Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for A Phase I, Open-Label, Single-Dose, Two-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function
Compound Number	:	GSK2140944
Effective Date	:	29-JUN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BTZ117352.
- 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 Clinical Study Report for Protocol BTZ117352

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Listings for hypersensitivity AEs will be included where an event has occurred	• Such listings will not be produced regardless of event occurrence	• Tracking of hypersensitivity AEs is not necessary for this compound.

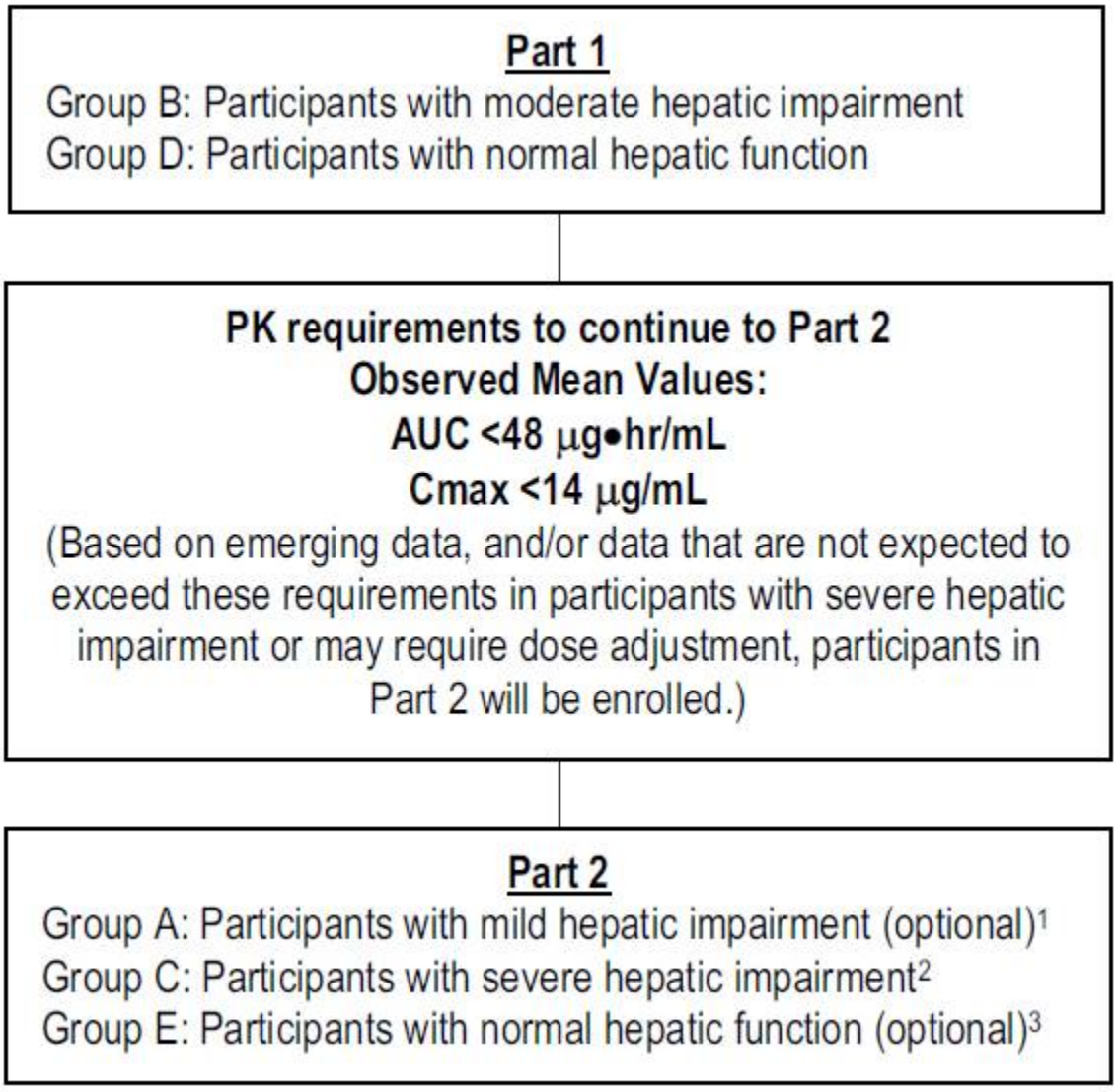
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare the plasma PK parameters of a 1500 mg oral dose of gepotidacin in normal healthy participants to participants with mild, moderate, and severe hepatic impairment	• Plasma gepotidacin AUC(0-∞) and Cmax, as data permit.
Secondary Objectives	**Secondary Endpoints**
• To assess the safety and tolerability of gepotidacin administered as a 1500 mg oral dose in normal healthy participants compared with participants with mild, moderate, and severe hepatic impairment • To compare the secondary plasma PK parameters of 1500 mg oral dose of gepotidacin in normal healthy participants with participants with mild, moderate, and severe hepatic impairment • To compare the urine PK parameters of a 1500 mg oral dose of gepotidacin in normal healthy participants with participants with	• 12-lead safety ECG readings, change from baseline in vital sign measurements (blood pressure and heart rate), monitoring of AEs, toxicity grading of clinical laboratory test results, and physical examinations • Plasma gepotidacin AUC(0-t), Tmax, tlag, CL/F, Vz/F, λz, and t1/2, as data permit • Urine gepotidacin PK endpoints: ○ Primary: Ae total, fe %, and CLr, as data permit ○ Secondary: Ae(t1-t2), AUC(0-12), AUC(0-24), and AUC(0-48), as data permit

Objectives	Endpoints
mild, moderate, and severe hepatic impairment	
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the saliva PK parameters of a 1500 mg oral dose of gepotidacin in normal healthy participants compared with participants with mild, moderate, and severe hepatic impairment	• Saliva gepotidacin PK endpoints: ○ Primary: AUC(0-∞) and Cmax, as data permit ○ Secondary: AUC(0-t), Tmax, λz, t1/2, CL/F, Vz/F, and saliva to unbound plasma AUC(0-t) and AUC(0-∞) ratios (RAUC) of gepotidacin, as data permit.

2.3. Study Design

Overview of Study Design and Key Features



1. Based on emergent data from Part 1, particpants with mild hepatic impairment (Group A) may not be enrolled in Part 2 if there is not a significant difference between participants with moderate hepatic impairment and participants with normal hepatic function.
2. If AUC and/or Cmax are predicted to exceed the threshold, the dose may be adjusted for participants with severe hepatic impairment (Group C). Due to the potential difficulty in identifying eligible participants with severe hepatic impairment, the sponsor may stop the study prior to full enrollment in Part 2 provided that a minimum of 6 evaluable participants with severe hepatic impairment have been enrolled.
3. Based on emergent data from Part 1, matching participants with normal hepatic function in Part 2 (Group E) may be enrolled (e.g. if a change in dose is needed or if the demographic data of the mild and/or severe hepatic impairment groups is not well matched to the moderate control data [Group D]).

Overview of Study Design and Key Features	
Design Features	• Phase I, nonrandomized, open-label, parallel-group, multi-center, two-Part study. • **Part 1**: Approximately 16 participants, 8 with moderate hepatic impairment (Group B) and 8 matched controls with normal hepatic function (Group D) will receive a single 1500 mg oral dose of gepotidacin. Controls will be matched on gender distribution, age (approximately ± 10 years), and BMI (approximately ± 20%). • **Part 2**: Approximately 8 to 32 participants will receive a single oral dose of gepotidacin. The dose is expected to be 1500 mg, but may be adjusted for participants with severe hepatic impairment if AUC and/or Cmax are predicted to exceed the threshold. Based on emergent data from Part 1, particpants with mild hepatic impairment (Group A) may not be enrolled in Part 2 if there is not a significant difference between participants with moderate hepatic impairment and participants with normal hepatic function. Due to the potential difficulty in identifying eligible participants with severe hepatic impairment, the sponsor may stop the study prior to full enrollment in Part 2 provided that a minimum of 6 evaluable participants with severe hepatic impairment have been enrolled. Based on emergent data from Part 1, matching participants with normal hepatic function in Part 2 (Group E) may be enrolled (e.g. if a change in dose is needed or if the demographic data of the mild and/or severe hepatic impairment groups is not well matched to the moderate control data [Group D]).
Dosing	• Participants will receive a single 1500 mg oral dose of gepotidacin delivered as two 750 mg tablets. The dose may be adjusted in Part 2 for participants with severe hepatic impairment if AUC and/or Cmax are predicted to exceed the threshold, based on emergent data from Part 1.
Time and Events	• See Appendix 1: Schedule of Activities
Treatment Assignment	• At Screening, participants will be enrolled to the appropriate groups based on the classification as defined in the Food and Drug Administration (FDA) Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [DHHS, 2003]. Participants with hepatic impairment will be classified using the Child-Pugh system. For more details, see Section 7.3 of the protocol.
Interim Analysis	• Formal interim analyses of the primary and secondary PK endpoints, will be conducted following completion of Part 1 of the study; with possible progression to Part 2 based on the following criteria: ○ Participants with mild hepatic impairment may be enrolled in Part 2 if there is a significant difference in pharmacokinetics between participants with moderate hepatic impairment compared with participants with normal hepatic function. ○ Participants with severe hepatic impairment will be enrolled in Part 2 provided that the PK requirements are met (observed mean values in participants with moderate impairment do not exceed the threshold:

Overview of Study Design and Key Features	
	AUC < 48 µg•hr/mL and Cmax < 14 µg/mL). The dose may be adjusted for participants with severe hepatic impairment if either PK parameter is predicted to exceed the threshold. • No formal interim analyses of the safety endpoints will be done, but GSK will review the safety data from Part 1 prior to proceeding to Part 2.

2.4. Statistical Analyses

An estimation approach will be taken to characterize the PK of gepotidacin in subjects with mild, moderate, and severe hepatic impairment compared with matched subjects with normal hepatic function.

3. PLANNED ANALYSES

3.1. Interim Analyses

Formal interim analyses of the primary and secondary PK endpoints (as detailed in Section 7.1 and Section 7.2 of this document) will be conducted following completion of Part 1 of the study; with possible progression to Part 2 based on the following criteria:

- Participants with mild hepatic impairment may be enrolled in Part 2 if there is a significant difference in pharmacokinetics between participants with moderate hepatic impairment compared with participants with normal hepatic function.
- Participants with severe hepatic impairment will be enrolled in Part 2 provided that the PK requirements are met (observed mean values in participants with moderate impairment do not exceed the threshold: AUC < 48 µg•hr/mL and Cmax < 14 µg/mL). The dose may be adjusted for participants with severe hepatic impairment if either PK parameter is predicted to exceed the threshold.

No formal interim analyses of the safety endpoints will be done, but GSK will review the safety data from Part 1 prior to proceeding to Part 2.

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.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Safety	• Consists of all subjects who receive at least 1 dose of study drug and have at least one postdose safety assessment.	• Study Population • Safety
PK Population	• Consists of all subjects who received at least 1 dose of gepotidacin and have evaluable PK data for gepotidacin. A subject is considered to have evaluable PK data for gepotidacin if the subject has at least 1 measurable post-dose PK concentration value for gepotidacin that was not excluded from the analysis due to a protocol deviation.	• PK Concentration
PK Parameter	• 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 parameter • PK statistical analysis

NOTES:

- Please refer to Appendix 8: List of Data Displays 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 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. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions[1]				
Study Part	Hepatic Impairment Group		Data Displays for Reporting	
	Code	Description	Description	Order[2]
1, 2	D, E[3]	Normal Hepatic Function	Normal	1
1	B	Moderate Hepatic Impairment	Moderate	3
2	A[4]	Mild Hepatic Impairment (optional)	Mild	2
2	C[5]	Severe Hepatic Impairment	Severe	4

NOTES:

1. Only groups that are present in the data will actually be presented.
2. Order represents treatments being presented in TFL, as appropriate.
3. Based on emergent data from Part 1, matching participants with normal hepatic function in Part 2 (Group E) may be enrolled (e.g., if a change in dose is needed or if the demographic data of the mild and/or severe hepatic impairment groups is not well matched to the moderate control data [Group D]). If there is no change in dose, then these two groups will be combined for presentation in the outputs.
4. Based on emergent data from Part 1, participants with mild hepatic impairment (Group A) may not be enrolled in Part 2 if there is not a significant difference between participants with moderate hepatic impairment and participants with normal hepatic function.
5. If AUC and/or Cmax are predicted to exceed the threshold, the dose may be adjusted for participants with severe hepatic impairment (Group C). Due to the potential difficulty in identifying eligible participants with severe hepatic impairment, the sponsor may stop the study prior to full enrollment in Part 2 provided that a minimum of 6 evaluable participants with severe hepatic impairment have been enrolled.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the last available assessment prior to time of study drug administration, unless noted otherwise.

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.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. 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
10.2	Appendix 2: Study Phases and Treatment Emergent Adverse Events
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Reporting Standards for Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 8: 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 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Standards for Pharmacokinetic). Only total gepotidacin plasma PK concentrations will be measured and reported. Therefore, unbound plasma PK concentrations will be derived by multiplying the total plasma PK concentrations by 0.67, to correct for the low plasma protein binding of gepotidacin (33%) observed in previous studies.

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. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time, calculated as: $AUC = AUC(0\text{-}t) + C(t) / \lambda z$ where C(t) is the last quantifiable concentration
Cmax	Maximum observed concentration, determined directly from the concentration-time data

NOTES:

- Additional parameters may be included as required.
- For the derivation of unbound plasma PK parameters; the total plasma PK parameters AUC(0-∞), and Cmax will be multiplied by 0.67, to correct for the low plasma protein binding of gepotidacin (33%) observed in previous studies.

7.1.2. Summary Measure

Area under concentration-time curve (AUC[0-∞]) and Cmax following single doses of gepotidacin in subjects with normal hepatic function and hepatically impaired subjects.

7.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the PK population for plasma PK concentrations and the PK parameter population for plasma PK parameters and statistical analysis, unless otherwise specified.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.1.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.4.1. Statistical Methodology Specification

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

Endpoint / Variables
• Plasma primary pharmacokinetic (PK) endpoints include AUC(0-∞) and Cmax of gepotidacin, as data permit.
Model Specification
• The plasma ln-transformed AUC(0-∞) and Cmax values for gepotidacin in the hepatic impairment groups and the normal hepatic function group will be compared using an analysis of variance (ANOVA).
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.
Model Results Presentation
• Statistical analysis by ANOVA will be presented in tabular format with geometric mean ratios between hepatic impairment groups and normal hepatic function group, and 90% CIs for the ratios of AUC(0-∞) and Cmax for gepotidacin.

7.2. Secondary Pharmacokinetic Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 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. All calculations of non-compartmental parameters will be based on actual sampling times.

Plasma pharmacokinetic parameters listed below will be determined from the total plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
Tmax	Time to first occurrence of Cmax
tlag	Lag time before observation of drug concentrations in sampled matrix
t½	Terminal half-life will be calculated as: t½ = ln2 / λz
λz	Terminal-phase rate constant
CL/F	The apparent oral clearance, calculated as: CL/F = Dose / AUC(0-∞)
Vz/F	The apparent volume of distribution during the terminal phase, calculated as: Vz/F = CL / λz

NOTES:

- Additional parameters may be included as required.
- For the derivation of unbound plasma PK parameters; the total plasma PK parameters AUC(0-t) will be multiplied by 0.67, and the total plasma PK parameter CL/F will be divided by 0.67, to correct for the low plasma protein binding of gepotidacin (33%) observed in previous studies.

Pharmacokinetic parameters listed will be determined from the urine concentration-time data, as data permits.

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 time intervals for predose, 0 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 hours after dosing for subjects with hepatic impairment; and 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 for subjects with normal hepatic function; calculated by multiplication of the urine concentration for a time interval and the length of this time interval.
AUC(0-t)	Area under the urine concentration-time curve over t hours where t = 12, 24, and 48 hours. The AUC(0-t) 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) where AUC(0-t) is the area under the plasma concentration-time curve over all the allotted time intervals of urine collections.

NOTES:

- Additional parameters may be included as required.

7.2.2. Summary Measure

Area under concentration-time curve (AUC[0-48]) and CLr following single doses of gepotidacin in subjects with normal hepatic function and hepatically impaired subjects.

7.2.3. Population of Interest

The secondary pharmacokinetic 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 and statistical analysis, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.4.1. Statistical Methodology Specification

Endpoint / Variables
• Plasma secondary PK endpoints include AUC(0-t), Tmax, tlag, CL/F, λz, and t1/2, as data permit. • Urine primary PK endpoints include AUC(0-48) and CLr of gepotidacin, as data permit. Urine secondary PK endpoints include Ae(t1-t2), AUC(0-12), AUC(0-24), and AUC(0-48) of gepotidacin, as data permit
Model Specification
• The plasma Tmax will be analyzed non-parametrically using the Mann Whitney U test (Wilcoxon rank sum test). The point estimates and 90% CI for the median differences will be derived for hepatic impairment and healthy participants based on Hodges-Lehmann estimation. • The urine ln-transformed AUC(0-48) and non-transformed CLr values for gepotidacin in the hepatic impairment groups and the normal hepatic function group will be compared using an analysis of variance (ANOVA).
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.
Model Results Presentation
• The point estimates and 90% confidence intervals for the median differences in plasma Tmax will be calculated for the cohort difference (hepatically impaired – healthy participants). • Statistical analysis by ANOVA will be presented in tabular format with geometric mean ratios between hepatic impairment groups and normal hepatic function group, and 90% CIs for the ratios of AUC(0-48) for gepotidacin. For non-transformed CLr for gepotidacin, least squares mean difference between hepatic impairment groups and normal hepatic function group, and 90% CIs for the difference will be presented.

7.3. Exploratory Pharmacokinetic Analyses

7.3.1. Endpoint / Variables

7.3.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 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. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the saliva concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of 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: $AUC(0\text{-}\infty) = AUC(0\text{-}t) + C(t) / \lambda z$
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to first occurrence of Cmax
t1/2	Terminal phase half-life will be calculated as: $t_{½} = \ln 2 / \lambda z$
λz	Terminal-phase rate constant
CL/F	The apparent oral clearance, calculated as: $CL/F = Dose / AUC(0\text{-}\infty)$
Vz/F	The apparent volume of distribution during the terminal phase, calculated as: $Vz/F = CL / \lambda z$
RAUC(0-t)	The ratio of the AUC(0-t) observed in saliva relative to the unbound AUC(0-t) in plasma, calculated as: RAUC(0-t) = AUC(0-t) saliva / AUC(0-t) plasma
RAUC(0-∞)	The ratio of the AUC(0-∞) observed in saliva relative to the unbound AUC(0-∞) in plasma, calculated as: RAUC(0-∞) = AUC(0-∞) saliva / AUC(0-∞) plasma

NOTES:

- Additional parameters may be included as required.
- Since plasma protein binding of gepotidacin is low (33%), only total plasma drug concentrations and total plasma PK parameters will be reported for the plasma PK analysis. However, to derive the saliva to unbound plasma AUC(0-t) and AUC(0-∞) ratios, a correction factor of 0.67 will be applied to the total plasma AUCs of gepotidacin to derive the unbound plasma AUCs.

7.3.2. Summary Measure

Area under concentration-time curve (AUC[0-∞]) and Cmax following single doses of gepotidacin in subjects with normal hepatic function and hepatically impaired subjects.

7.3.3. Population of Interest

The primary pharmacokinetic analyses will be based on the PK population for saliva PK concentrations and the PK parameter population for saliva PK parameters and statistical analysis, unless otherwise specified.

7.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.3.1 will be summarized using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.4.1. Statistical Methodology Specification

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

Endpoints
• Saliva exploratory pharmacokinetic (PK) endpoints include AUC(0-∞), Cmax, and Tmax of gepotidacin, as data permit.
Model Specification
• The plasma ln-transformed AUC(0-∞) and Cmax values for gepotidacin in the hepatic impairment groups and the normal hepatic function group will be compared using an analysis of variance (ANOVA). • Saliva Tmax will be analyzed non-parametrically using the Mann Whitney U test (Wilcoxon rank sum test). The point estimates and 90% CI for the median differences will be derived for hepatic impairment and healthy participants based on Hodges-Lehmann estimation.
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.
Model Results Presentation
• Statistical analysis by ANOVA will be presented in tabular format with geometric mean ratios between hepatic impairment groups and normal hepatic function group, and 90% CIs for the ratios of AUC(0-∞), Cmax, and AUC(0-48) for gepotidacin. • Scatter plots of natural ln-transformed saliva gepotidacin concentrations versus the natural ln-transformed unbound and total plasma gepotidacin concentrations will be plotted and a regression line will be fitted. • Scatter plots of natural ln-transformed saliva gepotidacin PK parameters versus the natural

ln-transformed unbound and total plasma gepotidacin PK parameters will also be performed for the AUC(0-∞), AUC(0-t), Cmax, CL/F, and t1/2.

- The point estimates and 90% confidence intervals for the median differences in Tmax will be calculated for the cohort difference (hepatically impaired – healthy participants).

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 8: List of Data Displays.

8.2. Adverse Events of Special Interest Analyses

Liver monitoring/stopping events and cardiovascular events will be considered AEs of Special Interest (AESIs). AESIs are flagged in the eCRF and details of events are collected on special eCRF pages. The details of the planned displays are provided in Appendix 8: List of Data Displays.

8.3. 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. DMID grading will be applied for all subjects, regardless of hepatic impairment. The details of the planned displays are in Appendix 8: List of Data Displays.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 8: List of Data Displays.

9. REFERENCES

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May 2003. [19 screens]. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf

GlaxoSmithKline Document Number 2017N352027_00 (Original – 15-FEB-2018): A Phase I, Open-Label, Single-Dose, Two-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function (15-FEB-2018)

10. APPENDICES

10.1. Appendix 1: Schedule of Activities

10.1.1. Protocol Defined Time and Events Table

Procedure[1]	Screening (up to 30 days prior to Day -1)	Check-in	Treatment Period (Days)			Follow-up (10 [±5] days postdose) or Early Termination	Notes
		–1	1	2	3		
Confined to clinic		X	X	X	X		Participants will be admitted to the clinic on Day –1 and will be discharged on Day 3. Confinement will be 4 days and 3 overnight stays
Informed consent	X						
Inclusion and exclusion criteria	X	X					Recheck clinical status before enrollment and/or study drug administration
Demographics	X						
Complete physical examination including height and weight	X						
Abbreviated physical examination		X			X	X	
Medical history (includes substance usage and history of hepatic disease)	X						Substances: drugs, alcohol, and caffeine. Participants with hepatic impairment should be on a stable regimen of chronic medications 7 days before study drug administration on Day 1
Past and current medical conditions (including hepatic impairment medical history, Child-Pugh score, and Clcr)	X						Child-Pugh as defined in the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function [DHHS 2003]
Pregnancy test	X	X				X	Urine (or serum) pregnancy test (if WOCBP), as appropriate (see Protocol, Table 5)

Procedure[1]	Screening (up to 30 days prior to Day -1)	Check-in	Treatment Period (Days)			Follow-up (10 [±5] days postdose) or Early Termination	Notes
		–1	1	2	3		
FSH	X						Estradiol and FSH at Screening (for women of non-childbearing potential), as appropriate (see Protocol, Table 5)
HIV antibody, hepatitis B surface antigen, and hepatitis C antibody testing	X						If test has otherwise been performed within 3 months before study drug administration, testing at Screening is not required
Drug and alcohol screen	X	X					See Protocol, Table 5
Laboratory assessments (include liver chemistries)	X	X		X		X	Including serum chemistry, hematology, and urinalysis. Results from 24 hours after dosing should be available before discharge on Day 3
12-lead ECG	X	X	X	X	X	X	See Section 10.1.2 for timing of assessments
Vital signs	X	X	X	X	X	X	Respiratory rate and body temperature collected at Screening only See Section 10.1.2 for timing of assessments
Genetic sample		X					Informed consent for optional substudies (e.g., genetics research) must be obtained before collecting a PGx sample. The PGx sample can be collected anytime, but Day −1 is recommended
Study drug administration			X				
Blood collection for pharmacokinetics			X	X	X		See Section 10.1.2 for time points

Procedure[1]	Screening (up to 30 days prior to Day -1)	Check-in	Treatment Period (Days)			Follow-up (10 [±5] days postdose) or Early Termination	Notes
		–1	1	2	3		
Urine collection for pharmacokinetics			X	X	X		Participants with normal hepatic function and participants with hepatic impairment will have different collection intervals See Section 10.1.2 for time points
Saliva collection for pharmacokinetics			X	X	X		See Section 10.1.2 for time points
AE/SAE review	X	X	←==========→			X	
Concomitant medication review		X	←==========→			X	

AE = adverse event, Clcr = estimated creatinine clearance; ECG = electrocardiogram, FDA = Food and Drug Administration; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; PGx = pharmacogenetic, SAE = serious AE; WOCBP = women of childbearing potential.

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

10.1.2. Protocol Defined Safety and PK Assessments

Procedure[1]		Treatment Period Time point (hours)													
	Predose	0	0.5	1	1.5	2	2.5	3	4	6	8	12	24[2]	36[2]	48[2]
12-lead electrocardiogram	X				X	X			X		X	X	X	X	X
Vital signs	X				X	X			X		X	X	X	X	X
Study drug administration		X													
Blood collection for pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for pharmacokinetics (participants with normal hepatic function)[3]	X	X				X			X	X	X	X	X	X	X
Urine collection for pharmacokinetics (participants with hepatic impairment)[4]	X	X								X		X	X	X	X
Saliva collection	X		X	X	X	X	X	X	X	X	X	X	X	X	X

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

2 The 24-, 36-, and 48-hour postdose time points correspond to time points on Day 2 and 3, respectively.

3 Urine collection intervals for participants with normal hepatic function (Group D and Group E, if applicable) 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.

4 Urine collection intervals for participants with hepatic impairment (Group A, Group B, and Group C) include 0 hour (pre-dose), 0 to 6 hours, 6 to 12 hours, 12 to 24 hours, 24 to 36, and 36 to 48 hours.

10.2. Appendix 2: Study Phases and Treatment Emergent Adverse Events

10.2.1. Study Phases

For Groups A, B, C, D, and E, assessments and events will be classified according to time of occurrence relative to the date/time of the study treatment.

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

10.2.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before enrollment date
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 5: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.2.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date/time is on or after treatment date/time & on or before the treatment stop date/time with 2 days lag time. • Study Treatment Date/Time ≤ AE Start Date/Time ≤ Study Treatment Date/Time + 2 days.

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Reporting Process

Software
• SAS version 9.3 or higher and WinNonlin version software (version 9.3) and WinNonlin version 6.4 or higher will be used.
Analysis Datasets
• Analysis datasets will be created according CDISC standards SDTM IG Version 3.2 & ADaM IG Version 1.0. • For creation of ADaM datasets (ADCM/ADCM1/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.

10.3.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• All data will be reported according to the actual treatment the participant 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, unless otherwise stated. • 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 (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.
  • 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 (mean figures only for PK concentrations), summaries and statistical analyses (excluding statistical analyses of PK parameters).

Unscheduled Visits	
• Unscheduled visits will be considered when calculating baseline and in Table 2.9 and Table 2.10, but will not be included in any other 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, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.3.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	

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	
Descriptive Summary Statistics, Graphical Displays and Listings	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of Ln-Transformed data)
Parameters Not Being Ln-Transformed	Tmax, tlag, CLr, lambda_z_lower, lambda_z_upper, and lambda_z_no. of points.
Parameters Not Being Summarized	lambda_z_lower, lambda_z_upper, and lambda_z_no. of points.
Listings	Include the first point, last point and number of points used in the determination of λz and Rsq_adjusted for listings.

10.4. Appendix 4: Derived and Transformed Data

10.4.1. 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. • 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. • Participants 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 date of study drug administration (Dose Date):
  • 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

10.4.2. 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 PPD • 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 RR interval (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.

ECG Parameters
• 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 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: $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$

10.5. Appendix 5: Reporting Standards for Missing Data

10.5.1. 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.

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: 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 clinical study report.

10.5.2.1. 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 study treatment; in this case the study treatment date will be used and hence the event is considered Treatment Emergent as per Appendix 2: Study Phases and Treatment Emergent Adverse Events. o Missing Stop Day: Last day of the month will be used, unless this is more than 2 days after the date of study treatment; in this case the study treatment date 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.

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	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	msec	≤ 30[2]	
	msec	> 30[1]	≤ 59[2]
	msec	≥ 60[2]	

NOTES:

1. Represent standard ECG values of PCI for HV studies.
2. Represent further subdivisions of ECG values for analysis.

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: Abbreviations & Trade Marks

10.7.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
Ae(t1-t2)	Amount of drug excreted in urine in a time intervals
Ae total	Total unchanged drug (total amount of drug excreted in urine)
AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of last quantifiable concentration
AUC(0-12)	Partial area under the curve estimated from urine concentrations samples collected from predose to 12 hours post dose
AUC(0-24)	Partial area under the curve estimated from urine concentrations samples collected from predose to 24 hours post dose
AUC(0-48)	Partial area under the curve estimated from urine concentrations samples collected from predose to 48 hours post dose
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL/F	Apparent oral clearance
CLr	Renal clearance of drug
Cmax	Maximum observed concentration
CVb	Coefficient of Variation (Between subjects)
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
fe%	Percentage of the given dose of drug excreted in urine
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
PCI	Potential Clinical Importance
PK	Pharmacokinetic(s)
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAUC(0-t)	The ratio of the AUC(0-t) observed in saliva relative to the AUC(0-t) in plasma
RAUC(0-∞)	The ratio of the AUC(0-∞) observed in saliva relative to the AUC(0-∞) in plasma
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
t1/2	Terminal phase half life

Abbreviation	Description
λz	Terminal-phase rate constant
TFL	Tables, Figures & Listings
tlag	Lag time before observation of drug concentrations in sampled matrix
Tmax	Time to first occurrence of Cmax
Vz/F	Apparent volume of distribution of the terminal phase

10.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

10.8. Appendix 8: List of Data Displays

10.8.1. 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 2.12	NA
Pharmacokinetic	3.1 to 3.11	3.1 to 3.11
Section	**Listings**	
ICH Listings	1 to 40	
Other Listings	41 to 46	

10.8.2. 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.'

10.8.3. Deliverables

Delivery	Description
IA	Interim Analysis (Part 1)
SAC	Final Statistical Analysis Complete

10.8.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition and Populations					
1.1.	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC
1.2.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
1.4.	Screened	DV1	Summary of Important Protocol Deviations		SAC
Demographics					
1.5.	Safety	DM1	Summary of Demographic Characteristics		SAC
1.6.	Safety	DM5	Summary of Race and Racial Combinations		SAC
1.7.	Safety	DM6	Summary of Race and Racial Combinations Details		SAC
1.8.	Safety	DM11	Summary of Age Ranges		SAC
1.9.	Safety	POP_T1	Summary of Child-Pugh Scores		SAC
Medical Conditions and Concomitant Medications					
1.10.	Safety	MH4	Summary of Current Liver Disease and Cardiovascular Related Medical Conditions		SAC

10.8.5. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
2.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term		SAC
2.2.	Safety	AE1	Summary of Drug-Related Adverse Events		SAC
2.3.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.4.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
Laboratory Values					
2.5.	Safety	LB1	Summary of Clinical Chemistry Values Change from Baseline		SAC
2.6.	Safety	LB1	Summary of Hematology Values Change from Baseline		SAC
2.7.	Safety	UR3	Summary of Urinalysis Dipstick Results		SAC
Electrocardiograms					
2.8.	Safety	EG1	Summary of ECG Findings		SAC
2.9.	Safety	SAFE_T1	Summary of Frequency of Maximum Post-Dose ECG Parameter Corrected QTc Interval		SAC
2.10.	Safety	SAFE_T2	Summary of Frequency of Maximum Change from Baseline for ECG Parameter Corrected QTc Interval		SAC
2.11.	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC
Vital Signs					
2.12.	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC

10.8.6. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK Concentration Data					
3.1	PK Concentration	PKCT1	Summary of Gepotidacin Plasma Pharmacokinetic Concentration-Time Data (units) by Hepatic Function Group		IA, SAC
3.2	PK Concentration	PKCT1	Summary of Gepotidacin Urine Pharmacokinetic Concentration-Time Data (units) by Hepatic Function Group		IA, SAC
3.3	PK Concentration	PKCT1	Summary of Gepotidacin Saliva Pharmacokinetic Concentration-Time Data (units) by Hepatic Function Group		IA, SAC
PK Parameters Tables					
3.4	PK Parameter	PKPT4	Summary of Derived Gepotidacin Plasma Pharmacokinetic Parameters by Hepatic Function Group	Parameters with units. If Group E are enrolled in part 2, then include a page of part 1 (Group B and D) alone in SAC deliverable as a reference for part 1 IA.	IA, SAC
3.5	PK Parameter	PKPT4	Summary of Derived Gepotidacin Urine Pharmacokinetic Parameters by Hepatic Function Group	Parameters with units.	IA, SAC
3.6	PK Parameter	PKPT4	Summary of Derived Gepotidacin Saliva Pharmacokinetic Parameters by Hepatic Function Group	Parameters with units.	IA, SAC

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK Analysis Tables					
3.7	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Plasma Pharmacokinetic Parameters: Analysis of Variance (ANOVA)	AUC(0-∞) and Cmax only by Hepatic Function Group. If Group E are enrolled in part 2, then include a page of part 1 (Group B and D) alone in SAC deliverable as a reference for part 1 IA.	IA, SAC
3.8	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Urine Pharmacokinetic Parameters: Analysis of Variance (ANOVA)	AUC(0-48) and CLr only by Hepatic Function Group.	IA, SAC
3.9	PK Parameter	PKPT3	Statistical Analysis of Gepotidacin Saliva Pharmacokinetic Parameters: Analysis of Variance (ANOVA)	AUC(0-∞) and Cmax only by Hepatic Function Group.	IA, SAC
3.10	PK Parameter	PK T1	Statistical Analysis of Gepotidacin Plasma Tmax		IA, SAC
3.11	PK Parameter	PK T1	Statistical Analysis of Gepotidacin Saliva Tmax		IA, SAC

10.8.7. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Concentration Plots					
3.1	PK Concentration	PKCF1P	Individual Gepotidacin Plasma Concentration-Time Plots by Hepatic Function Group (Linear and Semi-Logarithmic)	Dashed line represents the LLQ. Present all hepatic function groups in the same plots.	IA, SAC
3.2	PK Concentration	PKCF1P	Individual Gepotidacin Urine Concentration-Time Plots by Hepatic Function Group (Linear and Semi- Logarithmic)	Dashed line represents the LLQ. Present all hepatic function groups in the same plots. Plot concentration at the collection midpoint.	IA, SAC
3.3	PK Concentration	PKCF1P	Individual Gepotidacin Saliva Concentration-Time Plots by Hepatic Function Group (Linear and Semi- Logarithmic)	Dashed line represents the LLQ. Present all hepatic function groups in the same plots.	IA, SAC
3.4	PK Concentration	PKCF2	Mean Gepotidacin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	IA, SAC
3.5	PK Concentration	PKCF2	Mean Gepotidacin Urine Concentration-Time Plots (Linear and Semi-Logarithmic)	Dashed line represents the LLQ. Present all treatment groups in the same plots. Plot concentration at the collection midpoint.	IA, SAC
3.6	PK Concentration	PKCF2	Mean Gepotidacin Saliva Concentration-Time Plots (Linear and Semi-Logarithmic)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	IA, SAC

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.7	PK Concentration	PKCF3	Median Gepotidacin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	IA, SAC
3.8	PK Concentration	PKCF3	Median Gepotidacin Urine Concentration-Time Plots (Linear and Semi-Logarithmic)	Dashed line represents the LLQ. Present all treatment groups in the same plots. Plot concentration at the collection midpoint.	IA, SAC
3.9	PK Concentration	PKCF3	Median Gepotidacin Saliva Concentration-Time Plots (Linear and Semi-Logarithmic)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	IA, SAC
Exploratory Objectives					
3.10	PK Concentration	PK_F4	Scatter Plot of Gepotidacin Saliva and Unbound Plasma Concentrations by Hepatic Function Group	Present all treatment groups in the same plots.	IA, SAC
3.11	PK Parameter	PK_F5	Scatter Plot of Gepotidacin Saliva and Unbound Plasma PK Parameters by Hepatic Function Group	Present all treatment groups in the same plots. Repeat for PK parameters AUC(0-t), AUC(0-inf), Cmax, CL/F and t½.	IA, SAC
3.12	PK Concentration	PK_F4	Scatter Plot of Gepotidacin Saliva and Total Plasma Concentrations by Hepatic Function Group	Present all treatment groups in the same plots.	IA, SAC
3.13	PK Parameter	PK_F5	Scatter Plot of Gepotidacin Saliva and Total Plasma PK Parameters by Hepatic Function Group	Present all treatment groups in the same plots. Repeat for PK parameters AUC(0-t), AUC(0-inf), Cmax, CL/F and t½.	IA, SAC

10.8.8. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Group Assignment					
1.	Safety	TA1	Listing of Planned and Actual Group		SAC
Subject Disposition					
2.	Safety	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	Screened	ES7	Listing of Reasons for Screen Failure		SAC
4.	Screened	DV2	Listing of Important Protocol Deviations		SAC
5.	Safety	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
6.	Enrolled	SP3	Listing of Subjects Excluded from Any Population		SAC
7.	Safety	SAFE_L1	Listing of Subjects in Previous Clinical Trial		SAC
Demographics and Baseline Characteristics					
8.	Safety	DM4	Listing of Demographic Characteristics		SAC
9.	Safety	DM10	Listing of Race		SAC
10.	Safety	SAFE_L2	Listing of Child-Pugh Scores		SAC
Concomitant Medications					
11.	Safety	MH2	Listing of Cardiovascular and Liver Disease Related Medical Conditions		SAC
12.	Safety	CM3	Listing of Concomitant Medications		SAC
Exposure					
13.	Safety	SAFE_L3	Listing of Exposure Data		SAC

ICH : Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
14.	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC
15.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
16.	Safety	AE8	Listing of All Adverse Events		SAC
17.	Safety	AE8	Listing of Study Drug Related Adverse Events		SAC
18.	Safety	SAFE_L4	Listing of Serious Adverse Events (Fatal and Non-Fatal)		SAC
19.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study		SAC
20.	Safety	SAFE_L5	Listing of Liver Adverse Events	Conditional Display	SAC
21.	Safety	SAFE_L6	Listing of Cardiovascular Adverse Events	Conditional Display	SAC
Laboratory Values					
22.	Safety	SAFE_L7	Listing of Clostridium Difficile Testing		SAC
23.	Safety	LB5	Listing of Clinical Chemistry Toxicities of Grade 3 or Higher		SAC
24.	Safety	LB5	Listing of All Clinical Chemistry Data for Subjects with Toxicities of Grade 3 or Higher		SAC
25.	Safety	LB5	Listing of Hematology Toxicities of Grade 3 or Higher		SAC
26.	Safety	LB5	Listing of All Hematology Data for Subjects with Toxicities of Grade 3 or Higher		SAC
27.	Safety	UR2a	Listing of Urinalysis Toxicities of Grade 3 or Higher		SAC
28.	Safety	UR2a	Listing of All Urinalysis Data for Subjects with Toxicities of Grade 3 or Higher		SAC

ICH : Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Electrocardiograms					
29.	Safety	EG5	Listing of Abnormal ECG Findings		SAC
30.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC
31.	Safety	EG3	Listing of ECG Values of Potential Clinical Importance		SAC
32.	Safety	EG3	Listing of All ECG Values for Subjects with any Value of Potential Clinical Importance		SAC
Vital Signs					
33.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance		SAC
34.	Safety	VS4	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC
Liver Event					
35.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Conditional Display	SAC
36.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional Display	SAC
37.	Safety	SAFE_L8	Listing of Alcohol Intake at Onset of Liver Event	Conditional Display	SAC
38.	Safety	PKCL1X	Listing of Plasma Concentration Data for Subjects with Liver Stopping Events	Conditional Display	SAC
39.	Safety	LIVER7	Listing of Liver Biopsy Details	Conditional Display	SAC
40.	Safety	LIVER8	Listing of Liver Imaging Details	Conditional Display	SAC

10.8.9. Non-ICH Listings

Other (non-ICH) : Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic					
41.	PK Concentration	PKCL1P	Listing of Plasma Gepotidacin Concentrations (units) by Hepatic Function Group	Please list all the concentration data including unscheduled. Repeat for all Hepatic Function Groups.	IA, SAC
42.	PK Concentration	PKUL1P	Urine Gepotidacin Concentrations by Hepatic Function	Please list all the concentration data including unscheduled. Repeat for all Hepatic Function Groups.	IA, SAC
43.	PK Concentration	PKCL1X	Saliva Gepotidacin Concentrations by Hepatic Function	Please list all the concentration data including unscheduled. Repeat for all Hepatic Function Groups.	IA, SAC
44.	PK Parameter	PKPL1P	Listing of Gepotidacin Plasma Pharmacokinetic Parameters by Treatment		IA, SAC
45.	PK Parameter	PKPL1P	Listing of Gepotidacin Urine Pharmacokinetic Parameters by Treatment		IA, SAC
46.	PK Parameter	PKPL1P	Listing of Gepotidacin Saliva Pharmacokinetic Parameters by Treatment		IA, SAC