Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study BTZ117351: A Phase I, Multi-Center, Open-Label (Parts 1 and 2); Randomized, Double-Blind, Placebo-Controlled (Part 3); Single-Dose; 3-Part Study to Evaluate the Relative Bioavailability of Three Formulations in Healthy Subjects, Food Effect on Tablet Formulation in Healthy Subjects, and Pharmacokinetics of Gepotidacin (GSK2140944) in Japanese Subjects in Fasted and Fed States
Compound Number	:	GSK2140944
Effective Date	:	27-NOV-2017

Description:

- This RAP is amended from the original version dated 05-OCT-2016. The RAP has been updated per the changes from Protocol Amendment 2.
- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BTZ117351.
- 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) deliverable.

Author's Name and Functional Area:

PPD Ph.D.	27-NOV-2017
Biostatistician II (Biostatistics, Early Development Services, PPD)	
PPD Pharm.D.	27-NOV-2017
Pharmacokineticist (Biostatistics, Phase II-IV, PPD)	

Approved by:

PPD Ph.D.	27-NOV-2017
Director Clinical Statistics, GSK	

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS 4

2. SUMMARY OF KEY PROTOCOL INFORMATION 7
   2.1. Changes to the Protocol Defined Statistical Analysis Plan 7
   2.2. Study Objective(s) and Endpoint(s) 7
   2.3. Study Design 8
   2.4. Statistical Hypotheses 11

3. PLANNED ANALYSES 11
   3.1. Interim Analyses 11
   3.2. Final Analyses 11

4. ANALYSIS POPULATIONS 12
   4.1. Protocol Deviations 12

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS 13

6. STUDY POPULATION ANALYSES 14
   6.1. Overview of Planned Analyses 14

7. PRIMARY STATISTICAL ANALYSES 15
   7.1. Pharmacokinetic Analyses 15
      7.1.1. Overview of Planned Pharmacokinetic Analyses 15
      7.1.2. Drug Concentration Measures 15
      7.1.3. Pharmacokinetic Parameters 15
         7.1.3.1. Deriving Pharmacokinetic Parameters 15
         7.1.3.2. Statistical Analysis of Pharmacokinetic Parameters 17
      7.1.4. Interim Analysis 20
         7.1.4.1. Overview of Planned Analyses 20

8. SECONDARY STATISTICAL ANALYSES 23
   8.1. Safety Analyses 23

9. REFERENCES 24

10. APPENDICES 25
   10.1. Appendix 1: Time & Events 26
      10.1.1. Protocol Defined Time & Events 26
   10.2. Appendix 2: Treatment States and Phases 28
      10.2.1. Treatment States 28
         10.2.1.1. Treatment States for Safety Data 28
         10.2.1.2. Treatment States for AE Data 28
   10.3. Appendix 3: Data Display Standards & Handling Conventions 29
      10.3.1. Study Treatment & Sub-group Display Descriptors 29
      10.3.2. Baseline Definition & Derivations 29
         10.3.2.1. Baseline Definitions 29

10.3.2.2. Derivations and Handling of Missing Baseline Data 30
10.3.3. Reporting Process & Standards 30
10.4. Appendix 4: Derived and Transformed Data 33
10.4.1. General 33
10.4.2. Study Population 33
10.4.3. Safety 33
10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data 35
10.5.1. Premature Withdrawals 35
10.5.2. Handling of Missing Data 35
10.5.2.1. Handling of Missing Dates 35
10.5.2.2. Handling of Partial Dates 36
10.6. Appendix 6: Values of Potential Clinical Importance 37
10.6.1. ECG 37
10.6.2. Vital Signs 37
10.7. Appendix 7: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment 38
10.7.1. Laboratory Values 38
10.8. Appendix 8: Multiple Comparisons & Multiplicity 41
10.8.1. Handling of Multiple Comparisons & Multiplicity 41
10.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses. 42
10.9.1. Statistical Analysis Assumptions 42
10.10. Appendix 10 - Abbreviations & Trade Marks 43
10.10.1. Abbreviations 43
10.10.2. Trademarks 44
10.11. Appendix 11: List of Data Displays 45
10.11.1. Data Display Numbering 45
10.11.2. Mock Example Referencing 45
10.11.3. Deliverable [Priority] 45
10.11.4. Study Population Tables 46
10.11.5. Safety Tables 47
10.11.6. Pharmacokinetic Tables 48
10.11.7. Pharmacokinetic Figures 51
10.11.8. ICH Listings 53

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the Reporting and Analysis Plan
Purpose	• The purpose of this reporting and analysis plan (RAP) is to describe any planned analyses and output to be included in the clinical study report for Protocol BTZ117351.
Protocol	• This RAP is based on protocol amendment 2 (Dated: 05-SEP-2017) for study BTZ117351 [GlaxoSmithKline Document Number: 2016N281831_02.
Primary Objective	Part 1a: • Evaluate the relative bioavailability of a single 1500 mg dose of gepotidacin free base tablet formulations (related compound (RC) and high shear wet granulation (HSWG); 2 × 750 g) compared to the reference capsule formulation (3 × 500 mg). Part 1b: • Evaluate the effect of a moderate fat meal on the bioavailability of a single 1500 mg (2 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a Part 2: • Evaluate the pharmacokinetics of a single 1500 mg (2 × 750 mg) dose followed by a single 3000-mg (4 x 750 mg) does of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects Part 3: • Evaluate the pharmacokinetics of a single 1500 mg (2 × 750 mg) dose, a single 2250 mg (3 × 750 mg) dose, and a single 3000 mg (4 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state
Primary Endpoint	Parts 1a, 2 and 3: • Plasma gepotidacin AUC(0-∞), AUC(0-t), Frel (for Part 1a only), Cmax, tmax, tlag, and t1/2, as data permit. • Urine endpoints include Ae total, Ae(t1-t2), AUC(0-12), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit. Part 1b: • Plasma gepotidacin AUC(0-∞), AUC(0-t), Cmax, tmax, tlag, and t1/2, as data permit.
Secondary Objective	Part 1a: • To assess the safety and tolerability of a single 1500 mg dose of gepotidacin tablet formulations (RC and HSWG; 2 × 750 mg) compared to the reference capsule formulation (3 × 500 mg) Part 1b: • To assess the safety and tolerability of a single 1500 mg (2 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a when administered with a moderate fat meal Part 2: • To assess the safety and tolerability of a single 1500 mg (2 × 750 mg) dose

Overview	Key Elements of the Reporting and Analysis Plan
	followed by a single 3000 mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects • To assess dose proportionality following a single 1500 mg (2 × 750 mg) dose followed by a single 3000 mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects Part 3: • To assess the safety and tolerability of a single 1500 mg (2 × 750 mg) dose, a single 2250 mg (3 × 750 mg) dose, and a single 3000 mg (4 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state • To assess dose proportionality of a single 1500 mg (2 × 750 mg) dose, a single 2250 mg (3 × 750 mg) dose, and a single 3000 mg (4 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state
Secondary Endpoint	• Clinical safety data from adverse events (AEs), clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead electrocardiogram (ECG) readings. • Plasma gepotidacin AUC(0-∞) and Cmax, as data permit (for Parts 2 and 3 only)
Study Design	• This is a Phase I, multi-center, open-label, single-dose, 3-part study. Part 1a is being conducted to evaluate the relative bioavailability of 2 free base tablet formulations of gepotidacin compared to the reference capsule formulation under fasted conditions. Based upon safety and pharmacokinetic (PK) data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for Parts 1b and 2. Part 1b will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Part 2 will evaluate pharmacokinetics of 2 different doses of the formulation selected from Part 1a in Japanese subjects under fasted conditions. Part 3 will evaluate pharmacokinetics of 3 single escalating doses of the selected tablet formulation in Japanese subjects in the fed state. • Part 1a is a 3-period, cross-over study that will assess the relative bioavailability of a single 1500-mg dose of gepotidacin in 2 free base tablet formulations (2 × 750 mg RC and HSWG tablets) compared with the reference capsule formulation of Gepotidacin (3 × 500-mg capsules) under fasted conditions. Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA). • Part 1b is a 2-period, cross-over study and will evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation (selected in Part 1a). • Part 2 is a 2-period, fixed-sequence study and will evaluate the pharmacokinetics of a single dose of 1500 mg followed by a single dose of 3000 mg gepotidacin tablet formulation (RC or HSWG tablet) in a cohort of Japanese subjects under fasted conditions. A decision will be made whether to use the RC tablet formulation or the HSWG tablet formulation based upon the safety and PK data obtained from Part 1a. • Part 3 is a 3-period, randomized, double-blind, placebo-controlled, fixed-

Overview	Key Elements of the Reporting and Analysis Plan
	sequence study and will evaluate the safety tolerability, and pharmacokinetics of single ascending doses of 1500 mg, 2250 mg, and 3000 mg gepotidacin formulation selected from Part 1a or placebo in a cohort of Japanese subjects in the fed state.
Analysis Population	• Safety Population (All subjects who receive at least one dose of study drug and have at least 1 postdose safety assessment). • PK Population (All subjects who received at least 1 dose of gepotidacin and have evaluable PK data for gepotidacin). • PK Parameter Population (All subjects in the PK population for whom valid and evaluable PK parameters were derived. This population will be used in the assessment and characterization of PK parameters).
Hypothesis	• A formal hypothesis will not be tested; however, an estimation approach will be taken to characterize the relative bioavailability of the gepotidacin RC and HSWG tablet formulations relative to the reference gepotidacin capsule formulation in healthy subjects (Part 1a), estimate the effect of food on the tablet formulation selected in Part 1a (Part 1b), and to evaluate the pharmacokinetics of the tablet formulation selected in Part 1a in Japanese subjects (Parts 2 and 3).
Planned Analyses	• Safety and PK data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There was one change to the originally planned statistical analysis specified in protocol amendment 2 [Dated:05/SEP/2017]. For the fed Japanese subjects (Part 3), dose proportionality will be evaluated using a power model, in addition to dose-normalized PK parameters in the pooled analysis with Part 2.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
Part 1a • To evaluate the relative bioavailability of a single 1500-mg dose of gepotidacin free base tablet formulations (RC and HSWG; 2 × 750 mg) compared to the reference capsule formulation (3 × 500 mg)	**Part 1a** • Plasma gepotidacin AUC(0-∞), AUC(0-t), Frel, Cmax, tmax, tlag and t1/2, as data permit. • Urine endpoints include Ae total, Ae(t1-t2), AUC(0-12), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit.
Part 1b • To evaluate the effect of a moderate fat meal on the bioavailability of a single 1500-mg (2 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a	**Part 1b** • Plasma gepotidacin AUC(0-∞), AUC(0-t), Cmax, tmax, tlag, and t1/2, as data permit.
Part 2 • To evaluate the pharmacokinetics of a single 1500-mg (2 × 750 mg) dose followed by a single 3000-mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects	**Part 2** • Plasma gepotidacin AUC(0-∞), AUC(0-t), Cmax, tmax, tlag, and t1/2, as data permit. • Urine endpoints include Ae total, Ae(t1-t2), AUC(0-12), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit.
Part 3 • To evaluate the pharmacokinetics of a single 1500-mg (2 × 750 mg) dose, a single 2250-mg (3 x 750 mg) dose, and a single 3000-mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) in Japanese subjects in the fed state	**Part 3** • Plasma gepotidacin AUC(0-∞), AUC(0-t), Cmax, tmax, tlag, and t1/2, as data permit. • Urine endpoints include Ae total, Ae(t1-t2), AUC(0-12), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit.
Secondary Objectives	**Secondary Endpoints**
Part 1a • To assess the safety and tolerability of a single 1500-mg dose of gepotidacin tablet formulations (RC and HSWG; 2 × 750 mg) compared to the reference capsule formulation (3 × 500 mg)	**Parts 1a** • Clinical safety data from adverse events (AEs), clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead electrocardiogram (ECG) readings.
Part 1b • To assess the safety and tolerability of a single 1500-mg (2 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a when administered with a moderate fat meal	**Part 1b** • Clinical safety data from AEs, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings.
Part 2 • To assess the safety and tolerability of a single 1500-mg (2 × 750 mg) dose followed by a single 3000-mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects	**Part 2** • Clinical safety data from AEs, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings. • Plasma gepotidacin AUC(0-t), AUC(0-∞) and Cmax, as data permit.

Objectives	Endpoints
• To assess dose proportionality following a single 1500-mg (2 × 750 mg) dose followed by a single 3000-mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1 in Japanese subjects	
Part 3 • To assess the safety and tolerability of a single 1500-mg (2 × 750 mg) dose, a single 2250-mg (3 750 mg) dose, and a single 3000-mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state • To assess dose proportionality following a single 1500-mg (2 × 750 mg) dose, a single 2250-mg (3 x 750 mg) dose, and a single 3000-mg (4 x 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state	**Part 3** • Clinical safety data from AEs, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECG readings. • Plasma gepotidacin AUC(0-t), AUC(0-∞) and Cmax, as data permit.

2.3. Study Design

Overview of Study Design and Key Features

Part 1a Relative Bioavailability

Treatment	Cross-over						Follow-up
Capsule (reference)[a] RC and HSWG tablet[b]	Period 1	Wash-out At least 3 days	Period 2	Wash-out At least 3 days	Period 3	Wash-out At least 3 days	5 to 7 days after final dose
Sequence 1	A		B		C		
Sequence 2	C		A		B		
Sequence 3	B		C		A		

HSWG = high shear wet granulation, RC = related compound

a 1500 mg single dose given as 3 × 500 mg capsules (Treatment A; reference formulation) under fasted conditions

b 1500 mg single does given as 2 × 750 mg RC (Treatment B) or HSWG (Treatment C) tablets under fasted conditions

Part 1b (Optional) Food Effect

Treatment	Cross-over			Follow-up
RC or HSWG tablet fasted[a] RC or HSWG tablet fed[a]	Period 1	Wash-out At least 3 days	Period 2	5 to 7 days after final dose
Sequence 4	D		E	
Sequence 5	E		D	

HSWG = high shear wet granulation, RC = related compound

a 1500 mg single dose given as 2 × 750 mg tablets fasted (Treatment D) and fed (Treatment E) conditions

Overview of Study Design and Key Features

Part 2 Pharmacokinetic

Treatment	Sequence			Follow-up
RC or HSWG tablet fasted[a]	Period 1	Wash-out At least 3 days	Period 2	5 to 7 days after final dose
Sequence 6	B or C		F	

HSWG = high shear wet granulation, RC = related compound

a 1500 mg single dose given as 2 × 750-mg RC (Treatment B) or HSWG (Treatment C) tablets; 3000 mg single dose given as 4 x 750-mg RC or HSWG tablets (Treatment F), both under fasted conditions

Part 3 Pharmacokinetic – Fed State

Treatment	Sequence (EGH or III)					Follow-up
Capsule (reference)[a] RC and HSWG tablet[b]	Period 1	Wash-out At least 3 days	Period 2	Wash-out At least 3 days	Period 3	5 to 7 days after final dose
Sequence 7	E or I		G or I		H or I	

HSWG = high shear wet granulation, RC = related compound

a 1500 mg single dose given as 2 × 750-mg RC or HSWG (Treatment E) tablets – fed; 2250 mg single dose given as 3 × 750-mg RC or HSWG (Treatment G) tablets – fed; 3000 mg single dose given as 4 x 750-mg RC or HSWG (Treatment H) tablets – fed; or placebo (Treatment I) tablets - fed

Design Features

- Phase I, multi-centre, single-dose, 3-part study.
- Part 1a: Approximately 27 subjects in a 3-period, cross-over study that will assess the relative bioavailability of gepotidacin in 2 free base tablet formulations (2 × 750 mg related compound (RC) [Treatment B] and high shear wet granulation (HSWG) tablets [Treatment C]) compared with the reference capsule formulations of gepotidacin (3 × 500 mg capsules [Treatment A]) under fasted conditions. Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA). Each cohort will contain 9 subjects.
- Based upon safety and pharmacokinetic (PK) data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for Parts 1b and 2
- Part 1b: Approximately 16 subjects in a 2-period, cross-over study that will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Each cohort will contain 8 subjects.
- Part 2: Approximately 10 Japanese subjects in a 2-period, fixed-sequence study that will evaluate the pharmacokinetics of a single dose of 1500 mg (2 x 750 mg) followed by a single dose of 3000 mg (4 x 750 mg) gepotidacin tablet formulation (RC or HSWG tablet) under fasted conditions.
- Part 3: Approximately 12 Japanese subjects stratified by gender, randomized to

Overview of Study Design and Key Features	
	active or placebo in a 5:1 ratio in a 3-period, double-blind, placebo-controlled, fixed-sequence study that will evaluate the pharmacokinetics of a single dose of 1500 mg (2 x 750 mg), a single dose of 2250 mg (3 x 750 mg), and a single dose of 3000 mg (4 x 750 mg) gepotidacin tablet formulation (RC or HSWG tablet) selected from Part 1a or placebo under fed conditions.
Dosing	**Part 1a – Relative Bioavailability:** • Treatment A: Gepotidacin 1500 mg (3 × 500 mg) reference capsules • Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets • Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets **Part 1b (Optional) – Food Effect:** • Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted • Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed **Part 2: Pharmacokinetics in Japanese Subjects** • Treatment B or C: Gepotidacin 1500 mg (2 × 750 mg) RC (Treatment B) or HSWG (Treatment C) tablets selected from Part 1a – fasted • Treatment F: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted **Part 3: Pharmacokinetics in Japanese Subjects – Fed State** • Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed • Treatment G: Gepotidacin 2250 mg (3 × 750 mg) RC or HSWG tablets selected from Part 1a – fed • Treatment H: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets selected from Part 1a – fed • Treatment I: Placebo tablets – fed
Treatment Assignment	• **Part 1a – Relative Bioavailability**: On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (ABC, CAB, or BCA) to receive a single dose of gepotidacin 1500 mg (2 × 750 mg) RC tablet,1500 mg (2 × 750 mg) HSWG tablet, or 1500 mg (3 × 500 mg) reference capsule under fasted conditions in each period. • **Part 1b (Optional) – Food Effect:** On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (DE or ED) and receive a single 1500 mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted and fed conditions. • **Part 2 – Pharmacokinetics in Japanese Subjects**: On Day 1 of Period 1,

Overview of Study Design and Key Features	
	subjects will receive a single 1500 mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted conditions. On Day 1 of Period 2, subjects will receive a single 3000-mg (4 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted conditions. • **Part 3 – Pharmacokinetics in Japanese Subjects – Fed State**: On Day 1 (Period 1), subjects will be stratified by gender, randomized to active or placebo in a 5:1 ratio to receive gepotidacin tablet (RC or HSWG) selected from Part 1a in an ascending manner (Treatments E, G, and H) on Day 1 of Period 1, 2, and 3, respectively, or placebo (Treatment I). For each period, a sentinel group of up to four subjects will be dosed with study drug and evaluated for safety and tolerability prior to dosing remaining subjects.
Interim Analysis	• No formal interim analyses are planned for this study. However, all preliminary safety, tolerability, and available PK data will be reviewed by the study team after completing Part 1a of the study to select the formulation for Part 1b, Part 2, and Part 3, and also to determine if the effect of food on the selected formulation needs to be studied (Part 1b). The team will review unblinded data from Part 1a of this open-label study to select the appropriate formulation.

2.4. Statistical Hypotheses

A formal hypothesis will not be tested; however, an estimation approach will be taken to characterize the bioavailability of the gepotidacin RC and HSWG tablet formulations relative to the reference gepotidacin capsule formulation in healthy subjects (Part 1a), estimate the effect of food on the tablet formulation selected in Part 1a (Part 1b), and to evaluate the pharmacokinetics of the tablet formulation selected in Part 1a in Japanese subjects (Parts 2 and 3).

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses are planned for this study. However, all preliminary safety, tolerability, and available PK data will be reviewed by the study team after completing Part 1a of the study to select the formulation for Part 1b, Part 2, and Part 3, and also to determine if the effect of food on the selected formulation needs to be studied (Part 1b). The team will review unblinded data from Part 1a of this open-label study to select the appropriate formulation.

3.2. Final Analyses

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

1. All subjects 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.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Endpoint(s) Evaluated
Safety Population	• Will consist of all subjects who receive at least 1 dose of study drug and have at least 1 post dose safety assessment. • This population will be based on the treatment which the subject actually received.	• Study Population • Safety
PK Population	• Will consist of all subjects who received at least 1 dose of gepotidacin and have evaluable PK data for gepotidacin.	• PK Concentration
PK Parameter Population	• Will consist of all subjects in the PK Population, for whom valid and evaluable PK parameters were derived. This population will be used in the assessment and characterization of PK parameters.	• PK Parameters

NOTES:
- Please refer to Appendix 11 which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised 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 unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised 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 eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Time & Events
10.2	Appendix 2: Treatment States and Phases
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment
10.8	Appendix 8: Multiple Comparisons and Multiplicity
10.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
10.10	Appendix 10: Abbreviations & Trade Marks
10.11	Appendix 11: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Enrollment			
Number of Subjects Enrolled by Country and Site ID		Y	
Randomisation			
Randomisation			Y
Subject Disposition			
Subject Disposition		Y	
Reasons for Screening Failures		Y	Y
Reasons for Withdrawals			Y
Important Protocol Deviations		Y	Y
Inclusion and Exclusion Criteria Deviations			Y
Demography			
Demographics Characteristics		Y	Y
Study Populations			Y [1]
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)			Y
Concomitant Medication			Y

NOTES:

- Y = Yes display generated.

1. Listing of subjects excluded from any population will be generated only.

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacokinetic Analyses

7.1.1. Overview of Planned Pharmacokinetic Analyses

The PK analyses will be based on the PK Population for plasma PK concentrations, and PK Parameter Population for plasma/urine PK parameters, unless otherwise specified.

Table 3 provides an overview of the planned analyses, with full details being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Plasma PK Concentrations				Y	Y[1] [2]	Y[1]	Y					Y[1] [2]	Y[1]	
Urine PK Concentrations				Y	Y[1] [2]	Y[1]	Y					Y[1] [2]	Y[1]	
Plasma PK Parameters	Y	Y		Y			Y	Y			Y		Y	
Urine PK Parameters[3]				Y			Y				Y			

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Linear and Semi-Log plots will be created on the same display.

[2] Separate mean and median plots will be generated.

[3] Parts 1a, 2 and 3 only.

7.1.2. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 3 Reporting Process & Standards).

7.1.3. Pharmacokinetic Parameters

7.1.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 3 Reporting Process & Standards).
- The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin Version 6.2.1 or higher.

- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 4 will be determined from the plasma concentration-time data, as data permits.
- Pharmacokinetic parameters described in Table 5 will be determined from the urine concentration data, as data permits.

Table 4 Derived Plasma Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve (AUC) from time 0 (predose) to time of 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 concentration-time curve from time 0 (predose) extrapolated to infinite time, calculated as: $AUC(0-\infty) = AUC(0-t) + C(t) / \lambda z$ where C(t) is the last observed quantifiable concentration.
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: $[AUC(0-\infty) - AUC(0-t)] / AUC(0-\infty) \times 100$
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to first occurrence of Cmax
tlag	Lag time before observation of drug concentrations in sampled matrix
t½	Terminal phase half-life will be calculated as: $t_{½} = \ln 2 / \lambda z$
Frel	Relative bioavailability of drug, calculated as: $Frel = [AUC(0-\infty)_{tablet}]/[AUC(0-\infty)_{capsule}]$ (Part 1a only)
λz	Terminal-phase rate constant
DNAUC(0-t)	Dose normalized area under the concentration-time curve from time 0 (predose) to time of the last quantifiable concentration (Part 2 and Part 3 for use in the pooled analysis with Part 2), to be calculated as $DNAUC(0-t) = AUC(0-t) / Dose$
DNAUC(0-∞)	Dose normalized area under the concentration-time curve from time 0 (predose) extrapolated to infinite time (Part 2 and Part 3 for use in the pooled analysis with Part 2), calculated as: $DNAUC(0-\infty) = AUC(0-\infty) / Dose$
DNCmax	Dose normalized maximum observed concentration (Part 2 and Part 3 for use in the pooled analysis with Part 2), to be calculated as

Parameter	Parameter Description
	DNCmax = Cmax / Dose

NOTES:

- Additional parameters may be included as required.

Table 5 Derived Urine Pharmacokinetic Parameters (Parts 1a, 2, and 3 only)

Parameter	Parameter Description
Ae total	Total unchanged drug (total amount of drug excreted in urine), calculated by adding all the fractions of drug collected over all the allotted time intervals
Ae(t1-t2)	Amount of drug excreted in urine in a time intervals for predose, 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.
AUC(0-12)	Area under the urine concentration-time curve over time 0 (predose) to 12 hours after dosing. The AUC will be calculated by the linear trapezoidal rule based on the urine concentration data from each collection interval versus the corresponding urine collection interval.
AUC(0-24)	Area under the urine concentration-time curve over time 0 (predose) to 24 hours after dosing. The AUC will be calculated by the linear trapezoidal rule based on the urine concentration data from each collection interval versus the corresponding urine collection interval.
AUC(0-48)	Area under the urine concentration-time curve over time 0 (predose) to 48 hours after dosing. The AUC will be calculated by the linear trapezoidal rule based on the urine concentration data from each collection interval versus the corresponding urine collection interval.
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: CLr = Ae total/AUC(0-t)

NOTES:

- Additional parameters may be included as required.

7.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

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

Pharmacokinetic Statistical Analyses
Endpoint(s)
• Plasma primary PK endpoints include AUC(0-∞), AUC(0-t) and Cmax of gepotidacin, as data permit
Model Specification
• The log-transformed AUC(0-∞), AUC(0-t), and Cmax values for gepotidacin will be analyzed

Pharmacokinetic Statistical Analyses

separately using a mixed effects model as appropriate to the study design, fitting fixed effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% confidence intervals (CIs) for the differences of interest (RC tablets and HSWG tablets versus capsules) will be constructed using the residual variance

- In the optional food effects study in Part 1b, the log-transformed AUC(0-∞), AUC(0-t), and Cmax values for gepotidacin will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% CIs for the differences of interest (tablet formulation under fasted and fed conditions) will be constructed using the residual variance. The ratio of geometric mean and 90% CIs of ratio will be obtained by exponentiation of the point estimates and 90% CIs for the difference on the natural logarithmic scale.

- For the bioavailability assessment, Tmax will be analyzed nonparametrically using the Wilcoxon signed-rank test to compute the point estimate and 90% CI for the median difference for each comparison of interest.

- In Part 2, dose proportionality will be evaluated for the dose-normalized (DN) PK parameters for gepotidacin: DNAUC(0-∞), DNAUC(0-t), and DNCmax. An analysis of variance (ANOVA) model with log transformed DN PK parameters [DNAUC(0-∞), DNAUC(0-t), and DNCmax] as dependent variable, dose group as a fixed effect and subject as a random effect will be used to estimate the DN geometric means of each dose, and the ratio of geometric means between two doses (3000 mg vs 1500 mg) with 90% CI for Part 2 subjects alone. Additionally, subjects in Part 2 (fasted) and Part 3 (fed) will be pooled together in an exploratory analysis to assess the dose proportionality between 3000 mg and 1500 mg. There would be evidence of dose proportionality if the 90% CI for the ratio of DN geometric means lies within the limits (0.80, 1.25).

- For Parts 2 and 3, PK parameters will be summarized based on pooled data (for the doses (1500 mg and 3000 mg).

- Additionally, for Part 3, dose proportionality in the Japanese fed cohort portion of the study will be evaluated by using the power model:

$$y = \alpha \times (\text{dose})^{\beta}$$

where y denotes the PK parameter being analyzed [AUC(0-∞), AUC(0-t), and Cmax]. Dose proportionality implies that $\beta = 1$ and will be assessed by estimating β along with its 90% confidence interval. The exponent, β, in the power model will be estimated by regressing the natural log-transformed PK parameter on natural log-transformed dose.

$$\ln(y) = \ln(\alpha) + \beta * \ln(\text{dose})$$

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed with subject as a random effect, or a fixed effect power model will be fitted. The mean slope will be estimated from the power model and the corresponding 90% confidence interval calculated. Point estimates and confidence intervals for the slope will be reported to 4 decimal places with no rounding.

Pharmacokinetic Statistical Analyses

- PK parameters for all subjects will be evaluated using the Grubbs' test [Grubbs, 1950] on the natural log-transformed PK parameters by treatment. For study parts where subjects have been identified as outliers, additional analyses will be performed with outliers excluded.

Model Checking & Diagnostics

- Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Statistical analysis by analysis of variance (ANOVA) will be presented in tabular format with geometric mean ratios between RC tablets and HSWG tablets versus capsules, and 90% CIs for the ratios of AUC(0-∞) and Cmax for gepotidacin.
  Example SAS Code:

```
PROC MIXED;
CLASS USUBJID TRTA TRTSEQP APERIOD;
MODEL LOGPKPARM =TRTA TRTSEQP APERIOD /DDFM=KR;
RANDOM USUBJID(TRTSEQP);
LSMEANS TRTA;
ESTIMATE 'B VS A'   TRTA  -1  1  0/CL ALPHA=0.1;
ESTIMATE 'C VS A'   TRTA  -1  0  1/CL ALPHA=0.1;RUN;
```

- Statistical analysis by ANOVA for the optional food effect (Part 1b) will be presented in tabular format with geometric mean ratios between tablet formulation under fasted and fed conditions, and 90% CIs for the ratios of AUC(0-∞) and Cmax for gepotidacin.
  Example SAS Code:

```
PROC MIXED;
CLASS USUBJID TRTA TRTSEQP APERIOD;
MODEL LOGPKPARM =TRTA TRTSEQP APERIOD /DDFM=KR;
RANDOM USUBJID(TRTSEQP);
LSMEANS TRTA;
ESTIMATE 'E VS D'   TRTA  -1  1/CL ALPHA=0.1; RUN;
```

- Statistical analysis of Tmax will be analyzed nonparametrically using the Wilcoxon signed-rank test.
  Example SAS Code:

```
PROC UNIVARIATE DATA=PK WILCOXON;
VAR DIFF; /*DIFFERENCE OF AVAL FOR TREATMENT A-B */
CLASS TRTA;
ODS OUTPUT =PVAL;
RUN;
```

- Statistical analysis by ANOVA for Part 2 and Part 3 will be presented in tabular format with geometric mean ratios between 3000-mg and 1500-mg (Part 2 alone and Parts 2 and 3 pooled), and 90% CIs for the ratios of DNAUC(0-t), DNAUC(0-∞) and DNCmax for gepotidacin.
  Example SAS Code:

Pharmacokinetic Statistical Analyses
ODS OUTPUT LSMEANS=LSM DIFFS=PAIR; PROC MIXED DATA=PK3; CLASS USUBJID DOSE; MODEL LOGPP=DOSE/SOLUTION ALPHA=0.1 CL DDFM=KR; RANDOM SUBJECT; LSMEANS DOSE/PDIFF(CONTROL='1500 mg') ALPHA=0.1 CL; RUN; • Statistical analysis by REML for the Japanese food effect (Part 3) will be presented in tabular format to present the exponent β and 90% CI for the AUC(0-∞), AUC(0-t), and Cmax for gepotidacin in fed Japanese subjects. Example SAS Code: PROC MIXED; CLASS SUBJECT; MODEL LOGPKPARM =LOGDOSE /CL ALPHAS-0.1 SOLUTION; RUN;

7.1.4. Interim Analysis

7.1.4.1. Overview of Planned Analyses

Interim analysis is planned for Part 1a. Available PK data will be reviewed by the study team after completing Part 1a of the study to select the formulation for Part 1b, Part 2, and Part 3, and also to determine if the effect of food on the selected formulation needs to be studied (Part 1b).

Table 7 provides an overview of the planned analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Plasma concentrations of gepotidacin will be subjected to PK analyses using noncompartmental methods. Based on the individual concentration time data the following parameters will be estimated:

Table 6 Derived Plasma Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of 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.

Parameter	Parameter Description
AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time, calculated as: $AUC(0\text{-}\infty) = AUC(0\text{-}t) + C(t) / \lambda z$ where C(t) is the last observed quantifiable concentration.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to first occurrence of Cmax
tlag	Lag time before observation of drug concentrations in sampled matrix
t½	Terminal phase half-life will be calculated as: $t½ = \ln 2 / \lambda z$
Frel	Relative bioavailability of drug, calculated as: $Frel = [AUC(0\text{-}\infty)_{tablet}]/[AUC(0\text{-}\infty)_{capsule}]$ (Part 1a only)

NOTES:

- Additional parameters may be included as required.

The log-transformed AUC(0-∞), AUC(0-t), and Cmax values for gepotidacin will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect (Section 7.1.3.2).

For the bioavailability assessment, Tmax will be analyzed nonparametrically using the Wilcoxon signed-rank test to compute the point estimate and 90% CI for the median difference for each comparison of interest (Section 7.1.3.2).

Table 7 provides an overview of the planned interim analyses.

Table 7 Overview of Planned Interim Analyses

Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Plasma PK Concentrations				Y	Y[1] [2]	Y[1]	Y				Y	Y[1] [2]	Y[1]	
Urine PK Concentrations				Y	Y[1] [2]	Y[1]	Y				Y	Y[1] [2]	Y[1]	
Plasma PK Parameters	Y			Y			Y	Y			Y			
Urine PK Parameters				Y			Y				Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Linear and Semi-Log plots will be created on the same display.

[2] Separate mean and median plots will be generated.

8. SECONDARY STATISTICAL ANALYSES

8.1. Safety Analyses

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

Table 8 provides an overview of the planned safety analyses with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 8 Overview of Planned Safety Analyses

Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Extent of Exposure				Y				
Adverse Events								
All AEs	Y			Y				
All Drug-Related AEs	Y			Y				
Serious AEs	Y			Y				
Withdrawal AEs				Y				
Laboratory Values								
Clinical Chemistry				Y	Y			
Hematology				Y	Y			
Urinalysis (Dipstick)	Y			Y				
ECGs								
ECG Findings	Y			Y				
ECG Values				Y	Y			Y
Vital Signs								
Vital Signs				Y	Y			
Liver								
Liver Events [1]				Y				
Cardiovascular								
Cardiovascular [1]				Y				
Clostridium Difficile								
Clostridium difficile Testing [1]				Y				
Rash Events								
Rash Events [1]				Y				

NOTES :

1. Conditional displays, they will only be produced when an event has occurred.

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents TFL related to any displays of individual subject observed raw data.

9. REFERENCES

GlaxoSmithKline Document Numbers 2016N281831_02 (Original – 12-JUL-2016): A Phase I; Multi-Center; Open-Label (Parts 1 and 2); Randomized, Double-Blind, Placebo-Controlled (Part 3); Single-Dose, 3-Part Study to Evaluate the Relative Bioavailability of Three Formulations in Healthy Subjects, Food Effect on Tablet Formulation in Healthy Subjects, and Pharmacokinetics of Gepotidacin (GSK2140944) in Japanese Subjects in Fasted and Fed States (05-SEP-2017)

Grubbs FE. Sample Criteria for Testing Outlying Observations, Annals of Math. Statistics 1950, 21: 27-58.

10. APPENDICES

Section	Appendix
RAP Section 5: General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Time and Events
Section 10.2	Appendix 2: Treatment States & Phases
Section 10.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.4	Appendix 4: Derived and Transformed Data • General, Study Population & Safety • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.6	Appendix 6: Values of Potential Clinical Importance
Section 10.7	Appendix 7: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment
Section 10.8	Appendix 8: Multiple Comparisons and Multiplicity
Section 10.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.10	Appendix 10: Abbreviations & Trade Marks
Section 10.11	Appendix 11: List of Data Displays

10.1. Appendix 1: Time & Events

10.1.1. Protocol Defined Time & Events

Time and Events Table: Parts 1a, 1b, 2a, 2b, and 3

Procedure	Screening (up to 30 days prior to Day 1)	Part 1a - Relative Bioavailability: Periods 1, 2, and 3 Part 1b - Food Effect: Periods 1 and 2 Part 2 - Pharmacokinetics: Periods 1 and 2 Part 3 – Pharmacokinetics – Fed State: Periods 1, 2, and 3																Follow-up (5 to 7 days post-last dose)
		Day -1[a]	Day 1												Day 2		Day 3	
			Pre-dose	0h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	4 h	6 h	8 h	12 h	24 h	36 h	48 h	
Admission to Unit		X																
Informed Consent	X																	
Demographics including BMI	X																	
Full physical examination including height and weight[b]	X																	
Brief physical examination[b]		X																X
Medical/medication/drug/alcohol history	X																	
12-lead ECG[c]	X	X	X					X							X		X	X
Vital signs[d]	X	X	X					X							X		X	X
Drug/alcohol/cotinine screen	X	X																
Serum pregnancy, FSH, and estradiol (women)	X	X																X
HIV antibody, HBsAg, and hepatitis C antibody screen	X																	
Safety laboratory tests[e]	X	X															X	X
Study drug administration[f]				X														
Pharmacokinetic sampling			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine collection for pharmacokinetics (Parts 1a, 2, and 3 only)[g]			X						X		X	X	X	X	X	X	X	

Time and Events Table: Parts 1a, 1b, 2a, and 2b, cont.

Procedure	Screening (up to 30 days prior to Day 1)	Part 1a - Relative Bioavailability: Periods 1, 2, and 3 Part 1b - Food Effect: Periods 1 and 2 Part 2 - Pharmacokinetics: Periods 1 and 2																Follow-up (5 to 7 days post-last dose)
		Day -1[a]	Day 1												Day 2		Day 3	
			Pre-dose	0h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	4 h	6 h	8 h	12 h	24 h	36 h	48 h	
Pharmacogenetic sample[h]				←==========→														
AE/SAE Review	X	←==========→																X
Concomitant medication review		X		←==========→														X
Discharge[i]																	X	
Outpatient visit	X																	X

AE = adverse event, BMI = body mass index, ECG = electrocardiogram, FSH = follicle-stimulating hormone, HBsAg = hepatitis B surface antigen, HIV = human immunodeficiency virus, SAE = serious adverse event

[a] The Day -1 visit occurs in Period 1 only. Periods 2 (all parts) and 3 (Parts 1a and 3 only) begin on Day 1.

[b] A complete physical examination will include at a minimum, assessment of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded. A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen)

[c] Triplicate 12-lead ECGs will be measured in semi-supine position after 5 minutes rest and obtained at least 5 minutes apart on Day -1. Single 12-lead ECGs will be measured in semi-supine position after 5 minutes rest at all other time points during the study.

[d] Single vital signs will be measured in semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, and heart rate. Body temperature and respiratory rate will be collected at Screening only.

[e] Safety laboratory tests include serum chemistry, hematology, and urinalysis.

[f] Subjects will fast from food and drink (except water) for at least 10 hours before study drug administration on Day 1 of each period. For the fed group of the food effect evaluation in Part 1b, study drug will be administered within 30 minutes after the completion of a moderate fat meal. For Part 3, study drug will be administered within 30 minutes after completion of a standard Japanese meal.

[g] Urine collection intervals (Parts 1a, 2 and 3 only) for subjects 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.

[h] For subjects who consent only: collect 1 pharmacogenetic sample after the start of dosing (preferably Day 1). Informed consent for optional pharmacogenetic research must be obtained before collecting a sample.

[i] For Parts 1a and 3, subjects will be discharged from the clinic research unit on Day 3 of Period 3. For Parts 1b and 2, subjects will be discharged on Day 3 of Period 2.

10.2. Appendix 2: Treatment States and Phases

10.2.1. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment for the respective treatment period.

10.2.1.1. Treatment States for Safety Data

Treatment State	Definition
Pre-Treatment	Date/Time < Study Treatment Start Date/Time
On-Treatment	Study Treatment Start Date/Time ≤ Date/Time ≤ Study Treatment Stop Date/Time + 2 Days
Post-Treatment	Date/Time > Study Treatment Stop Date/Time +2 Days

NOTES:

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

10.2.1.2. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date/Time < Study Treatment Start Date/Time
On-Treatment	If AE onset date/time is on or after treatment start date/time & on or before the treatment stop date/time with 2 days lag time Study Treatment Start Date/Time ≤ AE Start Date/Time ≤ Study Treatment Stop Date/Time + 2 Days
Post-Treatment	If AE onset date/time is after the treatment stop date/time with 2 days lag time AE Start Date/Time > Study Treatment Stop Date/Time + 2 days
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.

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
Study Part	Treatment Group		Data Displays for Reporting	
	Code	Description	Description	Order [1]
1a	A	Gepotidacin 1500 mg (3 × 500 mg) reference capsules	Reference	1
1a, 2[3]	B	Gepotidacin 1500 mg (2 × 750 mg) RC tablets	RC 1500 mg	2
1a, 2[3]	C	Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets	HSWG 1500 mg	3
1b	D	Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted	RC 1500 mg Fasted or HSWG 1500 mg Fasted[2]	4
1b, 3	E	Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed	RC 1500 mg Fed or HSWG 1500 mg Fed[2]	5
2	F	Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets selected from Part 1a	RC 3000 mg or HSWG 3000 mg[2]	6
3	G	Gepotidacin 2250 mg (3 × 750 mg) RC or HSWG tablets selected from Part 1a – fed	RC 2250 mg Fed or HSWG 2250 mg Fed[2]	7
3	H	Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets selected from Part 1a – fed	RC 3000 mg Fed or HSWG 3000 mg Fed[2]	8
3	I	Placebo	Placebo	9

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.
2. The use of "RC" vs "HSWG" will be determined after study part 1a.
3. In part 2, one of Treatment B or Treatment C (determined after study part 1a) will be administered in period 1.

10.3.2. Baseline Definition & Derivations

10.3.2.1. Baseline Definitions

For all endpoints (expect as noted in the table) the baseline value will be the latest pre-dose assessment and are applicable to each period.

Table 9 Baseline Definitions

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Hematology	X	X		Day -1
Clinical Chemistry	X	X		Day -1
12 Lead ECG	X	X	X	Day 1 (Pre-dose)
Vital Signs	X	X	X	Day 1 (Pre-dose)

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

10.3.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.3.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.3.3. 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 3.1.3 & ADaM IG Version 1.0]. • For creation of ADaM datasets (ADCM/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: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables

Reporting Standards	
○ 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) 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 : ○ Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. ○ 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: ○ Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). ○ Unscheduled or unplanned readings will be presented within the subject's listings. ○ Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in figures. • 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, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 • NQs at the beginning of a subject 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 subject 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

Reporting Standards	
	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 subject 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).
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics. (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between subject coefficient of variation (CVb (%)) will be reported. CVb (%) = $\sqrt{(\exp(SD^2) - 1)} * 100$ [NOTE: SD = SD of log transformed data]
Parameters Not Being Log Transformed	Tmax, first point, last point and number of points used in the determination of λz.
Parameters Not Being Summarised	Additionally include tmax, first point, last point and number of points used in the determination of λz.
Listings	Include the first point, last point and number of points used in the determination of λz.
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.4. Appendix 4: Derived and Transformed Data

10.4.1. General

Multiple Measurements at One 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. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from randomisation date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

10.4.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date is imputed as:
  • Any subject with a missing day will have this imputed as day '15'.
  • Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**

10.4.3. Safety

ECG Parameters
RR Interval
• If ECG values are machine read and either RR interval (msec) is not provided directly, then these can be derived as : [1] If QTcB is machine read & RR is not provided, then :

ECG Parameters

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

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

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

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
- Important Note: 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 using Bazett's (QTcB) and Fredericia'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 :

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

- Important Note: Machine read values of QTcB and QTcF should not be replaced with re-derived values. If neither machine read QTcB or QTcF are available but QT and RR are collected, then a QTcB and QTcF can be derived however this should be discussed and agreed with the study team and the TLFs must have an appropriate footnote denoting those parameters are derived.

Adverse Events

AE's of Special Interest

- Liver events
- Cardiovsacular events
- Potential systemic allergic reactions
- GI events
- Acetylcholinesterase (AChE) Inhibition

10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as one who has completed all phases of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study. • All available data from subjects 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.

10.5.2. 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 :
	  • These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.5.2.1. Handling of Missing 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:
	  • Missing Start Day: First of the month will be used unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered On-treatment as per Appendix 2: Treatment States and Phases).
	  • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation

Element	Reporting Detail
	applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

10.5.2.2. Handling of Partial Dates

Element	Reporting Detail

Concomitant Medications	• Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • 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.

Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
	  • However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date.
	  • The AE will then be considered to start on-treatment (worst case).
	  • 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.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	Upper
Absolute			
Absolute QTc Interval[3]	msec	> 450[1]	
		> 450[2]	≤ 479[2]
		≥ 480[2]	≤ 499[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]	≤ 59[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.

10.6.2. Vital Signs

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

10.7. Appendix 7: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment

10.7.1. Laboratory Values

Parameter values are converted to use SI units.

HEMATOLOGY

	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	95 to 105 G/L	80 to 94 G/L	65 to 79 G/L	<65 G/L
Absolute neutrophil count	1.0 to 1.5 10^9/L	0.75 to 0.999 10^9/L	0.5 to 0.749 10^9/L	<0.5 10^9/L
Platelets	75 to 99.999 10^9/L	50 to 74.999 10^9/L	20 to 49.999 10^9/L	<20 10^9/L
White Blood Cells	11 to 13 10^9/L	13 to 15 10^9/L	15 to 30 10^9/L	>30 or <1 10^9/L
% Polymorphonuclear leukocytes + band cells	>80%	90 to 95%	>95%	N/A
Abnormal Fibrinogen	Low: 1 to 2 G/L High: 4 to 6 G/L	Low: <1 G/L High: >6 G/L	Low: <0.5 G/L High: N/A	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	0.020 to 0.040 G/L	0.041 to 0.050 G/L	0.051 to 0.060 G/L	>0.060 G/L
Prothrombin Time	1.01 to 1.25 × ULN	1.26 to 1.5 × ULN	1.51 to 3.0 × ULN	>3 × ULN
Activated Partial Thromboplastin	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 MMOL/L	123 to 129 MMOL/L	116 to 122 MMOL/L	<116 MMOL/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146 to 150 MMOL/L	151 to 157 MMOL/L	158 to 165 MMOL/L	>165 MMOL/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 to 3.4 MMOL/L	2.5 to 2.9 MMOL/L	2.0 to 2.4 MMOL/L or intensive replacement therapy of hospitalization required	<2.0 MMOL/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia

	Grade 1	Grade 2	Grade 3	Grade 4
Hyperkalemia	5.6 to 6.0 MMOL/L	6.1 to 6.5 MMOL/L	6.6 to 7.0 MMOL/L	>7.0 MMOL/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	3.0 to 3.55 MMOL/L	2.22 to 2.99 MMOL/L	1.67 to 2.21 MMOL/L	<1.67 MMOL/L or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	6.44 to 8.88 MMOL/L	8.89 to 13.88 MMOL/L	13.89 to 27.75 MMOL/L	>27.76 MMOL/L or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	2.10 to 1.95 MMOL/L	1.94 to 1.75 MMOL/L	1.74 to 1.52 MMOL/L	<1.52 MMOL/L or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	2.64 to 2.87 MMOL/L	2.88 to 3.12	3.13 to 3.37 MMOL/L	>3.37 MMOL/L or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	0.7 to 0.6 MMOL/L	0.59 to 0.45 MMOL/L	0.44 to 0.3 MMOL/L	<0.3 MMOL/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	0.7 to 0.8 MMOL/L	0.5 to 0.6 MMOL/L or replacement Rx required	0.3 to 0.4 MMOL/L intensive therapy or hospitalization required	<0.3 MMOL/L 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)	446 to 595 UMOL/L	596 to 714 UMOL/L	715 to 892 UMOL/L	>892 UMOL/L
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.

	Grade 1	Grade 2	Grade 3	Grade 4
ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Aspartate aminotransferase	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alanine aminotransferase	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	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.

10.8. Appendix 8: Multiple Comparisons & Multiplicity

10.8.1. Handling of Multiple Comparisons & Multiplicity

No adjustments for multiplicity will be made.

10.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

10.9.1. Statistical Analysis Assumptions

Endpoint(s)	• PK endpoints AUC(0-∞), AUC(0-t) and Cmax
Analysis	• Mixed Effects

Assumptions:

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data.
- 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.

10.10. Appendix 10 - Abbreviations & Trade Marks

10.10.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
Ae total	Total unchanged drug (total amount of drug excreted in urine)
Ae(t1-t2)	Amount of drug excreted in urine in a time interval
ANOVA	Analysis of variance
AUC(0-∞)	Area under the concentration-time curve from time zero (predose) extrapolated to infinite time
AUC(0-12)	Area under the urine concentration-time curve over time 0 (predose) to 12 hours after dosing.
AUC(0-24)	Area under the urine concentration-time curve over time 0 (predose) to 48 hours after dosing.
AUC(0-48)	Area under the urine concentration-time curve over time 0 (predose) to 48 hours after dosing.
AUC(0-t)	Area under the concentration-time curve from time zero (predose) to time of the last quantifiable concentration
BMI	Body mass index
CI	Confidence Interval
Cmax	Maximum observed concentration
CLr	Renal clearance of drug
CV	Coefficient of variance
DNAUC(0-t)	Dose normalized area under the concentration-time curve from time 0 (predose) to time of the last quantifiable concentration
DNAUC(0-∞)	Dose normalized area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
DNCmax	Dose normalized maximum observed concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
fe%	Percentage of the given dose of drug excreted in urine
Frel	Relative bioavailability of drug
GSK	GlaxoSmithKline
hrs	Hours
HSWG	High shear wet granulation
IDSL	Integrated Data Standards Library
λz	Terminal phase rate constant
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
msec	Milliseconds
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation
PK	Pharmacokinetic

RAP	Reporting and Analysis Plan
RC	Related compound
SAE	Serious Adverse Event(s)
SAS	Statistical Analysis Software
SD	Standard Deviation
t½	Terminal half-life
tlag	Lag time before observation of drug concentrations in sampled matrix
Tmax	Time to first occurrence of Cmax

10.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

10.11. Appendix 11: List of Data Displays

10.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.8	
Safety	2.1 to 2.12	
Pharmacokinetic	3.1 to 3.12	3.1 to 3.7.2
Section	**Listings**	
ICH Listings	1 to 44	

10.11.2. Mock Example Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 11.

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 / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.11.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
IA [X]	Interim Analysis
SAC [X]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

10.11.4. 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	Safety	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC [1]
1.2	Safety	ES1	Summary of Subject Disposition		SAC [1]
1.3	Screened	ES6	Summary of Reasons for Screening Failures		SAC [1]
1.4	Screened	DV1	Summary of Important Protocol Deviations		SAC [1]
Demographics and Baseline Characteristics					
1.5	Safety	DM3	Summary of Demographic Characteristics		SAC [1]
1.6	Safety	DM5	Summary of Race and Racial Combinations		SAC [1]
1.7	Safety	DM6	Summary of Race and Racial Combinations Details		SAC [1]
1.8	Safety	DM11	Summary of Age Ranges		SAC [1]

10.11.5. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1	Safety	AE1	Summary of All Adverse Events		IA [1], SAC [1]
2.2	Safety	AE1	Summary of All Drug- Related Adverse Events		IA [1], SAC [1]
2.3	Safety	AE15	Summary of Common (>=25%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		IA [1], SAC [1]
2.4	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		IA [1], SAC [1]
Laboratory Measurements					
2.5	Safety	LB1	Summary of Clinical Chemistry Change from Baseline		SAC [1]
2.6	Safety	LB1	Summary of Haematology Change from Baseline		SAC [1]
2.7	Safety	UR3b	Summary of Urinalysis Dipstick Results		SAC [1]
Electrocardiograms					
2.8	Safety	EG1	Summary of ECG Findings		SAC [1]
2.9	Safety	SAFE_T1	Summary of Frequency of Maximum Post-Dose ECG Parameter Corrected QTc Interval		SAC [1]
2.10	Safety	SAFE_T2	Summary of Frequency of Maximum Change from Baseline for ECG Parameter Corrected QTc Interval		SAC [1]
2.11	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC [1]
Vital Signs					
2.12	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC [1]

10.11.6. Pharmacokinetic Tables

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1.1	PK	PK01	Summary of Plasma Gepotidacin Pharmacokinetic Concentration (ng/mL) - Time Data		IA [1], SAC [1]
3.1.2	PK	PK01	Summary of Plasma Gepotidacin Pharmacokinetic Concentration (ng/mL) - Time Data – Excluding Outliers	exclude outliers	SAC [1]
3.2	PK	PK01	Summary of Urine Gepotidacin Pharmacokinetic Concentration (ug/mL) - Time Data		SAC [1]
PK Derived Parameters					
3.3.1	PK	PKPT1	Summary Statistics of Derived Plasma Gepotidacin Pharmacokinetic Parameters	Parameters with units	IA [1], SAC [1]
3.3.2	PK	PKPT1	Summary Statistics of Derived Plasma Gepotidacin Pharmacokinetic Parameters – Excluding Outliers	Parameters with units, exclude outliers	SAC [1]
3.3.3	PK	PKPT1	Summary Statistics of Pooled Derived Plasma Gepotidacin Pharmacokinetic Parameters – Part 2 and 3	Parameters with units	SAC [1]
3.3.4	PK	PKPT1	Summary Statistics of Pooled Derived Plasma Gepotidacin Pharmacokinetic Parameters – Part 2 and 3 Excluding Outliers	Parameters with units, exclude outliers	SAC [1]
3.4	PK	PKPT1	Summary Statistics of Derived Urine Gepotidacin Pharmacokinetic Parameters	Parameters with units	SAC [1]

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.5.1	PK	PKPT4	Summary Statistics of Log-Transformed Derived Plasma Gepotidacin Pharmacokinetic Parameters	Parameters with units	IA [1], SAC [1]
3.5.2	PK	PKPT4	Summary Statistics of Log-Transformed Derived Plasma Gepotidacin Pharmacokinetic Parameters – Excluding Outliers	Parameters with units, exclude outliers	SAC [1]
3.5.3	PK	PKPT4	Summary Statistics of Log-Transformed Pooled Derived Plasma Gepotidacin Pharmacokinetic Parameters – Part 2 and 3	Parameters with units	SAC [1]
3.5.4	PK	PKPT4	Summary Statistics of Log-Transformed Pooled Derived Plasma Gepotidacin Pharmacokinetic Parameters – Part 2 and 3 Excluding Outliers	Parameters with units, exclude outliers	SAC [1]
3.6	PK	PKPT4	Summary Statistics of Log-Transformed Derived Urine Gepotidacin Pharmacokinetic Parameters	Parameters with units	SAC [1]
PK Analysis Tables					
3.7	PK Parameter	PKPT3	Analysis of Plasma Gepotidacin Pharmacokinetic Parameters by Treatment	AUC(0-t), AUC(0-∞), Cmax only log-transformed	IA [1], SAC [1]
3.8	PK Parameter	PK_T1	Statistical Analysis of Plasma Gepotidacin Tmax by Treatment	Tmax Wilcox signed-rank test by group	IA [1], SAC [1]
3.9.1	PK Parameter	PKPT3	Analysis of Dose-Normalized Plasma Gepotidacin Pharmacokinetic Parameters for Fasted Japanese Subjects	DNAUC(0-t), DNAUC(0-∞), DNCmax only log-transformed by Treatment. Part 2 only.	SAC [1]
3.9.2	PK Parameter	PKPT3	Analysis of Dose-Normalized Plasma Gepotidacin Pharmacokinetic Parameters for Fasted Japanese Subjects – Excluding Outliers	DNAUC(0-t), DNAUC(0-∞), DNCmax only log-transformed by Treatment. Part 2 only, exclude outliers	SAC [1]

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.3	PK Parameter	PKPT3	Analysis of Dose-Normalized Plasma Gepotidacin Pharmacokinetic Parameters for Pooled Japanese Subjects	DNAUC(0-t), DNAUC(0-∞), DNCmax only log-transformed by Treatment. Pooled Part 2 and 3 only	SAC [1]
3.9.4	PK Parameter	PKPT3	Analysis of Dose-Normalized Plasma Gepotidacin Pharmacokinetic Parameters for Pooled Japanese Subjects – Excluding Outliers	DNAUC(0-t), DNAUC(0-∞), DNCmax only log-transformed by Treatment. Pooled Part 2 and 3 only, exclude outliers	SAC [1]
3.10	PK Parameter	PKPT3	Analysis of Dose Proportionality of Plasma Gepotidacin Pharmacokinetic Parameters for Fed Japanese Subjects	AUC(0-t), AUC(0-∞), Cmax only log-transformed by Treatment. Part 3 only.	SAC [1]
3.11	PK Parameter	PK_T2	Outliers Identified Using Grubbs' Test on Gepotidacin Plasma Pharmacokinetic Parameters	AUC(0-t), AUC(0-∞), Cmax	SAC [1]

10.11.7. Pharmacokinetic Figures

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1	PK	PKCF1P	Individual Plasma Gepotidacin Concentration-Time Plots by Subject (Linear and Semi-Log)	Paginate by Subject	IA [1], SAC [1]
3.2	PK	PKCF1P	Individual Urine Gepotidacin Concentration-Time Plots by Subject (Linear and Semi-Log)	Paginate by Subject	IA [1], SAC [1]
Mean / Median Concentration Plots					
3.3.1	PK	PKCF2	Mean Plasma Gepotidacin Concentration-Time Plots by Treatment (Linear and Semi-log)	All treatments for each Part on one page	IA [1], SAC [1]
3.3.2	PK	PKCF2	Mean Plasma Gepotidacin Concentration-Time Plots by Treatment – Excluding Outliers (Linear and Semi-log)	All treatments for each Part on one page	SAC [1]
3.4	PK	PKCF2	Mean Urine Gepotidacin Concentration-Time Plots by Treatment (Linear and Semi-log)	All treatments for each Part on one page	SAC [1]
3.5.1	PK	PKCF3	Median Plasma Gepotidacin Concentration-Time Plots by Treatment (Linear and Semi-log)	All treatments for each Part on one page	IA [1], SAC [1]
3.5.2	PK	PKCF3	Median Plasma Gepotidacin Concentration-Time Plots by Treatment – Excluding Outliers (Linear and Semi-log)	All treatments for each Part on one page	SAC [1]
3.6	PK	PKCF3	Median Urine Gepotidacin Concentration-Time Plots by Treatment (Linear and Semi-log)	All treatments for each Part on one page	SAC [1]

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.7.1	PK	PKPF3	Individual and Box plot of Dose-Normalized Gepotidacin Plasma Pharmacokinetic Parameters by Treatment	Present PK parameters for each dose level Pages: Part 2 (2 doses) in one page, Part 3 (3 doses) in one page, and Part 2 and 3 in one page (Part 2 1500 mg, Part 3 1500 mg, Part 2 3000 mg, and Part 3 3000 mg)	SAC [1]
3.7.2	PK	PKPF3	Individual and Box plot of Dose-Normalized Gepotidacin Plasma Pharmacokinetic Parameters by Treatment – Excluding Outliers	Present PK parameters for each dose level Pages: Part 2 (2 doses) in one page, Part 3 (3 doses) in one page, and Part 2 and 3 in one page (Part 2 1500 mg, Part 3 1500 mg, Part 2 3000 mg, and Part 3 3000 mg)	SAC [1]
3.7.3	PK	PKPF3	Individual and Box plot of Pooled Dose-Normalized Gepotidacin Plasma Pharmacokinetic Parameters by Treatment – Part 2 and 3	Present PK parameters for each dose level Pages: Pooled Part 2 and 3 DN parameters	SAC [1]
3.7.4	PK	PKPF3	Individual and Box plot of Pooled Dose-Normalized Gepotidacin Plasma Pharmacokinetic Parameters by Treatment – Part 2 and 3 Excluding Outliers	Present PK parameters for each dose level Pages: Pooled Part 2 and 3 DN parameters	SAC [1]

10.11.8. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomisation					
1	Safety	CP_TA1	Listing of Randomised and Actual Treatment		SAC [1]
Subject Disposition					
2	Safety	ES3	Listing of Reasons for Study Withdrawal		SAC [1]
3	Screened	ES7	Listing of Reasons for Screening Failure		SAC [1]
4	Screened	DV2	Listing of Important Protocol Deviations		SAC [1]
5	Safety	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC [1]
6	Safety	SP3	Listing of Subjects Excluded from Any Population		SAC [1]
Demographics					
7	Safety	DM4	Listing of Demographic Characteristics	Include height, weight and BMI	SAC [1]
8	Safety	DM10	Listing of Race		SAC [1]
Medical Conditions and Concomitant Medications					
9	Safety	MH3	Listing of Medical Conditions		SAC [1]
10	Safety	CM4	Listing of Concomitant Medications		SAC [1]
Exposure					
11	Safety	SAFE_L1	Listing of Exposure Data		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Safety					
12	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC[1]
13	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC [1]
14	Safety	SAFE_L2	Listing of All Adverse Events		IA[1], SAC [1]
15	Safety	AE9CP	Listing of Study Drug Related Adverse Events		SAC [1]
16	Safety	AE9CP	Listing of Serious Adverse Events		SAC [1]
17	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study		SAC [1]
18	Safety	SAFE_L3	Listing of Liver Adverse Events	Conditional display	SAC [1]
19	Safety	SAFE_L4	Listing of Cardiovascular Adverse Events	Conditional display	SAC [1]
20	Safety	SAFE_L5	Listing of Allergic Reaction Adverse Events	Conditional display	SAC [1]
21	Safety	SAFE_L6	Listing of Clostridium Difficile Testing	Conditional display	SAC [1]
22	Safety	SAFE_L7	Listing of Rash Events	Conditional display	SAC [1]
Laboratory Measurements					
23	Safety	LB6	Listing of Clinical Chemistry Toxicities of Grade 3 or Higher		SAC [1]
24	Safety	LB6	Listing of All Clinical Chemistry Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]
25	Safety	LB6	Listing of Haematology Toxicities of Grade 3 or Higher		SAC [1]
26	Safety	LB6	Listing of All Haematology Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]
27	Safety	UR2b	Listing of Urinalysis Toxicities of Grade 3 or Higher		SAC [1]
28	Safety	UR2b	Listing of All Urinalysis 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]**
ECGs					
29	Safety	EG6	Listing of Abnormal ECG Findings		SAC [1]
30	Safety	EG6	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC [1]
31	Safety	EG4	Listing of ECG Values of Potential Clinical Importance		SAC [1]
32	Safety	EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC [1]
33	Safety	SAFE_L8	Listing of ECG Change from Baseline of Potential Clinical Importance		SAC [1]
Vital Signs					
34	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance		SAC [1]
35	Safety	VS5	Listing of All Vital Signs for Subjects with Potential Clinical Importance Values		SAC [1]
Liver Events					
36	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Conditional display	SAC [1]
37	Safety	MH3	Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional display	SAC [1]
38	Safety	SAFE_L10	Listing of Alcohol Intake at Onset of Liver Event	Conditional display	SAC [1]
39	Safety	PKCL1X	Listing of Plasma Concentration Data for Subjects with Liver Stopping Events	Conditional display	SAC [1]
40	Safety	LIVER7	Listing of Liver Biopsy Details	Conditional display	SAC [1]
41	Safety	LIVER8	Listing of Liver Imaging Details	Conditional display	SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic					
42	PK	PKCL1X	Listing of Plasma Gepotidacin Concentrations (ng/mL) by Treatment	Please list all the concentration data including unscheduled. Repeat for all treatments and Part 2 if needed.	SAC [1]
43	PK	PKCL1X	Listing of Urine Gepotidacin Concentrations (ug/mL) by Treatment	Please list all the concentration data including unscheduled.	SAC [1]
44	PK Parameter	PKPL1P	Listing of Gepotidacin Plasma Pharmacokinetic Parameters by Treatment	Additional parameters include Frel (units) (B and C only), t½ (units) and tlag (units). Repeat for Treatment B and C. Repeat for Treatments D and E if needed.	SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
45	PK Parameter	PKPL1P	Listing of Gepotidacin Urine Pharmacokinetic Parameters by Treatment	Additional parameters include Ae(0-2) (units), Ae(2-4) (units), Ae(4-6) units), Ae(6-8) (units), Ae(8-12) (units), Ae(12-24) (units), Ae(24-36) (units), Ae(36-48) (units), AUC(0-12) (units), AUC(0-24) (units), AUC(0-48) (units). Repeat for Treatments B and C.	SAC [1]