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

Title	:	Reporting and Analysis Plan for A Phase I, Open-Label, Single-Dose, Multi-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Subjects with Varying Degrees of Renal Impairment and in Matched Control Subjects with Normal Renal Function
Compound Number	:	GSK2140944
Effective Date	:	02-SEP-2016

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BTZ116849.
- 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:

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
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 BTZ116849.
Protocol	• This RAP is based on the original protocol (Dated: 01-MAR-2016) of study BTZ116849 (GSK Document No. : 2014N209329_00).
Primary Objective	• To compare the pharmacokinetics of gepotidacin administered as a 750 mg IV dose in normal healthy subjects compared with subjects with mild, moderate, and severe renal impairment, and with subjects with end stage renal disease (ESRD).
Primary Endpoint	• Plasma primary PK endpoints include AUC(0-∞) and Cmax of gepotidacin, as data permit • Urine primary PK end points include Ae total, fe%, and CLr of gepotidacin, as data permit • Dialysate primary PK end points include AUC(t0-t1), CL_D, and Frem%(0-4), of gepotidacin, as data permit
Study Design	• This is a Phase I, nonrandomized, open-label, parallel-group, multi-center, multi-part study that will evaluate the pharmacokinetics, safety, and tolerability of a single IV dose of gepotidacin 750 mg over 2 hours in subjects with normal renal function; subjects with mild, moderate, and severe renal impairment; and subjects with end-stage renal disease (ESRD; on dialysis and not on dialysis).
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.
Analysis Populations	• Safety Population – defined as all subjects who receive at least 1 dose of study drug and have at least one postdose safety assessment. • Pharmacokinetic Population - defined as all subjects who received at least 1 dose of gepotidacin and have evaluable PK data for gepotidacin. • Pharmacokinetic Parameter Population - defined as 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 PK of gepotidacin in subjects with mild, moderate, severe renal impairment and in subjects with ESRD (on dialysis and not on dialysis) compared with matched subjects with normal renal function.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

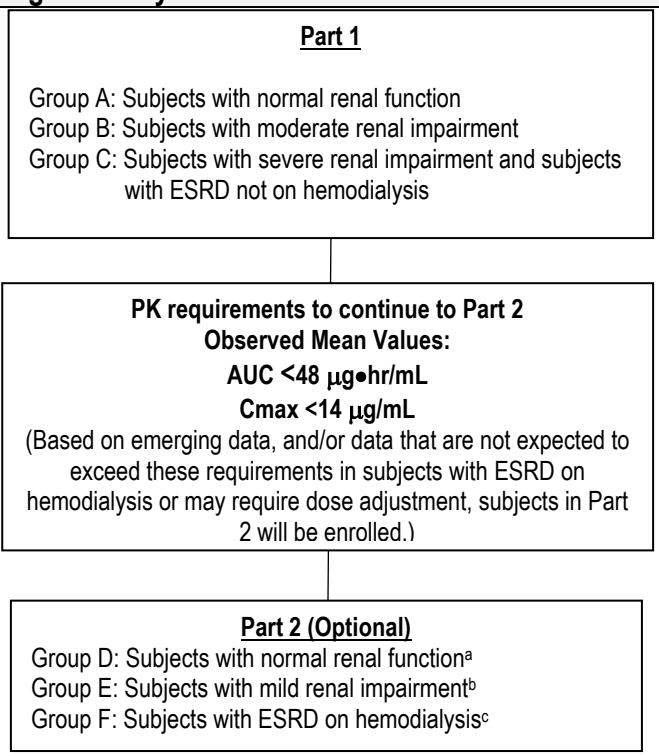
There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 01-MAR-2016).

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare the PK of gepotidacin administered as a 750 mg IV dose in normal healthy subjects compared with subjects with mild, moderate, and severe renal impairment, and with subjects with ESRD.	• Plasma primary PK endpoints include AUC(0-∞) and Cmax of gepotidacin, as data permit • Urine primary PK end points include Ae total, AUC(t0-t1), fe%, and CLr of gepotidacin, as data permit • Dialysate primary PK end points include AUC(t0-t1), CL_D, and Frem%(0-4), of gepotidacin, as data permit
Secondary Objectives	**Secondary Endpoints**
• To assess the safety and tolerability of gepotidacin administered as a 750-mg IV dose in normal healthy subjects compared with subjects with mild, moderate, severe renal impairment, and with subjects with ESRD	• 12-lead safety electrocardiogram readings, change from baseline in vital sign measurements (blood pressure and heart rate), monitoring of adverse events, toxicity grading of clinical laboratory test results, and physical examinations
• To evaluate the secondary PK parameters of gepotidacin administered as a 750-mg IV dose in normal healthy subjects compared with subjects with mild, moderate, and severe renal impairment, and with subjects with ESRD	• Plasma PK endpoints include AUC(0-t), CL, λz, t1/2, Tmax, Vss, and Vz, as data permit • Urine PK endpoint includes Ae(t1-t2) and AUC(0-t) as data permit • Dialysate PK endpoints include Arem(0-1), Arem(1-2), Arem(2-3), Arem(3-4), and Arem(0-4), as data permit
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the saliva pharmacokinetics of gepotidacin (subjects in Part 1 only).	• Primary saliva PK endpoints include AUC(0-∞) and Cmax of gepotidacin, as data permit • Secondary saliva PK endpoints include AUC(0-t), CL, λz, t1/2, Tmax, Vss, Vz, RAUC(0-t) and RAUC(0-∞) as data permit

2.3. Study Design

Overview of Study Design and Key Features



ESRD = end-stage renal disease; PK = pharmacokinetic

[a] If there are a sufficient number of subjects with normal renal function enrolled in Part 1 (Group A), a determination will be made regarding enrollment of matching subjects with normal renal function in Part 2 (Group D).

[b] Based on emerging data from Part 1, Group E (subjects with mild renal impairment) may not be enrolled in Part 2 if there is not a significant difference between subjects with moderate and severe impairment compared to subjects with normal renal function or if the PK can be accurately predicted.

[c] If AUC and/or Cmax is predicted to exceed the threshold, the dose may be adjusted in Group F (optional).

Design Features	• This will be a multi-part study, in which PK requirements must be met (observed mean values: AUC <48 μg•hr/mL and Cmax <14 μg/mL); and safety and tolerability will be reviewed before enrolling subjects into the next part of the study. In Part 1, subjects with normal renal function; subjects with moderate renal impairment; and subjects with severe renal impairment and subjects with ESRD not on hemodialysis will be enrolled. In Part 2 (optional), subjects with normal renal function, subjects with mild renal impairment, and subjects with ESRD on hemodialysis will be enrolled based on the PK, safety, tolerability, and data results of Part 1. • Subjects in Groups A, B, C, D, and E will enter the clinic at Check-in (Day - 1, Period 1) before study drug administration (Day 1, Period 1). In Parts 1 and 2, on Day 1 (Period 1), subjects in Group A, B, C, D, and E will receive a single dose of study drug as follows: gepotidacin 750 mg administered as a 2-hour IV infusion. All subjects will be discharged from the clinic on Day 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up Visit approximately 10 days (±5 days) after dose administration. The duration of the study (from Screening to the Follow-up

Overview of Study Design and Key Features	
	Visit) will be approximately 44 days. • In Part 2 (optional) of the study, subjects in Group F will participate in 2 treatment periods, with dosing in these periods separated by a washout period of at least 7 days. Subjects in Group F will enter the clinic at Check-in (Day –1, Period 1 and Day 7, Period 2) before each study drug administration (Day 1, Period 1 and Day 8, Period 2). On Day 1 (Period 1) and Day 8 (Period 2), subjects in Group F will receive a single dose of study drug as follows: gepotidacin 750 mg administered as a 2-hour IV infusion starting approximately 2 hours before the initiation of the last hemodialysis session of the week (Period 1) and gepotidacin 750 mg administered as a 2-hour IV infusion starting within 2 hours after completion of the last hemodialysis session of the week (Period 2). Subjects in Group F will be discharged from the clinic on Day 10, Period 2 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up Visit approximately 10 days (±5 days) after the last dose administration in Period 2. The duration of the study (from Screening to the Follow-up Visit) will be approximately 50 days.
Dosing	• All subjects in Group A, B, C, D, and E will receive a single dose of study drug as follows: gepotidacin 750 mg administered as a 2 hour IV infusion. • All subjects in Group F will receive a single dose of study drug as follows: gepotidacin 750 mg administered as a 2 hour IV infusion starting approximately 2 hours before the initiation of the last hemodialysis session of the week (Period 1) and gepotidacin 750 mg administered as a 2 hour IV infusion starting within 2 hours after completion of the last hemodialysis session of the week (Period 2).

Treatment Assignment	• Subjects will be enrolled into groups based on the classification as defined in the United States Food and Drug Administration draft guidance for industry, "Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling" [DHHS, 2010]
	• Subjects with normal renal function and subjects with renal impairment will be classified based on the estimated glomerular filtration rate (eGFR; based on the Modification of Diet in Renal Disease Study). Subjects with normal renal function will also be classified based on estimated creatinine clearance (Clcr).
	  • Group A - normal renal function (eGFR ≥90 mL/min/1.73m^2)
	  • Group B - moderate renal impairment (eGFR 30 to 59 mL/min/1.73m^2)
	  • Group C - ESRD not on hemodialysis (eGFR <30 mL/min/1.73m^2)
	  • Group D - normal renal function (eGFR ≥90 mL/min/1.73m^2)
	  • Group E - mild renal impairment (eGFR 60 to 89 mL/min/1.73m^2)
	  • Group F - ESRD on hemodialysis

Interim Analysis	• No formal interim analyses are planned for this study. However, all preliminary safety, tolerability, and available PK data will be reviewed internally at GSK after the approximate sample size has been reached in Part 1 and Part 2 (optional). • PK requirements must be met (observed mean values: AUC <48 μg•hr/mL and Cmax <14 μg/mL) and safety and tolerability will be reviewed before enrolling subjects into Part 2 of the study

Overview of Study Design and Key Features	
Sample Size	• The target sample size of 16 evaluable subjects with normal renal function and 8 evaluable renally impaired subjects was chosen based on feasibility, to address the objectives of the study. This sample size is considered sufficient to determine whether the pharmacokinetics in subjects with renal impairment is meaningfully different from subjects with normal renal function. • The between-subject variations of PK parameters from 1000 mg 2-hour IV administration on Day 1 in the BTZ115198 study were 26.3%, 27.4%, and 27.6% for the Cmax, from AUC from time 0 to infinity (AUC(0-∞)), and AUC(0-t), respectively [see report of Study BTZ115198]. • For a between-subject coefficient of variation of 26.3%, 27.4%, and 27.6%, and a sample size of 16 subjects for the subjects with normal renal function and 8 subjects for the renally impaired group, it is estimated that the half width of the 90% confidence interval (CI) for the difference on log-scale will be within 21.77%, 22.75%, and 23.00% of the point estimate for Cmax, AUC(0-∞), and AUC(0-t), respectively.

2.4. Statistical Hypotheses

A formal hypothesis will not be tested; however, an estimation approach will be taken to characterize the PK of gepotidacin in subjects with mild, moderate, severe renal impairment and in subjects with ESRD (on dialysis and not on dialysis) compared with matched subjects with normal renal function.

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 internally at GSK after the approximate sample size has been reached in Part 1 and Part 2 (optional).

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	Analyses Evaluated
Safety	• Consist 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	• Consist of all subjects who received at least 1 dose of gepotidacin and have evaluable PK data for gepotidacin.	• 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 parameter statistical analysis

NOTES :

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each displays 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 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
9.1	Appendix 1: Time & Events
9.2	Appendix 2: Treatment States and Phases
9.3	Appendix 3: Data Display Standards & Handling Conventions
9.4	Appendix 4: Derived and Transformed Data
9.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
9.6	Appendix 6: Values of Potential Clinical Importance
9.7	Appendix 7: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment
9.8	Appendix 8: Multiple Comparisons & Multiplicity
9.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
9.10	Appendix 10: Abbreviations & Trade Marks.
9.11	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 Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y		Y
Reason for Screening Failures	Y		Y
Reason for Withdrawals	Y		Y
Protocol Deviations	Y		Y
Inclusion and Exclusion Criteria Deviations			Y
Demography			
Demographic Characteristics	Y		Y
Study Populations	Y		Y
Renal Function			Y
Medical Conditions and Concomitant Medications			
Concomitant Medication	Y		Y
Medical Conditions (Current/Past)	Y		Y

NOTES :
Y = Yes display generated.

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacokinetic Analyses

7.1.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic population, 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
PK Concentrations				Y	Y[1] [2]	Y[1]	Y				Y	Y	Y	
Plasma PK Parameters	Y			Y	Y	Y	Y	Y	Y	Y	Y	Y		
Urine PK Parameters	Y			Y	Y	Y	Y	Y	Y	Y	Y	Y		
Saliva PK Parameters	Y			Y	Y	Y	Y	Y	Y	Y	Y	Y		
Dialysate PK Parameters[3]	Y			Y	Y	Y	Y	Y	Y	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] Group F subjects in Part 2 only (if needed).

7.1.2. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 9.3.3 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 9.3.3 Reporting Process & Standards).
- The pharmacokinetic 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.
- Pharmacokinetic parameters described in Table 6 will be determined from the dialysate concentration data, as data permits.
- Pharmacokinetic parameters described in Table 7 will be determined from the saliva concentration data, as data permits.

Table 4 Derived Plasma Pharmacokinetic Parameters

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: $AUC = AUC(0\text{-}t) + C(t) / \lambda z$
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: $[AUC(0\text{-}inf) - AUC(0\text{-}t)] / AUC(0\text{-}inf) \times 100$
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to first occurrence of Cmax
t½	Terminal half-life will be calculated as: $t_{1/2} = \ln 2 / \lambda z$
λz	Terminal-phase rate constant
CL	Systemic clearance, calculated as: $CL = Dose / AUC(0\text{-}\infty)$
Vss	Volume of distribution at steady-state of parent drug, calculated as: $Vss = MRT(0\text{-}inf)*CL$
Vz	Volume of distribution of the terminal phase, calculated as: $Vz = Dose/(AUC(0\text{-}inf)* \lambda z)$

NOTES:

- Additional parameters may be included as required.

Table 5 Derived Urine Pharmacokinetic Parameters

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 6, 6 to 12, 12 to 24, or 24 to 36, and 36 to 48 hours after dosing for subjects with renal 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 renal function
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: $fe\% = (Ae\ total/Dose) \times 100$
CLr	Renal clearance of drug, calculated as: $CLr = Ae\ total/AUC(0\text{-}t)$

NOTES:

- Additional parameters may be included as required.

Table 6 Derived Dialysate Pharmacokinetic Parameters

Parameter	Parameter Description
Arem(0-1)	Amount of drug removed by hemodialysis from time 0 to 1 hours after the start of hemodialysis
Arem(1-2)	Amount of drug removed by hemodialysis from time 1 to 2 hours after the start of hemodialysis
Arem(2-3)	Amount of drug removed by hemodialysis from time 2 to 3 hours after the start of hemodialysis
Arem(3-4)	Amount of drug removed by hemodialysis from time 3 to 4 hours after the start of hemodialysis (or to the end of dialysis if less than 4 hours)
Arem(0-4)	Cumulative amount of drug removed by hemodialysis from time 0 to 4 hours after the start of hemodialysis (or to the end of dialysis if less than 4 hours)
AUC(t0-t1)	Partial area under the curve estimated from predialyzer samples collected from start of dialysis (t0) to end of dialysis (t1)
CLD	Dialysis clearance, calculated as the total amount of the analyte recovered in the dialysate over 4 hours (or the total dialysis interval if less than 4 hours) divided by the partial area under the curve during the period of dialysis, which will be calculated using the predialyzer samples
Frem%(0-4)	Fraction (%) of the dose removed by hemodialysis from 0 to 4 hours after the start of hemodialysis (or to the end of dialysis if less than 4 hours)

NOTES:

- Additional parameters may be included as required.

Table 7 Derived Saliva Pharmacokinetic Parameters (subjects in Part 1 only)

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: $AUC = AUC(0\text{-}t) + C(t) / \lambda z$
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: $[AUC(0\text{-}inf) - AUC(0\text{-}t)] / AUC(0\text{-}inf) \times 100$
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	Systemic clearance, calculated as: $CL = Dose / AUC(0\text{-}inf)$
Vss	Volume of distribution at steady-state of parent drug, calculated as: $Vss = MRT(0\text{-}inf)*(CL)$
Vz	Volume of distribution of the terminal phase, calculated as: $Vz = Dose/(AUC(0\text{-}inf)* \lambda z)$
RAUC(0-t)	The ratio of the AUC(0-t) observed in saliva relative to the 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 AUC(0-∞) in plasma, calculated as: RAUC(0-∞) = AUC(0-∞) saliva / AUC(0-∞) plasma

NOTES:

- Additional parameters may be included as required.

7.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

The following pharmacokinetic 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 pharmacokinetic (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 in the renal impairment groups and normal renal function groups will be compared using an analysis of variance. • Linear regression analysis will be used to evaluate the relationships between estimated renal function and relevant PK parameters (e.g., AUC, Cmax, and CL). • An exploratory analysis will be performed to explore the relationship between saliva and plasma concentrations and PK parameters.
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Statistical analysis by ANOVA will be presented in tabular format with geometric mean ratios between renal impairment groups and normal renal function groups, and 90% CIs for the ratios of AUC(0-∞) and Cmax for gepotidacin. Example SAS Code: PROC MIXED; CLASS GRPID; MODEL LOGPKPARM = GPRID/DDFM=KR; LSMEANS GRPID; ESTIMATE 'B VS A' GPRID -1 1 0/CL ALPHA=0.1; ESTIMATE 'C VS A' GPRID -1 0 1/CL ALPHA=0.1;RUN; • Statistical analysis by linear regression will be presented in tabular format if the data permits with identification of linear functions that fit the data well, the resulting slopes will provide a comparison of any difference in the response of the gepotidacin IV treatment as renal function changes. Example SAS Code: PROC MIXED; MODEL LOGPKPARM = RENAL_FUNCTION/S DDFM=KR; ODS OUTPUT SOLUTIONF=S; RUN; • Statistical analysis by linear regression will be presented in graphical format with scatter plots of PK parameters by eGFR and PK parameters by Clcr with identification of linear functions

Pharmacokinetic Statistical Analyses
that fit the data well. • Scatter plots of natural log-transformed saliva gepotidacin concentrations versus the natural log-transformed plasma gepotidacin concentrations will be plotted and a regression line will be fitted. • Scatter plots of natural log-transformed saliva gepotidacin PK parameters versus the natural log-transformed plasma gepotidacin PK parameters will also be performed for the AUC(0-∞), AUC(0-t), and Cmax.

7.2. Safety Analyses

7.2.1. Overview of Planned Analyses

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

Table 8 provides an overview of the planned analyses, with further 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				
Withdrawal AEs				Y				
Laboratory Values								
Clinical Chemistry	Y			Y	Y			
Hematology	Y			Y	Y			
Urinalysis (Dipstick)	Y			Y				
ECGs								
ECG Findings	Y			Y				
ECG Values	Y			Y	Y			
Vital Signs								
Vital Signs	Y			Y	Y			
Liver								
Liver Events [1]				Y				
Cardiovascular								
Cardiovascular [1]				Y				
Clostridium Difficile								
Clostridium difficile Testing [1]				Y				
Infusion Site Reactions								
Infusion Site Reaction Events [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.

8. REFERENCES

GlaxoSmithKline Document Number 2014N209329_00 (Original – 01-MAR-2016): A Phase I, Open-Label, Single-Dose, Multi-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Subjects with Varying Degrees of Renal Impairment and in Matched Control Subjects with Normal Renal Function.

Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling" [Department of Health and Human Services (DHHS), Food and Drug Administration, 2010]

9. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 9.1	Appendix 1: Time and Events
Section 9.2	Appendix 2: Treatment States & Phases
Section 9.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 9.4	Appendix 4: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 9.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 9.6	Appendix 6: Values of Potential Clinical Importance
Section 9.7	Appendix 7: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment
Section 9.8	Appendix 8: Multiple Comparisons and Multiplicity
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Other RAP Appendices	
Section 9.10	Appendix 10: Abbreviations & Trade Marks
Section 9.11	Appendix 11: List of Data Displays

9.1. Appendix 1: Time & Events

9.1.1. Protocol Defined Time & Events

Time and Events Tables (Groups A, B, C, D, and E)

Procedure	Screening (up to 30 days prior to Day -1)	Check-in	Treatment Period (Days)			Follow-up (10 [±5] days post-last dose) or Early Termination	Notes
		–1	1	2	3		
Confined to clinic		X	X	X	X		Subjects 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					
Demographics	X						
Complete physical examination including height and weight	X						
Abbreviated physical examination		X			X	X	
Medical history (includes substance usage and history of renal disease)	X						Substances: drugs, alcohol, and caffeine. Subjects with renal impairment should be on a stable regimen of chronic medications 7 days before the first dose of study drug on Day 1.
Past and current medical conditions (including renal impairment medical history and eGFR)	X						eGFR as defined in the FDA draft guidance for industry, "Pharmacokinetics in Patients with Impaired Renal Function" [DHHS, 2010] Subjects with normal renal function will also be classified based on Clcr.

Procedure	Screening (up to 30 days prior to Day -1)	Check-in	Treatment Period (Days)			Follow-up (10 [±5] days post-last dose) or Early Termination	Notes
		–1	1	2	3		
Serum or urine pregnancy test/FSH	X	X				X	Serum (or urine) pregnancy test (if WCBP); estradiol and FSH at Screening, as appropriate
HIV antibody, hepatitis B surface antigen, and hepatitis C antibody testing[a]	X						
Drug and alcohol screen	X	X					See protocol Table 6.
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	
Vital signs	X	X	X	X	X	X	Respiratory rate and body temperature collected at Screening only.
Genetic sample[b]		X					Collect a pharmacogenomics (PGx) sample only if the subject has a signed consent specific for this purpose. The PGx sample can be collected anytime, but Day –1 is recommended.
Study drug administration			X				
Blood collection for pharmacokinetics			X	X	X		See protocol Table 3 for time points.
Urine collection for pharmacokinetics			X	X	X		Subjects with normal renal function and subjects with renal impairment will have different collection intervals. See protocol Table 3 for time points.
Saliva collection for pharmacokinetics[c]			X	X	X		See protocol Table 3 for time points.
AE/SAE review	X	X	←==========→			X	
Concomitant medication review		X	←==========→			X	

AE = adverse event, Clcr = estimated creatinine clearance; eGFR = estimated glomular filtration rate, ECG = electrocardiogram, FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; PGx = pharmacogenetic, SAE = serious AE; WCBP = women of childbearing potential.

[a] If test has otherwise been performed within 3 months before the first dose of study treatment, testing at Screening is not required.

[b] Informed consent for optional substudies (e.g., genetics research) must be obtained before collecting a sample.

[c] Subjects in Part 1 only. It should be noted that subjects with renal impairment may be on medications that may prevent saliva collections.

Safety and PK Assessments (Groups A, B, C, D, and E)

		Treatment Period Time point (hours)														
Procedure[a]	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**24[b]**	**36[b]**	**48[b]**
12-lead electrocardiogram	X					X	X			X		X	X	X	X	X
Vital signs	X					X	X			X		X	X	X	X	X
Treatment administration 2-hour IV gepotidacin infusion		X														
Blood collection for pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for pharmacokinetics (subjects with normal renal function)[c]	X	X					X			X	X	X	X	X	X	X
Urine collection for pharmacokinetics (subjects with renal impairment)[d]	X	X									X		X	X	X	X
Saliva collections[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

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

[c] Urine collection intervals for subjects with normal renal function (Group A and Group D) 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.

[d] Urine collection intervals for subjects with renal impairment (Group B, Group C, and Group E) 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.

[e] Subjects in Part 1 only. It should be noted that subjects with renal impairment may be on medications that may prevent saliva collections.

Time and Events Tables (Group F)

Procedure[a]	Screening (up to 30 days prior to Day -1)	Check -in	Treatment Period (Days)								Follow-up (10 [±5] days post-last dose) or Early Termination	Notes
			1				2					
		–1	1	2	3	4 to 6	7	8	9	10		
Confined to clinic[b]		X	X	X	X		X	X	X	X		Subjects will be admitted to the clinic on Day –1 and Day 7, and will be discharged on Day 3 (Period 1) and Day 10 (Period 2). Confinement will be 8 days and 6 overnight stays) total.
Informed consent	X											
Inclusion and exclusion criteria	X	X					X					
Demographics	X											
Complete physical examination including height and weight	X											
Abbreviated physical examination		X					X			X	X	
Medical history (includes substance usage and history of renal disease)	X											Substances: drugs, alcohol, and caffeine. Subjects with renal impairment should be on a stable regimen of chronic medications 7 days before the first dose of study drug on Day 1.

Procedure[a]	Screening (up to 30 days prior to Day -1)	Check -in	Treatment Period (Days)								Follow-up (10 [±5] days post-last dose) or Early Termination	Notes
			1				2					
		–1	1	2	3	4 to 6	7	8	9	10		
Past and current medical conditions (including renal impairment medical history and eGFR)	X											eGFR defined in the FDA draft guidance for industry, [DHHS, 2010]
Serum or urine pregnancy test/FSH	X	X					X				X	Serum (or urine) pregnancy test (if WCBP); estradiol and FSH at Screening as appropriate.
HIV antibody, hepatitis B surface antigen, and hepatitis C antibody testing[c]	X											
Drug and alcohol screen	X	X					X					See protocol Table 6.
Laboratory assessments (include liver chemistries)	X	X		X			X		X		X	Including serum chemistry, and hematology. Results from 24 hours after dosing should be available before discharge on Day 3 (Period 1) and Day 10 (Period 2)
12-lead ECG	X	X	X	X	X		X	X	X	X	X	
Vital signs	X	X	X	X	X		X	X	X	X	X	Respiratory rate and body temperature collected at Screening only.

Procedure[a]	Screening (up to 30 days prior to Day -1)	Check -in	Treatment Period (Days)								Follow-up (10 [±5] days post-last dose) or Early Termination	Notes
			1				2					
		–1	1	2	3	4 to 6	7	8	9	10		
Genetic sample[d]		X										Collect a pharmacogenomics (PGx) sample only if the subject has a signed consent specific for this purpose. The PGx sample can be collected anytime, but Day –1 is recommended.
Study drug administration			X[b]					X[b]				
Blood collection for pharmacokinetics			X	X	X			X	X	X		See protocol Table 5 for time points.
Urine collection for pharmacokinetics			X	X	X			X	X	X		See protocol Table 5 for time points. Subjects may not be able to produce a urine sample.
Dialysate collections for pharmacokinetics			X	X	X							See protocol Table 5 for time points.
AE/SAE review	X	X	←==========							→	X	
Concomitant medication review		X	←==========					←==========		→	X	

AE = adverse event, eGFR = estimated glomular filtration rate, ECG = electrocardiogram, FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus, PGx = pharmacogenetic, SAE = serious AE; WCBP = women of childbearing potential.

[a] For subjects on hemodialysis (Part 2 [optional], Group F), assessments performed on scheduled hemodialysis days are to be done before hemodialysis (except for PK sample collection, which will be done before and after hemodialysis).

[b] Subjects in Group F will participate in 2 treatment periods, with dosing in these periods separated by a washout period of at least 7 days. Subjects in Group F will enter the clinic at Check-in (Day –1, Period 1 and Day 7, Period 2) before each study drug administration (Day 1, Period 1 and Day 8, Period 2). On Day 1 (Period 1) and Day 8 (Period 2), subjects in Group F will receive a single dose of study drug as follows: gepotidacin 750 mg administered as a 2-hour IV infusion starting approximately 2 hours before initiation of the last hemodialysis session of the week (Period 1) and gepotidacin 750 mg administered as a 2-hour IV infusion starting within 2 hours after completion of the last hemodialysis session of the week (Period 2). Subjects in Group F will be discharged from the clinic on Day 10, Period 2.

[c] If test has otherwise been performed within 3 months prior to first dose of study treatment, testing at Screening is not required.

[d] Informed consent for optional substudies (e.g., genetics research) must be obtained before collecting a sample.

Safety and PK Assessments (Group F)

		Treatment Periods 1 and 2 Time point (hours)[a]														
Procedure[a]	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**24[b]**	**36[b]**	**48[b]**
12-lead electrocardiogram	X						X[c]			X		X	X	X	X	X
Vital signs	X						X[c]			X		X	X	X	X	X
Treatment administration 2-hour IV gepotidacin infusion[d]		X														
Blood collection for pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for pharmacokinetics[e]	X	X										X	X	X	X	X
Dialysate collection for pharmacokinetics[f]	X	X			X		X		X							

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

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

[c] Performed post infusion.

[d] Subjects in Group F will participate in 2 treatment periods, with dosing in these periods separated by a washout period of at least 7 days. Subjects in Group F will enter the clinic at Check-in (Day –1, Period 1 and Day 7, Period 2) before each study drug administration (Day 1, Period 1 and Day 8, Period 2). On Day 1 (Period 1) and Day 8 (Period 2), subjects in Group F will receive a single dose of study drug as follows: gepotidacin 750 mg administered as a 2-hour IV infusion starting approximately 2 hours before initiation of the last hemodialysis session of the week (Period 1) and gepotidacin 750 mg administered as a 2-hour IV infusion starting within 2 hours after completion of the last hemodialysis session of the week (Period 2). Subjects in Group F will be discharged from the clinic on Day 10, Period 2.

[e] It should be noted that subjects in Group F may not be able to produce urine samples due to their medical condition. All sampling times are relative to the start of the infusion.

[f] Dialysate fluid will be collected on Day 1 after dosing (Period 1 only) over each 1-hour collection interval of the hemodialysis session.

9.2. Appendix 2: Treatment States and Phases

9.2.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to dosing.

Treatment Phase	Definition
Pre-Treatment	Date/Time < Study Treatment Start Date/Time
On-Treatment	Study Treatment Start Date/Time ≤ Date/Time ≤ Study Treatment Stop Date/Time
Post-Treatment	Date/Time > Study Treatment Stop Date /Time

9.2.2. Treatment States

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

For Group F, assessments and events will be classified according to the time of occurrence relative to dosing for the respective session.

9.2.2.1. 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

9.2.2.2. 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 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 1st 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

Treatment State	Definition
Drug-related	If relationship is marked 'YES' on CRF OR value is missing.

NOTES:

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

9.3. Appendix 3: Data Display Standards & Handling Conventions

9.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
Study Part [1]	Renal Impairment Group		Data Displays for Reporting	
	Code	Description	Description	Order [2]
1	A	Normal Renal Function	Normal	1
1	B	Moderate Renal Impairment	Moderate	2
1	C	Severe Renal Impairment and ESRD not on Hemodialysis	Severe/ESRD not on hemodialysis	3
2	D*	Normal Renal Function	Normal	4
2	E	Mild Renal Impairment	Mild	5
2	F	Severe Renal Impairment with ESRD and on Hemodialysis	ESRD on hemodialysis	6

NOTES:

1. TFLs will be presented separately for Part 1 and Part 2 of the study.
2. Order represents treatments being presented in TFL, as appropriate.
3. * If there are a sufficient number of subjects with normal renal function enrolled in Part 1 (Group A) that match subjects with renal impairment in other groups, a determination will be made regarding the enrollment of matching subjects with normal renal function in Part 2 (Group D).

9.3.2. Baseline Definition & Derivations

9.3.2.1. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment and are applicable to each period. For Groups A, B, C, D, and E there is one treatment period and the baseline value will be the latest pre-dose assessment in that period.

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.

9.3.2.2. 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 9.3.2.1 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.

9.3.3. Reporting Process & Standards

Reporting Process
Software
• The currently supported versions of SAS software [Insert Other Software as Required] 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 o 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

Reporting Standards	

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 Assign zero to NQ values (Refer to GUI_51487 for further details)
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 and or within] geometric coefficient of variation (CVb/w (%)) will be reported. CV_b (%) = √ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log Transformed	Tmax, %AUCex, lambda_z, lambda_z_lower, lambda_z_upper, lambda_z_no. of points, tlast
Summary Tables	lambda_z_lower, lambda_z_upper, lambda_z_no. of points, tlast
Listings	Include all following PK parameters: Plasma - C_{max}, AUC0-∞, AUC0-t, t1/2, Tmax, %AUCex, tlast, lambda_z, lambda_z_lower, lambda_z_upper, lambda_z_no. of points, Vss, Vz, CL Urine - Ae total, Ae(t1-t2), AUC(0-12), AUC(0-24), AUC(0-48), fe%, CLr Dialysate - Arem(0-1), Arem(1-2), Arem(2-3), Arem(3-4), Arem(0-4), AUC(t0-t1), CLD, Frem%(0-4) Saliva - C_{max}, AUC0-∞, AUC0-t, t1/2, CL, Vss, Vz, Tmax, %AUCex, tlast, lambda_z, lambda_z_lower, lambda_z_upper, lambda_z_no. of points, RAUC(0-t), RAUC(0-∞)
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

9.4. Appendix 4: Derived and Transformed Data

9.4.1. 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 treatment date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Treatment Date → Study Day = Ref Date – Treatment Date
  • Ref Data ≥ Treatment Date → Study Day = Ref Date – (Treatment Date) + 1

9.4.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ 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**

Extent of Exposure
• The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)**

9.4.3. 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: $$RR = \left[\left(\frac{QT}{QTcF}\right)^{3}\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive. • Important Note: Machine read values of RR should not be replaced with re-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 : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$ • 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 • CV events • Infusion site reactions • Potential systemic allergic reactions • GI events • Acetylcholinesterase (AChE) Inhibition

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

9.5.1. 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.

9.5.2. 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.

9.5.2.1. 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 study treatment; 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 applied. Consequently, time to onset and duration of such events will be missing.

Element	Reporting Detail
	• Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

9.5.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• 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.
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: 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 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. o The AE will then be considered to start on-treatment (worst case). 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.

9.6. Appendix 6: Values of Potential Clinical Importance

9.6.1. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450	
		> 450	≤ 479
		≥ 480	≤ 499
		≥ 500	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec	> 60	
	msec	> 30	≤ 59
	msec	≥ 60	

9.6.2. 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

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

9.7.1. 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
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.

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.

9.8. Appendix 8: Multiple Comparisons & Multiplicity

9.8.1. Handling of Multiple Comparisons & Multiplicity

No adjustments for multiplicity will be made.

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

9.9.1. Statistical Analysis Assumptions

Endpoint(s)	• PK endpoints include AUC(0-∞), AUC(0-t) and Cmax
Analysis	• Analysis of variance • Linear regression
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.	

9.10. Appendix 10 – Abbreviations & Trade Marks

9.10.1. 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)
A&R	Analysis and Reporting
Arem(0-1)	Amount of drug removed by hemodialysis from time 0 to 1 hour after the start of hemodialysis
Arem(1-2)	Amount of drug removed by hemodialysis from time 1 to 2 hours after the start of hemodialysis
Arem(2-3)	Amount of drug removed by hemodialysis from time 2 to 3 hours after the start of hemodialysis
Arem(3-4)	Amount of drug removed by hemodialysis from time 3 to 4 hours after the start of hemodialysis
Arem(0-4)	Cumulative amount of drug removed by hemodialysis from time 0 to 4 hours after the start of hemodialysis
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-t)	Area under the urine concentration-time curve from time 0 to the corresponding urine collection interval.
AUC(t0-t1)	Partial area under the curve estimated from predialyzer samples collected from start of dialysis (t0) to end of dialysis (t1)
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
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Systemic clearance
CLD	Dialysis clearance
CLr	Renal clearance of drug
Cmax	Maximum observed concentration
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth

Abbreviation	Description
DP	Decimal Places
Frem%(0-4)	Fraction (%) of the dose removed by hemodialysis from 0 to 4 hours after the start of hemodialysis (or to the end of dialysis if less than 4 hours)
fe%	Percentage of the given dose of drug excreted in urine
GUI	Guidance
GSK	GlaxoSmithKline
eCRF	Electronic Case Record Form
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IP	Investigational Product
GUI	Guidance
PCI	Potential Clinical Importance
PK	Pharmacokinetic
QC	Quality Control
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
SOP	Standard Operation Procedure
t1/2	Terminal phase half life
λz	Terminal-phase rate constant
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Tmax	Time to first occurrence of Cmax
Vss	Volume of distribution at steady-state of parent drug
Vz	Volume of distribution of the terminal phase
GSK	GlaxoSmithKline

9.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

9.11. Appendix 11: List of Data Displays

9.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.5	
Safety	2.1 to 2.11	
Pharmacokinetic	3.1 to 3.11	3.1 to 3.11
Section	**Listings**	
ICH Listings	1 to 50	
Other Listings		

9.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in the TLF Specification documents.

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.'

9.11.3. Deliverable [Priority]

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

NOTES:

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

9.11.4. 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	ES1	Summary of Subject Disposition		SAC [1]
1.2	Screened	ES6	Summary of Reasons for Screening Failures		SAC [1]
1.3	Screened	DV1	Summary of Important Protocol Deviations		SAC [1]
Demographics and Baseline Characteristics					
1.4	Safety	DM1	Summary of Demographic Characteristics		SAC [1]
Medical Conditions and Concomitant Medications					
1.5	Safety	MH1	Summary of Medical Conditions		SAC [1]

9.11.5. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1	Safety	AE2	Relationship of Adverse Event System Organ Classes, Preferred Terms and Verbatim Text		SAC [1]
2.2	Safety	AE1	Summary of All Adverse Events		SAC [1]
Laboratory Measurements					
2.3	Safety	LB1	Summary of Clinical Chemistry Change from Baseline		SAC [1]
2.4	Safety	LB1	Summary of Haematology Change from Baseline		SAC [1]
2.5	Safety	UR3b	Summary of Urinalysis Dipstick Results		SAC [1]
Electrocardiograms					
2.6	Safety	EG1	Summary of ECG Findings		SAC [1]
2.7	Safety	SAFE_T1	Summary of Frequency of Maximum Post-Dose ECG Parameter Corrected QTc Interval		SAC [1]
2.8	Safety	SAFE_T2	Summary of Frequency of Maximum Change from Baseline for ECG Parameter Corrected QTc Interval		SAC [1]
2.9	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC [1]
Vital Signs					
2.10	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC [1]

9.11.6. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1	PK	PK01	Summary of Gepotidacin Plasma Pharmacokinetic Concentration-Time Data (units) by Group	Blood samples for PK analysis will be collected at 1 predose time point and 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24 ,36 and 48 hours after dosing. If mean is below the level of quantification, report the mean value as NQ.	SAC [1]
3.2	PK	PK01	Summary of Gepotidacin Urine Concentrations (units)	Urine collection intervals for subjects with normal renal function (Group A and Group D) 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. Urine collection intervals for subjects with renal impairment (Group B, Group C, and Group E) 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. If mean is below the level of quantification, report the mean value as NQ.	SAC[1]

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.3	PK	PK01	Summary of Gepotidacin Saliva Concentrations (units) by Renal Function	Blood samples for PK analysis will be collected at 1 predose time point and 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24 ,36 and 48 hours after dosing.If mean is below the level of quantification, report the mean value as NQ. Part 1 subjects only.	SAC [1]
3.4	PK	PK01	Summary of Gepotidacin Dialysate Concentrations (units)	Blood samples for PK analysis will be collected at 1 predose time point and 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24 ,36 and 48 hours after dosing. If mean is below the level of quantification, report the mean value as NQ. Part 2 subjects only. Part 2 subjects in Group F only	SAC[1]
3.5	PK	PK01	Summary of Gepotidacin Dialyzer Plasma Concentration (units)	Blood samples for PK analysis will be collected at 1 predose time point and 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24 ,36 and 48 hours after dosing. If mean is below the level of quantification, report the mean value as NQ. Part 2 subjects in Group F only	SAC[1]

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Parameters Tables					
3.6	PK Parameters	PKPT4	Summary of Gepotidacin Plasma Parameters by Group	Additional parameters include untransformed and log-transformed for AUC(0-t) (units), AUC(0-∞) (units), Cmax (units);only untransformed – Tmax (units), CL (units), t½ (units), Vss (units), Vz (units), and lambda-z (units). Repeat for part 2 if needed.	SAC [1]
3.7	PK Parameters	PKPT1	Summary of Gepotidacin Urine Pharmacokinetic Parameters by Renal Function	Normal Subjects: Ae(0-2), Ae(2-4), Ae(4-6), Ae(6-8), Ae(8-12), Ae(12-24), Ae(24-36), Ae(36-48), Ae total, fe%, Clr, AUC(0-12), AUC(0-24), AUC(0-48) Renal Impaired: Ae(0-6), Ae(6-12), Ae(12-24), Ae(24-36), Ae(36-48), Ae total, fe%, CLr, AUC(0-12), AUC(0-24), AUC(0-48). Repeat for Part 2.	SAC [1]
3.8	PK Parameters	PKPT4	Summary of Gepotidacin Saliva Pharmacokinetic Parameters by Renal Function	AUC(0-t), AUC(0-∞), Cmax; only untransformed – Tmax, CL, t½, Vz, Vss, RAUC(0-t), RAUC(0-∞) and lambda-z. Part 1 subjects only.	SAC [1]
3.9	PK Parameters	PKPT4	Summary of GSK2140944 Dialysate and Dialyzer Parameters by Group	Arem(0-1), Arem(1-2), Arem(2-3), Arem(3-4), Arem(0-4), AUC(t0-t1), CLD, Frem%(0-4). Part 2 Group F only if needed.	SAC [1]

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Analysis Tables					
3.10	PK Parameters	PKPT3	ANOVA of Gepotidacin Plasma Pharmacokinetic Parameters by Renal Function	AUC(0-t), AUC(0-∞), Cmax only log-transformed vs eGFR. Repeat for CrCL. Repeat for Part 2.	SAC [1]
3.11	PK Parameters	PK_T1	Linear Regression of Gepotidacin Plasma Pharmacokinetic Parameters by Renal Function	AUC(0-t), AUC(0-∞), Cmax only log-transformed. Repeat for Part 2.	SAC [1]

9.11.7. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Concentration Plots					
3.1	PK	PKCF4	Mean Gepotidacin Plasma Concentrations by Renal Function (Linear and Semi-Log)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	SAC [1]
3.2	PK	PKCF4	Mean Gepotidacin Urine Concentrations by Renal Function (Linear and Semi-Log)	Dashed line represents the LLQ. Present all treatment groups in the same plots. Plot concentration at the collection midpoint.	SAC [1]
3.3	PK	PKCF4	Mean Gepotidacin Saliva Concentrations by Renal Function (Linear and Semi-Log)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	SAC [1]
3.4	PK	PKCF1P	Individual Gepotidacin Plasma Concentrations by Renal Function (Linear and Semi-Log)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	SAC [1]
3.5	PK	PKCF1P	Individual Gepotidacin Urine Concentrations by Renal Function (Linear and Semi-Log)	Dashed line represents the LLQ. Present all treatment groups in the same plots. Plot concentration at the collection midpoint.	SAC [1]
3.6	PK	PKCF1P	Individual Gepotidacin Saliva Concentrations by Renal Function (Linear and Semi-Log)	Dashed line represents the LLQ. Present all treatment groups in the same plots.	SAC [1]

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Parameter Plots					
3.6	PK Parameters	PK_F1	Scatter Plot to Explore the Relationship between Gepotidacin Plasma Pharmacokinetic Parameters by Renal Function	Present all treatment groups in the same plots. Repeat for CrCL. Repeat for parameter AUC(0-t) and CL	SAC [1]
3.7	PK Parameters	PK_F2	Scatter Plot to Explore the Relationship between Gepotidacin Urine Pharmacokinetic Parameters by Renal Function	Present all treatment groups in the same plots. Repeat for CrCL.	SAC [1]
3.8	PK Parameters	PK_F3	Scatter Plot to Explore the Relationship between Gepotidacin Saliva Pharmacokinetic Parameters by Renal Function	Present all treatment groups in the same plots. Repeat for CrCL. Repeat for parameter AUC(0-t) and CL	SAC [1]
Exploratory Objectives					
3.9	PK	PK_F4	Scatter Plot of Gepotidacin Saliva and Plasma Concentrations by Renal Function	Present all treatment groups in the same plots.	SAC [1]
3.10	PK Parameters	PK_F5	Scatter Plot of Gepotidacin Saliva and Plasma Pharmacokinetic Parameters by Renal function	Present all treatment groups in the same plots. Repeat for parameter AUC(0-t), AUC(0-inf) and CL	SAC [1]

9.11.8. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomisation					
1	Safety	SAFE_L1	Listing of Renal Function and Group		SAC [1]
Subject Disposition					
2	Safety	ES2	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	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC [1]
Demographics					
6	Safety	DM2	Listing of Demographic Characteristics	Include height, weight and BMI	SAC [1]
7	Safety	DM9	Listing of Race		SAC [1]
Medical Conditions and Concomitant Medications					
8	Safety	MH2	Listing of Medical Conditions		SAC [1]
9	Safety	CM3	Listing of Concomitant Medications		SAC [1]
Exposure					
10	Safety	SAFE_L1	Listing of Exposure Data		SAC [1]
Safety					
11	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC[1]
12	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC [1]
13	Safety	AE8	Listing of All Adverse Events		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
14	Safety	AE8	Listing of Study Drug Related Adverse Events		SAC [1]
15	Safety	SAFE_L2	Listing of Serious Adverse Events		SAC [1]
16	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study		SAC [1]
17	Safety	SAFE_L3	Listing of Infusion Site Reaction Adverse Events	Conditional display	SAC [1]
18	Safety	SAFE_L4	Listing of Liver Adverse Events	Conditional display	SAC [1]
19	Safety	SAFE_L5	Listing of Cardiovascular Adverse Events	Conditional display	SAC [1]
20	Safety	SAFE_L6	Listing of Allergic Reaction Adverse Events	Conditional display	SAC [1]
21	Safety	SAFE_L7	Listing of Clostridium Difficile Testing	Conditional display	SAC [1]
22	Safety	SAFE_L8	Listing of Rash Events	Conditional display	SAC [1]
Laboratory Measurements					
23	Safety	LB5	Listing of Clinical Chemistry Toxicities of Grade 3 or Higher		SAC [1]
24	Safety	LB5	Listing of All Clinical Chemistry Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]
25	Safety	LB5	Listing of Haematology Toxicities of Grade 3 or Higher		SAC [1]
26	Safety	LB5	Listing of All Haematology Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]
27	Safety	UR2a	Listing of Urinalysis Toxicities of Grade 3 or Higher		SAC [1]
28	Safety	UR2a	Listing of All Urinalysis Data for Subjects with Toxicities of Grade 3 or Higher		SAC [1]
ECGs					
29	Safety	EG5	Listing of Abnormal ECG Findings		SAC [1]
30	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
31	Safety	EG3	Listing of ECG Values of Potential Clinical Importance		SAC [1]
32	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC [1]
Vital Signs					
33	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance		SAC [1]
34	Safety	VS4	Listing of All Vital Signs for Subjects with Potential Clinical Importance Values		SAC [1]
Liver Events					
35	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Conditional display	SAC [1]
36	Safety	MH3	Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional display	SAC [1]
37	Safety	SAFE_L9	Listing of Alcohol Intake at Onset of Liver Event	Conditional display	SAC [1]
38	Safety	PKCL1X	Listing of Plasma Concentration Data for Subjects with Liver Stopping Events	Conditional display	SAC [1]
39	Safety	LIVER7	Listing of Liver Biopsy Details	Conditional display	SAC [1]
40	Safety	LIVER8	Listing of Liver Imaging Details	Conditional display	SAC [1]
Pharmacokinetic					
41	PK	PKCL1X	Plasma Gepotidacin Concentrations by Renal Function	Please list all the concentration data including unscheduled. Repeat for part 2 if needed.	SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
42	PK	PKUL1P	Urine Gepotidacin Concentrations by Renal Function	Please list all the concentration data including unscheduled. Repeat for part 2 if needed.	SAC [1]
43	PK	PKCL1X	Saliva Gepotidacin Concentrations by Renal Function	Please list all the concentration data including unscheduled. Repeat for part 2 if needed.	SAC [1]
44	PK	PKCL1X	Dialysate Gepotidacin Concentrations	Please list all the concentration data including unscheduled. Repeat for part 2 if needed.	SAC [1]
45	PK	PKCL1X	Dialyzer Plasma Gepotidacin Concentrations	Please list all the concentration data including unscheduled. Repeat for part 2 if needed.	SAC [1]
46	PK Parameter	PKPL1P	Geotadacin Plasma Pharmacokinetic Parameters by Renal Function	Additional parameters include CL (units), t½ (units), Vss (units), Vz (units), Lambda-z (units)	SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
47	PK Parameter	PKPL1P	Gepotidacin Urine Pharmacokinetic Parameters by Renal Function	Additional parameters include Ae(0-6) (units), Ae(6-12) (units), Ae(12-24) (units), Ae(24-36) (units), Ae(36-48) (units)	SAC [1]
48	PK Parameter	PKPL1P	Gepotidacin Saliva Pharmacokinetic Parameters by Renal Function	Additional parameters include CL (units), t½ (units), Vss (units), Vz (units), Lambda-z (units)	SAC [1]
49	PK Parameter	PKPL1P	Gepotidacin Dialysate Pharmacokinetic Parameters	Additional parameters include Arem(0-4) (units), AUC(t0-t1) (units), CLd (units), Frem%(0-4)(units). Only incldue treatment part 2 treatment F.	SAC [1]
50	PK Parameter	PKPL1P	Gepotidacin Dialyzer Plasma Pharmacokinetic Parameters	Additional parameters include Arem(0-4) (units), AUC(t0-t1) (units), CLd (units), Frem%(0-4)(units). Only incldue part 2 treatment F.	SAC [1]