Diarrhoea
Drooling
Dyspnoea
Dyspnoea at rest
Dyspnoea exertional
Epigastric discomfort
Epilepsy
Epilepsy with myoclonic-atonic seizures
Faeces soft
Febrile convulsion

Febrile infection-related epilepsy syndrome
Flatulence
Focal dyscognitive seizures
Frequent bowel movements
Frontal lobe epilepsy
Gastrointestinal disorder
Gastrointestinal pain
Gastrointestinal tract irritation
Generalised non-convulsive epilepsy
Generalised tonic-clonic seizure
Heart rate decreased
Hyperhidrosis
Hyperkinesia
Hypocalcaemic seizure
Hypoglycaemic seizure
Hyponatraemic seizure
Idiopathic generalised epilepsy
Idiopathic partial epilepsy
Irregular breathing
Lacrimation increased
Lafora's myoclonic epilepsy
Lennox-Gastaut syndrome
Myoclonic epilepsy
Nausea
Night sweats
Partial seizures
Partial seizures with secondary generalisation
Petit mal epilepsy
Psychomotor hyperactivity
Retching
Salivary hypersecretion
Seizure
Seizure cluster
Simple partial seizures
Status asthmaticus
Status epilepticus
Sweat gland disorder
Syncope

Tonic clonic movements
Tonic convulsion
Unilateral bronchospasm
Vomiting
Vomiting projectile
Wheezing

11.9. Appendix 9: Multiple Comparisons & Multiplicity

11.9.1. Handling of Multiple Comparisons & Multiplicity

No adjustments for multiplicity will be made.

11.10. Appendix 10: Abbreviations & Trade Marks

11.10.1. Abbreviations

λz	terminal phase rate constant
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
Ae total	total amount excreted in urine (drug or biomarker)
Ae (t1-t2)	amount excreted in urine in a time interval (drug)
AUC	area under the concentration-time curve
AUC(0-∞)	area under the concentration-time curve from time 0 (predose) extrapolated to infinite time (plasma)
AUC(0-24)	area under the concentration-time curve from time 0 (predose) to 24 hours post dose administration following the first dose (plasma or urine)
AUC(0-48)	area under the concentration-time curve from time 0 (predose) to 48 hours post dose administration following the first dose (plasma or urine)
AUC(0-t)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (plasma, serum, or urine)
AUC(0-τ)	area under the concentration-time curve from time 0 (predose) to time tau (plasma or urine)
BMI	body mass index
CI	confidence interval
CL/F	Apparent plasma oral clearance
CLr	renal clearance (drug or biomarker)
Cmax	maximum observed plasma concentration
Cmin	minimum observed plasma concentration
CSR	Clinical Study Report
DDI	drug-drug interaction
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
eCRF	electronic case report form
fe%	percentage of the given dose of drug excreted in urine
GSK	GlaxoSmithKline
ICF	informed consent form
IA	Interim Analysis
IDSL	Integrated Data Standards Library
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
mmHg	millimeters of mercury
msec	millisecond
PK	pharmacokinetic
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
RAP	Reporting and Analysis Plan
RoAUC	accumulation ratio based on AUC(0-τ) (plasma)
RoCmax	accumulation ratio based on Cmax (plasma)
SAC	Statistical Analysis Complete

SAE	serious adverse event
SAS	Statistical Analysis Software
SD	single dose
SoA	schedule of activities
t1/2	Apparent plasma terminal phase half life
Tlag	lag time before observation of drug concentration in plasma
Tmax	time to reach maximum observed plasma concentration
Vz/F	Apparent plasma volume of distribution

11.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline Group of Companies
MedDRA
SAS
WHODrug
WinNonlin

11.11. Appendix 11: List of Data Displays

11.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.10	NA
Safety	2.1 to 2.22	2.1 to 2.5
Pharmacokinetic	3.1 to 3.33	3.1 to 3.37
Biomarker	4.1 to 4.5	4.1 to 4.3
Section	**Listings**	
ICH Listings	1 to 46	
Other Listings	47 to 65	

11.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.11.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

11.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition and Analysis Sets					
1.1	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC [1]
1.2	Safety	ES1xo	Summary of Subject Disposition		SAC [1]
1.3	Enrolled	ES4	Summary of Subject Disposition at Each Study Period	Cohorts 3 and 4 only	SAC [1]
1.4	Screened	ES6	Summary of Reasons for Screening Failures		SAC [1]
1.5	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC [1]
1.6	Enrolled	DV1	Summary of Important Protocol Deviations		SAC [1]
Demographics and Baseline Characteristics					
1.7	Safety	DM1xo	Summary of Demographic Characteristics		SAC [1]
1.8	Safety	DM6xo	Summary of Race and Racial Combinations		SAC [1]
1.9	Enrolled	DM11xo	Summary of Age Ranges		SAC [1]
1.10	Safety	MH4	Summary of Current Cardiovascular and Liver Disease Related Medical Conditions		SAC [1]

11.11.5. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1	Safety	AE5B	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Grade		SAC [1]
2.2	Safety	AE5B	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade		SAC [1]
2.3	Safety	AE15	Summary of Common Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC [1]
2.4	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC[1]
2.5	Safety	AE5B	Summary of Potential Acetylcholinesterase-Inhibition Adverse Events of Special Interest by System Organ Class and Preferred Term and Maximum Grade		SAC [1]
2.6	Safety	SAFE_T1	Summary of Cumulative Grades of Potential Acetylcholinesterase-Inhibition Adverse Events of Special Interest		SAC[1]
Laboratory Measurements					
2.7	Safety	LB1	Summary of Chemistry Change from Baseline		SAC [1]
2.8	Safety	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC [1]
2.9	Safety	LB1	Summary of Hematology Change from Baseline		SAC [1]
2.10	Safety	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC [1]
2.11	Safety	UR1	Summary of Worst Case Urinalysis Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC [1]

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12	Safety	LIVER1	Summary of Liver Stopping Event Reporting		SAC [1]
Electrocardiograms					
2.13	Safety	EG1	Summary of ECG Findings		SAC [1]
2.14	Safety	EG11	Summary of Maximum QTc Values Post-Baseline ECG Parameter Corrected QTc Interval		SAC [1]
2.15	Safety	EG11	Summary of Maximum Increase in QTc Values Post- Baseline Relative to Baseline by Category		SAC [1]
2.16	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC [1]
Vital Signs					
2.17	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC [1]
2.18	Safety	VS3	Summary of Worst Case Vital Sign Results Relative to Normal Range Post- Baseline Relative to Baseline		SAC [1]
Cardiovascular Risk Factors					
2.19	Safety	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC [1]
2.20	Safety	SU1	Summary of Substance Use		SAC [1]
2.21	Safety	EG2	Summary of QTcF Values		SAC[1]
COVID-19					
2.22	Safety	PAN1	Summary of COVID-19 Assessment		SAC [1]

11.11.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1.	PK	PKCT1	Summary of Gepotidacin Plasma Pharmacokinetic Concentration-Time Data (ug/mL) by Cohort and Treatment	Cohorts 1, 2, and 4; Paginate by treatment; For Cohort 4 only show periods 1/2 (fasted v fed)	SAC [1]
3.2.	PK	PKCT1	Summary of Cimetidine Plasma Pharmacokinetic Concentration-Time Data (units)	Cohort 1 (Period 2 only)	SAC [1]
3.3.	PK	PKCT1	Summary of Digoxin Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment	Paginate by treatment; Cohort 3	SAC [1]
3.4.	PK	PKCT1	Summary of Midazolam and 1-Hydoxymidazolam Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment	Paginate by treatment; by-variable for analyte; Cohort 3	SAC [1]
3.5.	PK	PKCT1	Summary of Gepotidacin Plasma Pharmacokinetic Concentration-Time Data (ug/mL) for 1500 mg Dose: Japanese versus Western Participants	Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period – Period 1); Paginate by ethnicity.	SAC [1]
3.6.	PK	PKCT1	Summary of Gepotidacin Plasma Pharmacokinetic Concentration-Time Data (ug/mL) for Two 3000 mg Doses: Japanese versus Western Participants	Japanese: Cohort 4 (Period 3); Western: Cohort 3; Paginate by ethnicity.	SAC [1]
3.7.	PK	PKCT1	Summary of Gepotidacin Urine Pharmacokinetic Concentration-Time Data (ug/mL) by Treatment by Cohort and Treatment	Cohorts 1, 2, and 4; Paginate by treatment; For Cohort 4 only show period 1/2 (fasted v fed)	SAC [1]
3.8.	PK	PKCT1	Summary of Gepotidacin Urine Pharmacokinetic Concentration-Time Data (ug/mL) for 1500 mg Dose: Japanese versus Western Participants	Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period – Period	SAC [1]

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				1); Paginate by ethnicity.	
3.9.	PK	PKCT1	Summary of Gepotidacin Urine Pharmacokinetic Concentration-Time Data (ug/mL) for Two 3000 mg Doses: Japanese versus Western Participants	Japanese: Cohort 4 (Period 3); Western: Cohort 3; Paginate by ethnicity.	SAC [1]
PK Derived Parameters					
3.10.	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Plasma Pharmacokinetic Parameters by Treatment by Cohort and Treatment	Cohorts 1, 2, and 4; Parameters with units. Do not ln-transform Tmax or Tlag; Treatments side-by-side; For Cohort 4 only show period 1/2 (fasted v fed)	SAC [1]
3.11.	PK Parameter	PKPT4	Summary Statistics of Derived Digoxin Plasma Pharmacokinetic Parameters by Treatment	Parameters with units. Do not ln-transform Tmax or Tlag; Treatments side-by-side; Cohort 3	SAC [1]
3.12.	PK Parameter	PKPT4	Summary Statistics of Derived Midazolam and 1-Hydroxymidazolam Plasma Pharmacokinetic Parameters by Treatment	Parameters with units. Do not ln-transform Tmax or Tlag;. Treatments side-by-side; Cohort 3; by-variable for analyte.	SAC [1]
3.13.	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Plasma Pharmacokinetic Parameters for 1500 mg Dose: Japanese versus Western Participants	Parameters with units. Do not ln-transform Tmax or Tlag; Ethnicity side-by-side; Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period – Period 1)	SAC [1]

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.14.	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Plasma Pharmacokinetic Parameters for Two 3000 mg Doses: Japanese versus Western Participants	Parameters with units. Do not ln-transform Tmax or Tlag; Ethnicity side-by-side; Japanese: Cohort 4 (Period 3); Western: Cohort 3; by-variable for dose number	SAC [1]
3.15.	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Urine Pharmacokinetic Parameters by Cohort and Treatment	Parameters with units; Treatments side-by-side; by-variable for Cohort; Cohorts 1, 2, and 4; for Cohort 4 period 1/2 (fasted/fed) only	SAC [1]
3.16	PK Parameter	PKPT4	Summary Statistics of Derived Digoxin Urine Pharmacokinetic Parameters by Treatment	Parameters with units; Treatments side-by-side; Cohort 3.	SAC [1]
3.17	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Urine Pharmacokinetic Parameters for 1500 mg Dose: Japanese versus Western Participants	Parameters with units. Ethnicity side-by-side; Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period – Period 1)	SAC [1]
3.18	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Urine Pharmacokinetic Parameters for Two 3000 mg Doses: Japanese versus Western Participants	Parameters with units. Do not ln-transform Tmax or Tlag; Ethnicity side-by-side; Japanese: Cohort 4 (Period 3); Western: Cohort 3; by-variable for dose number	SAC [1]
PK Analysis					
3.19	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Plasma and Urine Pharmacokinetic Parameters: Parametric Analysis – Cohort 1	Linear mixed-effect model: plasma: AUCs, Cmax, t1/2; urine:	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				AUCs, Ae total, CLr; contains inferential analysis	
3.20	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Plasma Pharmacokinetic Parameters: Non-parametric Analysis – Cohort 1	Wilcoxon signed-rank test: Tmax; contains inferential analysis	SAC
3.21	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Plasma and Urine Pharmacokinetic Parameters: Parametric Analysis – Cohort 2	Linear mixed-effect model: plasma: AUCs, Cmax; urine: AUCs Ae total, CLr; contains inferential analysis	SAC
3.22	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Plasma Pharmacokinetic Parameters: Non-parametric Analysis – Cohort 2	Wilcoxon signed-rank test: Tmax and Tlag; contains inferential analysis	SAC
3.23	PK Parameter	PKPT3	Statistical Analysis of Digoxin Plasma and Urine Pharmacokinetic Parameters: Parametric Analysis – Cohort 3	Linear mixed-effect model: plasma: AUCs, Cmax, t1/2, Cmin, Vz/F, CL/F; urine: Ae total and CLr; contains inferential analysis	SAC
3.24	PK Parameter	PKPT3	Statistical Analysis of Midazolam and 1'-Hydroxymidazolam Plasma Pharmacokinetic Parameters: Parametric Analysis – Cohort 3	Linear mixed-effect model: plasma: AUCs, Cmax, t1/2, Cmin, Vz/F, CL/F; contains inferential analysis,	SAC
3.25	PK Parameter	PKPT3	Statistical Analysis of Digoxin Plasma Pharmacokinetic Parameters: Non-parametric Analysis – Cohort 3	Wilcoxon signed-rank test: Tmax and Tlag; contains inferential analysis	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.26	PK Parameter	PKPT3	Statistical Analysis of Midazolam and 1'-Hydroxymidazolam Plasma Pharmacokinetic Parameters: Non-parametric Analysis – Cohort 3	Wilcoxon signed-rank test: Tmax and Tlag; contains inferential analysis	SAC
3.27	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Plasma Pharmacokinetic Parameters: Food Effect, Parametric Analysis – Cohort 4	Linear mixed-effect model: plasma: AUC(0-t), AUC(0-∞), Cmax; Periods 1 and 2 only; contains inferential analysis	SAC
3.28	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Plasma Pharmacokinetic Parameters: Food Effect, Non-parametric Analysis – Cohort 4	Wilcoxon signed-rank test: Tmax and Tlag; Periods 1 and 2 only; contains inferential analysis	SAC
Emesis vs. No Emesis					
3.29	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Plasma Pharmacokinetic Parameters by Cohort and Treatment for Participants with Emesis and Participants without Emesis	Emesis v No Emesis side-by-side; Cohort 3 and Cohort 4 (period 3).	SAC
3.30	PK Parameter	PKPT3	Statistical Analysis of Digoxin Plasma and Urine Pharmacokinetic Parameters Excluding Participants with Emesis: Parametric Analysis – Cohort 3	Linear mixed-effect model: plasma: AUCs, Cmax, t1/2, Cmin, CL/F, and Vz/F; urine: Ae total, CLr; contains inferential analysis	SAC
3.31	PK Parameter	PKPT3	Statistical Analysis of Midazolam and 1'-Hydroxymidazolam Plasma Pharmacokinetic Parameters Excluding Participants with Emesis: Parametric Analysis – Cohort 3	Linear mixed-effect model: plasma: AUCs, Cmax, t1/2, Cmin, CL/F, Vz/F; contains inferential analysis,	SAC
3.32	PK Parameter	PKPT3	Statistical Analysis of Digoxin Plasma Pharmacokinetic Parameters Excluding Participants with Emesis: Non-parametric Analysis – Cohort 3	Wilcoxon signed-rank test: Tmax and Tlag; contains inferential analysis	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.33	PK Parameter	PKPT3	Statistical Analysis of Midazolam and 1'-Hydroxymidazolam Plasma Pharmacokinetic Parameters Excluding Participants with Emesis: Non-parametric Analysis – Cohort 3	Wilcoxon signed-rank test: Tmax and Tlag; contains inferential analysis	SAC

11.11.7. Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarker Concentration Data					
4.1	PK	PKCT1	Summary of Biomarker Concentration-Time Data (units) by Treatment	Cohort 1; Creatinine (serum), 1-NMN (plasma), eGFR; Paginate by treatment; Baseline-corrected values	SAC [1]
Biomarker Derived Parameters					
4.2	PK Parameter	PKPT4	Summary Statistics of Derived Biomarker Parameters by Treatment	Cohort 1; Parameters with units. Treatments side-by-side.	SAC [1]
4.3	PK Parameter	PKPT4	Summary Statistics of Derived Biomarker Urine Parameters by Treatment	Cohort 1; Parameters with units. Treatments side-by-side; include creatinine-normalized parameters.	SAC [1]
Statistical Analysis					
4.4	PK Parameter	PKPT3	Statistical Analysis of 1-NMN Plasma and Urine Biomarker Parameters: Parametric Analysis – Cohort 1	Linear mixed-effect model: plasma: AUCs, Cmax; urine: Ae total and CLr; contains inferential analysis	SAC
4.5	PK Parameter	PKPT3	Statistical Analysis of Creatinine Serum and Urine Biomarker Parameters: Parametric Analysis – Cohort 1	Linear mixed-effect model: plasma: AUC and Cmax; urine: Ae total and CLr; contains inferential analysis	SAC

11.11.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
2.1	Safety	AE10	Gastrointestinal Adverse Events of Special Interest Adverse Events		SAC [1]
2.2	Safety	SAFE_F1	Plot of Distribution of Cumulative Grades of Acetylcholinesterase-Inhibition Adverse Events of Special Interest		SAC [1]
2.3	Safety	SAFE_F2	Plot of duration and severity of Adverse Events for Individual Participants		SAC [1]
2.4	Safety	EG8	Distribution of QTcF Change By Time And Treatment		SAC [1]
2.5	Safety	SAFE_F3	Individual and Mean Plot of QTcF Over Time And Treatment		SAC [1]

11.11.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1.	PK	PKCF1P	Individual Gepotidacin Plasma Concentration-Time Plots by Cohort and Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ; Participants Overlaid; By-variable for Cohort; all cohorts	SAC [1]
3.2.	PK	PKCF1P	Individual Digoxin Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ; Participants Overlaid; Cohort 3	SAC [1]
3.3.	PK	PKCF1P	Individual Midazolam and 1'-Hydroxymidazolam Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ; Participants Overlaid; by-variable for analyte; Cohort 3	SAC [1]
3.4.	PK	PKCF1P	Individual Gepotidacin Urine Concentration-Time Plots by Cohort and Treatment (Linear and Semi Logarithmic)	Paginate by Treatment; Dashed line represents the LLQ; Participants Overlaid; By-variable for Cohort; All cohorts; Plot based on the actual relative mid-point time for each interval.	SAC [1]
Mean / Median Concentration Plots					
3.5.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Plasma Concentration-Time Plots by Cohort and Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; By-variable for Cohort; Cohorts 1, 2, and 4. For Cohort 4 only show period 1/2 (fasted v fed)	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Plasma Concentration-Time Plots for Japanese Participants (Linear and Semi-Logarithmic)	Cohort 4 – single dose fed and two doses (period 3) overlaid.	SAC [1]
3.7.	PK	PKCF2	Mean (± Standard Deviation) Digoxin Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; Cohort 3	SAC [1]
3.8.	PK	PKCF2	Mean (± Standard Deviation) Midazolam and 1-Hydoxymidazolam Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; By-variable for analyte; Cohort 3	SAC [1]
3.9.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Plasma Concentration-Time Plots for 1500 mg Dose: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period).	SAC [1]
3.10.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Plasma Concentration-Time Plots for Two 3000 mg Doses: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (Period 3); Western: Cohort 3.	SAC [1]
3.11.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Urine Concentration-Time Plots by Cohort and Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; By-variable for Cohort; For Cohort 4 only show period 1/2 (fasted v fed). Cohorts 1, 2, and 4; Plot based on the planned relative mid-point time for each interval.	SAC [1]
3.12.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Urine Concentration-Time Plots for Japanese Participants (Linear and Semi-Logarithmic)	Cohort 4 – single dose fed and two doses (period 3) overlaid; Plot based on the planned relative mid-point time for each interval.	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.13.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Urine Concentration-Time Plots for 1500 mg Dose: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period); Plot based on the planned relative mid-point time for each interval.	SAC [1]
3.14.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Urine Concentration-Time Plots for Two 3000 mg Doses: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (Period 3); Western: Cohort 3; Plot based on the planned relative mid-point time for each interval.	SAC [1]
3.15.	PK	PKCF3	Median (Range) Gepotidacin Plasma Concentration-Time Plots by Cohort and Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; By-variable for Cohort; For Cohort 4 only show period 1/2 (fasted v fed); Cohorts 1, 2, and 4.	SAC [1]
3.16.	PK	PKCF3	Median (Range) Gepotidacin Plasma Concentration-Time Plots for Japanese Participants (Linear and Semi-Logarithmic)	Cohort 4 – single dose fed and two doses (period 3) overlaid	SAC [1]
3.17.	PK	PKCF3	Median (Range) Digoxin Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; Cohort 3	SAC [1]
3.18.	PK	PKCF3	Median (Range) Midazolam and 1-Hydoxymidazolam Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; By-variable for analyte; Cohort 3	SAC [1]
3.19.	PK	PKCF3	Median (Range) Gepotidacin Plasma Concentration-Time Plots for 1500 mg Dose: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period).	SAC [1]
3.20.	PK	PKCF3	Median (Range) Gepotidacin Plasma Concentration-Time Plots for Two 3000 mg Doses: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (Period 3); Western: Cohort 3.	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.21.	PK	PKCF3	Median (Range) Gepotidacin Urine Concentration-Time Plots by Cohort and Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid; By-variable for Cohort; For Cohort 4 only show period 1/2 (fasted v fed); Cohorts 1, 2, and 4; Plot based on the planned relative mid-point time for each interval.	SAC [1]
3.22.	PK	PKCF3	Median (Range) Gepotidacin Urine Concentration-Time Plots for Japanese Participants (Linear and Semi-Logarithmic)	Cohort 4 – single dose fed and two doses (period 3) overlaid; Plot based on the planned relative mid-point time for each interval.	SAC [1]
3.23.	PK	PKCF3	Median (Range) Gepotidacin Urine Concentration-Time Plots for 1500 mg Dose: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period).	SAC [1]
3.24.	PK	PKCF3	Median (Range) Gepotidacin Urine Concentration-Time Plots for Two 3000 mg Doses: Japanese versus Western Participants (Linear and Semi-Logarithmic)	Ethnicities overlaid; Japanese: Cohort 4 (Period 3); Western: Cohort 3.	SAC [1]
3.25.	PK Parameter	PK25	Spaghetti and Box Plots of Gepotidacin PK Parameters With and Without Cimetidine	Cohort 1; Primary PK parameters	SAC [1]
3.26.	PK Parameter	PK25	Spaghetti and Box Plots of Gepotidacin PK Parameters With and Without Rifampin	Cohort 2; Primary PK parameters	SAC [1]
3.27.	PK Parameter	PK25	Spaghetti and Box Plots of Digoxin PK Parameters With and Without Gepotidacin	Cohort 3; Primary PK parameters	SAC [1]
3.28.	PK Parameter	PK25	Spaghetti and Box Plots of Midazolam and 1-Hydroxymidazolam PK Parameters With and Without Gepotidacin	Cohort 3; Primary PK parameters	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.29.	PK Parameter	EFF_F1	Box Plot of Gepotidacin PK Parameters With and Without Food in Japanese Participants	Cohort 4 Period 1/2; Primary PK parameters	SAC [1]
3.30.	PK Parameter	EFF_F1	Box Plot of Gepotidacin PK Parameters for 1500 mg Dose: Japanese versus WesternParticipants	Ethnicity side-by-side; Japanese: Cohort 4 (single dose fed only); Western: Cohorts 1 and 2 (Gepo-only period); Include data from BTZ117351	SAC [1]
3.31.	PK Parameter	EFF_F1	Box Plot of Gepotidacin PK Parameters for Two 3000 mg Doses: Japanese versus Western Participants	Ethnicity side-by-side; Japanese: Cohort 4 (Period 3); Western: Cohort 3; by-variable for dose number	SAC [1]
3.32.	PK Parameter	EFF_F2	Mean Urinary Gepotidacin Excretion With and Without Cimetidine	Cohort 1	SAC [1]
3.33.	PK Parameter	EFF_F3	Geometric Mean Treatment Ratio and 90% Confidence Interval of Gepotidacin Pharmacokinetic Parameters	Cohorts 1 and 2; Include data from BTZ117349	SAC [1]
3.34.	PK Parameter	EFF_F3	Geometric Mean Treatment Ratio and 90% Confidence Interval of Digoxin, Midazolam, and 1-Hydroxymidazolam Pharmacokinetic Parameters	Cohort 3	SAC [1]
3.35.	Safety	PKPF2	Change from Baseline QTcF Data Versus Gepotidacin Plasma Concentrations	Combine gepotidacin-only data from Cohorts 1, 2, 3 and 4; indicate cohort and ethnicity in legend; contains inferential analysis	SAC [1]
Emesis vs No Emesis					
3.36.	PK	PKCF1P	Individual Gepotidacin Plasma Concentration-Time Plots by Treatment for Participants with Emesis and Participants without Emesis (Linear and Semi-Logarithmic)	Cohorts 3 and 4 (Period 3); only programmed if emesis is observed	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.37.	PK	PKCF2	Mean (± Standard Deviation) Gepotidacin Plasma Concentration-Time Plots by Treatment for Participants with Emesis and Participants without Emesis (Linear and Semi-Logarithmic)	Cohorts 3 and 4 (Period 3); only programmed if emesis is observed	SAC [1]

11.11.10. Biomarker Figures

Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
4.1	PK	PKCF1P	Individual Biomarker Concentration-Time Plots by Treatment (Linear)	Paginate by treatment; Dashed line represents the LLQ; Participants Overlaid; Cohort 1	SAC [1]
Mean / Median Concentration Plots					
4.2	PK	PKCF2	Mean (± Standard Deviation) Biomarker Concentration-Time Plots by Treatment (Linear)	Treatments Overlaid; Cohort 1	SAC [1]
4.3	PK	PKCF3	Median (Range) Biomarker Concentration-Time Plots by Treatment (Linear)	Treatments Overlaid; Baseline-corrected data; Cohort 1	SAC [1]

11.11.11. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomization					
1	Enrolled	TA1xo	Listing of Randomised and Actual Treatment		SAC [1]
Subject Disposition					
2	Safety	ES2xo	Listing of Reasons for Study Withdrawal		SAC [1]
3	Safety	SD2xo	Listing of Reasons for Study Treatment Discontinuation		SAC [1]
4	Randomized	BL1xo	Listing of Subjects for Whom the Treatment Blind was Broken During the Study		SAC [1]
5	Screened	ES7	Listing of Reasons for Screening Failure		SAC [1]
6	Enrolled	DV2xo	Listing of Important Protocol Deviations		SAC [1]
7	Screened	IE3xo	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC [1]
8	Enrolled	SP3xo	Listing of Subjects Excluded from Any Population		SAC [1]
Demographics					
9	Safety	DM2xo	Listing of Demographic Characteristics	Include height, weight and BMI and childbearing potential	SAC [1]
10	Safety	DM9xo	Listing of Race		SAC [1]
Medical Conditions and Concomitant Medications					
11	Safety	MH2xo	Listing of Medical Conditions		SAC [1]
12	Safety	CM3xo	Listing of Concomitant Medications		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
13	Safety	EX3xo	Listing of Exposure Data		SAC [1]
Safety					
14	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC[1]
15	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC [1]
16	Safety	AE8xo	Listing of All Adverse Events		SAC [1]
17	Safety	AE8xo	Listing of Study Drug Related Adverse Events		SAC [1]
18	Safety	AE8xo	Listing of Serious Adverse Events		SAC [1]
19	Safety	AE8xo	Listing of Adverse Events Leading to Withdrawal from Study		SAC [1]
20	Safety	AE8xo	Listing of Cardiovascular Adverse Events of Special Interest	Conditional display	SAC [1]
21	Safety	AE8xo	Listing of Gastrointestinal Adverse Events of Special Interest	Conditional display	SAC [1]
22	Safety	AE8xo	Listing of Potential Acetylcholinesterase-Inhibition Adverse Events of Special Interest	Conditional display	SAC [1]
23	Safety	AE8xo	Listing of Liver Adverse Events	Conditional display	SAC [1]
24	Safety	SAFE_L2	Listing of Clostridium Difficile Testing	Conditional display	SAC [1]
Laboratory Measurements					
25	Safety	LB5xo	Listing of All Chemistry Data for Subjects with Any Value		SAC [1]
26	Safety	LB5xo	Listing of All Chemistry Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]
27	Safety	LB5xo	Listing of All Hematology Data for Subjects with Any Value		SAC [1]
28	Safety	LB5xo	Listing of All Hematology Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
29	Safety	UR2xo	Listing of All Urinalysis Data for Subjects with Any Value		SAC [1]
30	Safety	UR2xo	Listing of All Urinalysis Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]
ECGs					
31	Safety	EG5xo	Listing of Abnormal ECG Findings		SAC [1]
32	Safety	EG5xo	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC [1]
33	Safety	HM10	Listing of Clinically Significant Holter Abnormalities		SAC [1]
34	Safety	EG3xo	Listing of ECG Values of Potential Clinical Importance		SAC [1]
35	Safety	EG3xo	Listing of ECG Change from Baseline of Potential Clinical Importance		SAC [1]
36	Safety	EG3xo	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC [1]
37	Safety	EG4	Listing of ECG Values		
Vital Signs					
38	Safety	VS4xo	Listing of Vital Signs of Potential Clinical Importance		SAC [1]
39	Safety	VS4xo	Listing of All Vital Signs for Subjects with Potential Clinical Importance Values		SAC [1]
66	Safety	VS4xo	Listing of Vital Signs Values		SAC [1]
Liver Events					
40	Safety	LIVER5	Listing of Liver Stopping Event Reporting	Conditional display	SAC [1]
41	Safety	LIVER10	Listing of Hepatobiliary Laboratory Abnormalities	Conditional display	SAC [1]
42	Safety	MH2x	Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional display	SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
43	Safety	PKCL1X	Listing of Plasma Concentration Data for Subjects with Liver Stopping Events	Conditional display	SAC [1]
44	Safety	SAFE_L3	Listing of Alcohol Intake at Onset of Liver Event	Conditional display	SAC [1]
45	Safety	SAFE_L4	Listing of Liver Biopsy Details	Conditional display	SAC [1]
46	Safety	SAFE_L5	Listing of Liver Imaging Details	Conditional display	SAC [1]

11.11.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
COVID-19					
47	Safety	PAN12	Listing of COVID-19 Assessments and Symptom Assessment		SAC [1]
Pharmacokinetics					
48	PK	PKCL1P	Listing of Gepotidacin Plasma Concentrations (ug/mL) by Cohort and Treatment	All Cohorts	SAC [1]
49	PK	PKCL1P	Listing of Cimeditine Plasma Concentrations (units)	Cohort 1 (Period 2 only)	SAC [1]
50	PK	PKCL1P	Listing of Digoxin Plasma Concentrations (units) by Treatment	Cohort 3	SAC [1]
51	PK	PKCL1P	Listing of Midazolam and 1-Hydroxymidazolam Plasma Concentrations (units) by Treatment	Cohort 3	SAC [1]
52	PK	PKUL1P	Listing of Gepotidacin Urine Concentrations (ug/mL) by Cohort and Treatment	All Cohorts	SAC [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
53	PK	PKUL1P	Listing of Digoxin Urine Concentrations (units) by Treatment	Cohort 3	SAC [1]
54	PK Parameter	PKPL1P	Listing of Gepotidacin Plasma Pharmacokinetic Parameters by Cohort and Treatment	All cohorts; Include by-variable for dose number for Cohorts 3/4	SAC [1]
55	PK Parameter	PKPL1P	Listing of Digoxin Plasma Pharmacokinetic Parameters by Treatment	Cohort 3	SAC [1]
56	PK Parameter	PKPL1P	Listing of Midazolam and 1-Hydroxymidazolam Plasma Pharmacokinetic Parameters by Treatment	By-variable for analyte; Cohort 3	SAC [1]
57	PK Parameter	PKPL1P	Listing of Gepotidacin Urine Pharmacokinetic Parameters by Cohort and Treatment	All cohorts	SAC [1]
58	PK Parameter	PKPL1P	Listing of Digoxin Urine Pharmacokinetic Parameters by Treatment	Cohort 3	SAC [1]
Biomarker					
59	PK	PKCL1P	Listing of Biomarker Concentrations (units) by Treatment	Creatinine (serum) and 1-NMN (plasma); Cohort 1; by-variable for analyte; include eGFR for predose time point	SAC [1]
60	PK	PKUL1P	Listing of Biomarker Urine Concentrations (units) by Treatment	Creatinine and 1-NMN; Cohort 1; by-variable for analyte	SAC [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
61	PK Parameter	PKPL1P	Listing of Biomarker Parameters by Treatment	Creatinine (serum) and 1-NMN (plasma); Cohort 1; by-variable for analyte	SAC [1]
62	PK Parameter	PKPL1P	Listing of Biomarker Urine Parameters by Treatment	Creatinine and 1-NMN; include creatinine-normalized parameters; Cohort 1; by-variable for analyte	SAC [1]
63	Safety	SAFE_L4	Listing of Subject Recruitment by Country and Site Number		SAC [1]
64	Safety	SU2	Listing of Substance Use		SAC [1]
65	Safety	SAFE_L1	Listing of Subjects in Previous Clinical Trial		SAC [1]

11.12. Appendix 12: Example Mock Shells for Data Displays

Data Display Specification will be made available on request

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 16-Dec-2020 14:14:39 GMT+0000

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