TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	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

Development Phase I

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SPONSOR SIGNATORY:

PPD

01 MAR 2016

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Date

PPD

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number: IND 111885

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY BTZ116849

Rationale

This study will be conducted to determine if altered renal function affects the plasma pharmacokinetics of gepotidacin, which will inform if dosing recommendations based upon renal impairment are required. The proposed single IV infusion dose of gepotidacin 750 mg administered over 2 hours will provide an approximate 2.5-fold margin for area under the plasma concentration-time curve (AUC) and maximum observed concentration (Cmax) based on the highest single IV dose of gepotidacin (1800 mg) evaluated in adult healthy subjects.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• 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)	• Plasma primary pharmacokinetic (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
Secondary	
• 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), 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	
• To evaluate the saliva pharmacokinetics of gepotidacin (subjects in Part 1 only)	• Primary PK endpoints include AUC(0-∞) and Cmax of gepotidacin, as data permit • Secondary PK endpoints include AUC(0-t), CL, λz, t1/2, Tmax, Vss, and Vz, as data permit

ESRD = end-stage renal disease; PK = pharmacokinetic

Overall 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).

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).

This will be a multi-part study, in which pharmacokinetic (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 with renal impairment will be matched to subjects with normal renal function in terms of gender distribution, age (approximately ±10 years), and body mass index (approximately ±20%).

Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic and will be enrolled as follows:

Part 1:

- Group A: subjects with normal renal function (eGFR ≥90 mL/min/1.73m^2)
- Group B: subjects with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m^2)
- Group C: subjects with severe renal impairment and subjects with ESRD not on hemodialysis (eGFR <30 mL/min/1.73m^2)

If PK, safety, and tolerability requirements are not met in Part 1, and based on the emerging data, and/or data that are not expected to exceed the requirements in the subjects with ESRD on hemodialysis or may require dose adjustment, subjects for Part 2 will be enrolled. In addition, based on emerging data from Part 1, Group E may not be enrolled in Part 2 (optional).

Part 2 (Optional):

- Group D: subjects with normal renal function (eGFR ≥90 mL/min/1.73m^2)*
- Group E: subjects with mild renal impairment (eGFR 60 to 89 mL/min/1.73m^2)
- Group F: subjects with ESRD on hemodialysis

* 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).

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 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.

Type and Number of Subjects

In Part 1, up to 16 subjects with normal renal function will be matched to approximately 8 subjects with moderate renal impairment, and approximately 8 subjects with severe renal impairment and/or subjects with ESRD not on hemodialysis for a total of approximately 32 subjects. In Part 2 (optional), approximately 4 to 8 subjects with normal renal function (if enrolled), approximately 4 to 8 subjects with mild renal impairment, and approximately 4 to 8 subjects with ESRD on hemodialysis will be enrolled for a total of approximately 12 to 24 subjects.

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 enrollment of matching subjects with normal renal function in Part 2 (Group D). In addition, if subjects prematurely discontinue the study, additional replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

Analysis

Plasma and saliva concentrations of gepotidacin will be analyzed (as data permit) by noncompartmental PK analysis to determine the following PK metrics: AUC from hour 0 to the last measurable plasma concentration (AUC(0-t)), AUC extrapolated to infinity (AUC(0-∞)), Cmax, time to maximum concentration (Tmax), apparent terminal phase half-life (t1/2), systemic clearance (CL), volume of distribution at steady-state of parent drug (Vss; plasma only), and volume of distribution of the terminal phase (Vz).

Urine concentrations of gepotidacin will be analyzed (as data permit) by noncompartmental PK analysis to determine the following PK metrics: total unchanged drug (Ae total), amount of drug excreted in urine (Ae (t1-t2)), percentage of the given dose excreted in urine (fe%), and renal clearance (Clr).

Plasma, urine, and saliva (subjects in Part 1 only) concentrations of gepotidacin and the associated PK parameters will be listed, and summary statistics (n, mean, median, standard deviation, minimum, maximum, and coefficient of variation) will be presented by day and treatment. Mean and individual plasma concentration versus time profiles will be presented graphically on linear and semilogarithmic scales.

Dialysate concentration of gepotidacin will be analyzed for all subjects with ESRD on dialysis (Group F subjects in Part 2 [optional]) to determine the following PK metrics: total amount of unchanged amount of drug removed by hemodialysis (Arem) from time 0 to 1 hour after the start of hemodialysis (Arem(0-1)), Arem from time 1 to 2 hours after the start of hemodialysis (Arem(1-2)), Arem from time 2 to 3 hours after the start of hemodialysis (Arem(2-3)), Arem from time 3 to 4 hours after the start of hemodialysis (Arem(3-4)), cumulative amount of drug removed by hemodialysis from time 0 to 4 hours (or to the end of dialysis if less than 4 hours; Arem(0-4)), partial area under the curve estimated from predialyzer samples collected from start of dialysis (t0) to end of dialysis (t1; AUC(t0-t1)), dialysis clearance (CL_D), and 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; Frem%(0-4)). Dialysate concentrations (Group F) of gepotidacin and the associated PK parameters will be listed, and summary statistics (n, mean, median, standard deviation, minimum, maximum, and coefficient of variation) will be presented by day and treatment.

Safety endpoints will include monitoring adverse events, clinical laboratory results, vital sign measurements 12-lead electrocardiogram measurements, and physical examination findings.

2. INTRODUCTION

Gepotidacin is a novel triazaacenaphthylene bacterial topoisomerase inhibitor, which inhibits bacterial DNA replication and has *in vitro* activity against susceptible and drug-resistant pathogens associated with a range of conventional and biothreat infections.

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

2.1. Study Rationale

In a previous absorption, distribution, metabolism, and excretion study for gepotidacin (See GSK Document Number 2014N189951_00 Study ID Study BTZ115774), the mean recovery of radioactivity in urine accounted for approximately 60% of [^{14}C]-gepotidacin administered as a single IV dose. In addition, renal clearance of gepotidacin has been estimated to be approximately 40% of total systemic drug clearance. Therefore, renal impairment has the potential to adversely affect the elimination of gepotidacin.

It is expected that potential patients in future gepotidacin Phase III studies may have at least some degree of renal impairment. The results from this study will enable the development of appropriate dosing recommendations in patients with impaired renal function.

2.2. Brief Background

Gepotidacin has demonstrated clinical efficacy in a Phase II study for acute bacterial skin and skin structure infections, and is currently being evaluated in a Phase II study for gonorrhea.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• 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)	• Plasma primary pharmacokinetic (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
Secondary	
• 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), 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	
• To evaluate the saliva pharmacokinetics of gepotidacin (subjects in Part 1 only)	• Primary PK endpoints include AUC(0-∞) and Cmax of gepotidacin, as data permit • Secondary PK endpoints include AUC(0-t), CL, λz, t1/2, Tmax, Vss, and Vz, as data permit

ESRD = end-stage renal disease; PK = pharmacokinetic

4. STUDY DESIGN

4.1. Overall 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). Subjects with renal impairment will be matched to subjects with normal renal function in terms of gender distribution, age (approximately ±10 years), and body mass index (BMI; approximately ±20%).

At Screening, subjects will be enrolled to the appropriate groups based on the classification as defined in the Food and Drug Administration (FDA) 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). For more details see Section 6.2.

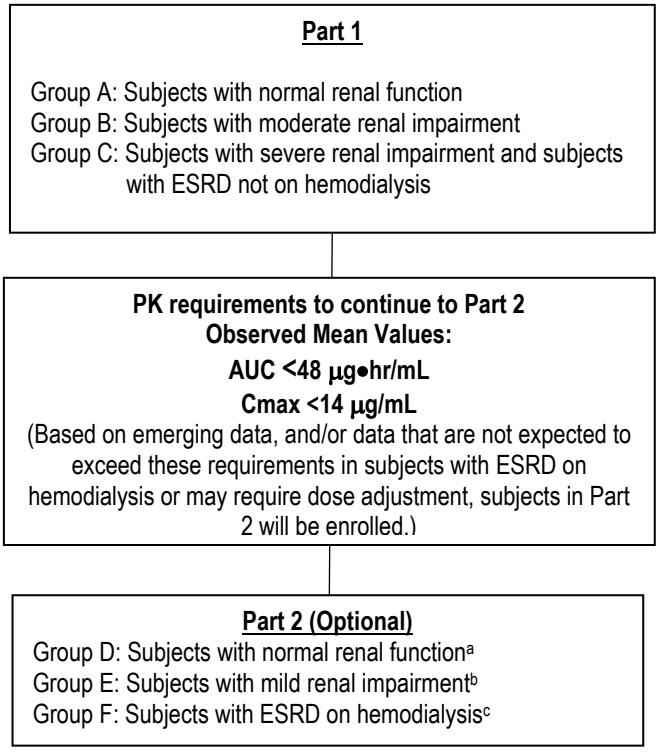
This will be a multi-part study, in which pharmacokinetic (PK) requirements must be met (observed mean values: area under the curve [AUC] <48 μg•hr/mL and maximum observed concentration [Cmax] <14 μg/mL); and safety and tolerability will be reviewed before enrolling subjects into the next part of the 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, and tolerability data of Part 1. Subjects with mild renal impairment may be studied if there is a significant difference in PK between subjects with moderate and severe renal impairment compared to subjects with normal renal function and modelling cannot accurately predict PK in subjects with mild renal impairment. Subjects with ESRD on hemodialysis will be studied provided that the PK requirements are met (observed mean values in subjects with severe impairment do not exceed the threshold: area under the curve [AUC] <48 μg•hr/mL and maximum observed concentration [Cmax] <14 μg/mL). The dose may be adjusted for subjects with ESRD on hemodialysis if either PK parameter is predicted to exceed the threshold. See the study schematic in Figure 1 for more details.

For subjects with normal renal function, subjects with mild, moderate, and severe renal impairment, and subjects with ESRD not on dialysis: subjects will participate in 1 treatment period and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Tables (Table 2 and Table 3). In addition, saliva samples (subjects in Part 1 only) will be collected for the PK analysis of gepotidacin concentrations according to the Time and Events Tables (Table 2 and Table 3). Blood, urine, and saliva samples will be collected up to approximately 48 hours after dosing.

For subjects with ESRD on hemodialysis: subjects will participate in 2 treatment periods and blood and urine (if applicable) samples in Period 1 will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Tables (Table 4 and Table 5). Blood and urine (if applicable) samples will be collected up to approximately 48 hours after dosing (i.e., the last sample will be collected before the next hemodialysis session). In addition, dialysate samples will be collected for the determination of gepotidacin concentrations according to the Time and Events Tables (Table 4 and Table 5).

Optional PK Assessment: with the subject's consent, if a kidney or bladder tissue sample is collected for a nonstudy purpose during this study, excess tissue may be collected and used for the purposes of measuring tissue gepotidacin concentrations.

Figure 1 BTZ116849 Study Schematic



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).

4.2. Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic and will be enrolled as follows:

Part 1:

- Group A: subjects with normal renal function (eGFR ≥90 mL/min/1.73m^2)
- Group B: subjects with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m^2)
- Group C: subjects with severe renal impairment and subjects with ESRD not on hemodialysis (eGFR <30 mL/min/1.73m^2)

If PK, safety, and tolerability requirements are not met in Part 1, and based on the emerging data, and/or data that are not expected to exceed the requirements in the subjects with ESRD on hemodialysis or may require dose adjustment, subjects for Part 2 will be enrolled. In addition, based on emerging data from Part 1, Group E may not be enrolled in Part 2 (optional).

Part 2 (Optional):

- Group D: subjects with normal renal function (eGFR ≥90 mL/min/1.73m^2)*
- Group E: subjects with mild renal impairment (eGFR 60 to 89 mL/min/1.73m^2)
- Group F: subjects with ESRD on hemodialysis

* 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).

Subjects with renal impairment will be matched to subjects with normal renal function in terms of gender distribution, age (approximately ±10 years), and BMI (approximately ±20%).

Subjects in Groups A, B, C, D (if enrolled; see Section 4.3 for more details), and E will enter the clinic at Check-in (Day –1, Period 1) before study drug administration (Day 1, Period 1). 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 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 of 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.

4.3. Type and Number of Subjects

In Part 1, up to 16 subjects with normal renal function will be matched to approximately 8 subjects with moderate renal impairment, and approximately 8 subjects with severe renal impairment and/or subjects with ESRD not on hemodialysis for a total of approximately 32 subjects. In Part 2 (optional), approximately 4 to 8 subjects with normal renal function (if enrolled), approximately 4 to 8 subjects with mild renal impairment, and approximately 4 to 8 subjects with ESRD on hemodialysis will be enrolled for a total of approximately 12 to 24 subjects.

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 enrollment of matching subjects with normal renal function in Part 2 (Group D). In addition, if subjects prematurely discontinue the study, additional replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

4.4. Design Justification

This study design is commonly used when evaluating the pharmacokinetics of a drug entity in subjects with impaired renal function. It is based on recommendations given in the FDA draft guidance for industry, Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling [DHHS, 2010].

Gepotidacin exhibits linear and time-independent pharmacokinetics, which indicates a single-dose study is adequate to achieve study objectives. A multiple-dose study is not necessary since there are no safety concerns with metabolites of this study drug.

4.5. Dose Justification

The proposed single IV infusion dose of gepotidacin 750 mg administered over 2 hours will provide an approximate 2.5-fold margin for mean Cmax and AUC based on the highest single IV dose of gepotidacin (1800 mg) evaluated in adult healthy subjects.

A physiologically-based pharmacokinetic (PBPK) model was developed for gepotidacin using the SimCYP population based absorption, distribution, metabolism, and excretion (ADME) simulator Version 15 (Certara USA, Inc, Princeton, NJ). Pharmacokinetic data from healthy Caucasian subjects following single 2-hour IV infusion doses of 400 mg, 1000 mg, and 1800 mg (see GSK Document Number 2014N198291_00 Study ID BTZ115198) was used to predict the intrinsic hepatic clearance. The predictive performance of the PBPK model was verified by comparing the observed AUC from time 0 to the time of the last quantifiable concentration (AUC(0-t)) and Cmax of gepotidacin to the predicted values at the 3 doses of 400 mg, 1000 mg, and 1800 mg. This model was further validated using a 750-mg IV 2-hour infusion dosing regimen in Japanese subjects from the same clinical study [see report of Study BTZ115198]. The model predictions agreed well with the observed data for the Caucasian population for all 3 dosing regimens, with predicted and observed values of a 5% to 12% difference in AUC(0-t) and a 1% to 5% difference, respectively, in Cmax. Simulations were also in good agreement with PK data in Japanese subjects. The model input parameters are listed in Appendix 11.

The PBPK model was then utilized to predict exposure for the proposed dosing regimen (750-mg IV 2-hour infusion) in healthy Caucasian subjects with normal renal function and subjects with various levels of impaired renal function as implemented in SimCYP with a female to male ratio of 0.5. The simulations were performed with the assumption of only GFR changes in subjects with renal impairment (software “RenalGFR30-60” and “RenalGFR_less_30”) and no active renal secretion due to the limited understanding of renal uptake mechanism for gepotidacin. The predicted geometric mean in gepotidacin exposure (AUC(0-t)) for subjects with moderate and severe renal impairment was

increased up to 2.0-fold compared with healthy subjects with normal renal function (Table 1).

Table 1 Simulated Gepotidacin Pharmacokinetic Parameters in Healthy (Normal) and Renally Impaired Populations

Pharmacokinetic Parameters	Predicted Geomean (CV%) [N = 100]		
	Healthy (Normal Renal Function) (GFR ≥90 mL/min)	Moderate Renal Impairment (GFR 30 to 60 mL/min)	Severe Renal Impairment (GFR 15 to <30 mL/min)
Cmax (μg/mL)	5.65 (18)	7.29 (19)	7.93 (20)
AUC(0-t) (μg•h/mL)	17.5 (23)	25.8 (24)	28.9 (26)

CV = coefficient of variation; GFR = glomular filtration rate; N = number of subjects included in the simulation

4.6. Benefit:Risk Assessment

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

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) Gepotidacin		
Gastrointestinal (GI) Effects	Lower GI effects (soft stools, flatulence, and diarrhoea) are the most common GI-associated adverse events (AEs) reported in human subjects dosed with gepotidacin. In the Phase I studies, out of approximately 400 healthy subjects who have received gepotidacin, *C. difficile* has been reported in 8 subjects.	Exclusion criterion and close monitoring of clinical parameters and AEs will be conducted to mitigate and assess GI effects. Patients with significant GI symptoms will obtain the appropriate work-up (Appendix 8). Subject stopping criteria: Subjects experiencing Grade 3 or Grade 4 AEs will have permanent discontinuation of the investigational medication and will be followed as appropriate until resolution of the AE.
Cardiovascular Effects Reversible increase in QT prolongation and a mild increase in heart rate in human subjects.	In Study BTZ115775 [see GlaxoSmithKline Document Number 2015N227098_00 Study ID BTZ115775], the infusion of gepotidacin at a dose of 1000 mg and 1800 mg over 2 hours caused a mild heart rate effect of approximately 6 bpm to 10 bpm and a QT prolongation, measured as ΔΔQTcF, of 12 msec to 22 msec. The QT prolongation evolved during the infusion and was quickly reversed over 2 hours after the end of the infusion. Blood pressure observations were within normal ranges.	Exclusion criteria, close monitoring of clinical parameters, and AEs will be conducted and stopping criteria will be utilized to mitigate and assess cardiovascular effects. Note: Subjects with a QRS duration <70 and >120 msec will be excluded. Subject stopping criteria: Subjects experiencing a QTcB and/or QTcF >500 msec and/or a change from baseline in QTc >60 msec.
Acetylcholinesterase (AChE) Inhibition In a mass spectrometry model performed with gepotidacin, AChE was inhibited with a concentration of inhibitor where the response (or binding) was reduced by half (inhibitory concentration) of approximately 5 µg/mL (7.5 µg/mL of total drug concentration).	At higher doses, some subjects have experienced effects consistent with increased cholinergic tone, including central nervous system and GI effects (increased salivation, slurred speech, blurred vision, dizziness, light-headedness, and GI upset). These effects appear to be related to Cmax and are significantly attenuated when Cmax is below 14 µg/mL.	Coadministration of anticholinergics and administration in subjects with certain concomitant conditions will be excluded. Close monitoring of clinical parameters and AEs will be conducted to assess effects potentially related to AChE inhibition. The Cmax will be below 14 µg/mL in this study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion-Site Reactions	Infusion-site reactions (mild to moderate), including phlebothrombosis, have been observed more frequently following repeat dosing at higher doses (≥750 mg BID). Infusion-site reaction events were reported as AEs for 2 of 122 subjects (2%) and consisted of mild, related infusion-site pain (see GSK Document Number 2015N243789_00 Study ID BTZ116704).	Intravenous administration of gepotidacin is given by a slow infusion following carefully defined procedures to minimize risk of infusion site reactions. Infusion-site reactions will be evaluated in an ongoing fashion throughout the study with interventions implemented as appropriate.
Rash/Hypersensitivity	A fine, mild, generalized pruritic macular skin rash was seen in 3 of 8 subjects following 10 days of dosing 1500 mg 3 times daily (see the report of Study BTZ115198). Rash was reported as an AE for 4 of 122 subjects (3%) and consisted of mild, related urticaria; moderate, related rash maculopapular; mild, related rash; mild, related urticaria; and mild, not related arthropod bite (see report of Study ID BTZ116704). There has been no other evidence of hypersensitivity in human subjects to date.	Exclusion criterion**:** History of sensitivity to any of the study drugs, components thereof, or a history of drug or other allergy that, in the opinion of the investigator or GlaxoSmithKline medical monitor, contraindicates their participation. Subject monitoring: Patients will be monitored closely for cutaneous effects throughout the study, and specialist advice will be sought as needed to evaluate any clinically significant finding. Subject stopping criteria**:** Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement.

4.6.2. Benefit Assessment

Since this Phase I study is being conducted in healthy subjects with normal renal function; in subjects with mild, moderate, and severe renal impairment; and in subjects with ESRD (on and not on hemodialysis), there is no direct clinical benefit to study subjects. Participation in this study will contribute to the process of developing new antibiotic therapies in areas of growing unmet need.

4.6.3. Overall Benefit:Risk Conclusion

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

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Male or female subject between 18 and 80 years of age, inclusive.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy subject must be in clinically stable health as determined by the investigator based on medical history, clinical laboratory results (serum chemistry, hematology, urinalysis, and serology), vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings. Subject with renal impairment must have clinical laboratory values consistent with their disease and are approved by the investigator. 3. Subject with renal impairment (mild, moderate, severe, or subjects with ESRD) may be taking medications, which in the opinion of the investigator, are believed to be therapeutic but do not affect study drug absorption, distribution, metabolism, or excretion. These medications must be stable doses taken for at least 7 days before the first dose of study drug. Any exceptions will be discussed with the sponsor or medical

monitor on a case-by-case basis and the reasons documented.

4. Subject with normal renal function or renal impairment (estimated eGFR corresponding to the calculated eGFR [the estimated eGFR may be rounded to the nearest integer]) at Screening (Section 6.2).
5. Subjects with ESRD on hemodialysis should be on hemodialysis for at least 3 months before Screening and is able to tolerate a hemodialysis treatment lasting 3 to 4 hours with blood flow rates of >200 mL/min.
6. Alanine aminotransferase (ALT) and bilirubin <1.5 × upper limit of normal (ULN; isolated bilirubin >1.5 × ULN is acceptable, if bilirubin is fractionated and direct bilirubin <35%).

WEIGHT

7. Body weight ≥50 kg and BMI within the range 18.5 and 40 kg/m^2, inclusive.

SEX

8. Male or Female

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin test), not lactating, and at least one of the following conditions applies:

a Nonreproductive potential defined as:

- Premenopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy
  - Documented bilateral oophorectomy
- Postmenopausal defined as 12 months of continuous spontaneous amenorrhea (in questionable cases a blood sample will be obtained to test for simultaneous follicle-stimulating hormone and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

b Reproductive potential and agrees to follow 1 of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (Appendix 7) requirements from 30 days prior to the first dose until completion of the Follow-up Visit.

c For subjects with indeterminate pregnancy test results or a persistently low human chorionic gonadotropin results, nonpregnancy status must be documented by other means (subjects with ESRD only).

The investigator is responsible for ensuring that subjects understand how to properly use

methods of contraception.

INFORMED CONSENT
9. Capable of giving signed informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Subject has a clinically significant abnormality in past medical history or at the Screening physical examination (excluding renal insufficiency and other related stable medical conditions within the renally impaired population of subjects [e.g., hypertension, diabetes, or anemia, which should be stable for at least 3 months before the first dose of study drug]) that in the investigator's opinion may place the subject at risk or interfere with outcome variables of the study. This includes, but is not limited to, history or current cardiac, hepatic, neurologic, gastrointestinal (GI), respiratory, hematologic, or immunologic disease.
2. Subject has any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study drug, or any other condition that may place the subject at risk, in the opinion of the investigator.
3. Subject has a functioning renal transplant.
4. Subject with renal impairment has a systolic blood pressure outside the range of 90 to 200 mm Hg, a diastolic blood pressure outside the range of 45 to 110 mm Hg, or a heart rate outside the range of 40 to 120 bpm.
5. Subject with renal impairment has a hemoglobin value <9 g/dL.
6. Female subject has a positive pregnancy test result or is lactating at Screening or upon admission to the clinic.
7. Use of a systemic antibiotic within 30 days of Screening
8. Within 2 months before Screening, either a confirmed history of *Clostridium difficile* diarrhoea infection or a past positive *Clostridium difficile* toxin test.
9. Subject has a history of drug and/or alcohol abuse within 6 months before Screening, as determined by the investigator, or subject has a positive drug screen at Screening or upon admission to the clinic. For subjects with renal impairment, a positive drug screen result related to the use of prescription medications is allowed per investigator review and approval, and tetrahydrocannabinol use is allowed per investigator review and approval.
10. History of sensitivity to any of the study drugs, components thereof, or a history of drug or other allergy that, in the opinion of the investigator or GSK medical monitor, contraindicates their participation.
11. History of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinic

uses heparin to maintain IV cannula patency).

CONCOMITANT MEDICATIONS
12. Subject has used medications known to affect the elimination of serum creatinine (e.g., trimethoprim or cimetidine) or competitors of renal tubular secretion (e.g., probenecid) within 30 days before dosing. 13. Subjects cannot use any over-the-counter, or prescription medication (except for hormonal contraceptives and/or acetaminophen; see Section 6.11 for more details), vitamin supplement, or herbal medication within 7 days (or 5 half-lives, whichever is longer) before dosing and during the study within 7 days before dosing and during the study. Any exceptions (including subjects with renal impairment that will be on medications during the study) will be discussed with the sponsor or medical monitor on a case-by-case basis and the reasons will be documented.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
14. Subjects with normal renal function have a presence of hepatitis B surface antigen or positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment. A subject with renal impairment with stable hepatitis C who has normal liver function test results is allowed with investigator approval. 15. A positive test for human immunodeficiency virus antibody. 16. Subject has clinically significant abnormal findings in serum chemistry, hematology, or urinalysis results obtained at Screening or Day –1 (and Day 7 for Group F only), other than those associated with underlying renal conditions or other stable medical conditions consistent with the disease process. 17. Subject with normal renal function has a baseline corrected QT interval using the Fridericia formula (QTcF) of >450 milliseconds (msec) and subject with renal impairment has a baseline QTcF of >480 msec.

OTHER EXCLUSION CRITERIA
18. Donation of blood in excess of 500 mL within 12 weeks prior to dosing or participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period. 19. Previous exposure to gepotidacin within 12 months prior to the first dosing day. 20. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the investigational product (whichever is longer). 21. Subject is unable to comply with all study procedures, in the opinion of the investigator. 22. The subject should not participate in the study, in the opinion of the investigator or Sponsor.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently dosed. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials publishing requirements, and respond to queries from regulatory authorities, a minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, and serious adverse events (SAEs).

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The clinic must attempt to contact the subject and reschedule the missed visit as soon as possible.
- The clinic must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed "lost to follow-up", the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, emails, or text messages; and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the clinic study records.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology in alignment with the FDA guidance, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," [DHHS, 2009].

Study treatment will be stopped if the following liver chemistry stopping criterion is met:

- ALT $\geq 3 \times$ ULN

Although stopping criteria for continued dosing of investigational product due to liver chemistry parameters are not applicable for single-dose studies, and, in this case, for subjects that will receive the gepotidacin dose twice (Group F), if subjects are found to have values consistent with usual stopping parameters, it is appropriate to institute evaluation and monitoring criteria according to standard GSK criteria. Therefore, liver

function tests should be evaluated according to stopping criteria and work-up instituted if defined parameters are reached.

For details of the required assessments if a subject meets the above criteria, refer to Appendix 2, Liver Chemistry Follow-up Procedures.

5.4.2. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
    - For example, if a subject is eligible for the protocol based on the corrected QT interval using the Fridericia formula, then the corrected QT interval using the Fridericia formula must be used for discontinuation of this individual subject as well.
    - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other nonprotocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5 to 10 minute) recording period.

A subject who meets either of the bulleted criterion below will be withdrawn from the study:

- QTcF >500 msec
- Change from baseline of QTc >60 msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 to 480 msec	≥530 msec

5.4.3. Gastrointestinal Stopping Criteria

Subjects experiencing Grade 3 or Grade 4 AEs (confluent pseudomembranes or ulcerations OR mucosal bleeding with minor trauma; tissue necrosis OR diffuse spontaneous mucosal bleeding OR life-threatening consequences, e.g., aspiration, choking) will be followed as appropriate until resolution of the AE(s).

Furthermore, subjects who experience diarrhoea or enteritis should be evaluated with additional fecal occult blood tests and stool cultures as deemed appropriate by the investigator as outlined in Appendix 8 and Appendix 9.

5.4.4. Rash/Hypersensitivity Stopping Criteria

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

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the Follow-up Visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term "study treatment" is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may, therefore, refer to the individual study treatments or the combination of those study treatments.

	Study Treatment
Product name:	Gepotidacin (GSK2140944)
Dosage form:	IV
Unit dose strength/Dosage level:	750 mg
Route of Administration/Duration	Single IV dose over 2 hours
Dosing instructions:	Instructions for the preparation of the IV drug are included in the Study Procedures Manual.
Physical description:	Gepotidacin lyophile is a pale yellow to greyish yellow cake. Reconstituted solution: A clear, dark brown to dark brownish-yellow solution after reconstitution, free from visible particulate matter.
Manufacturer/Source of procurement:	GlaxoSmithKline

6.2. Treatment Assignment

This is a nonrandomized, open-label study. Clinic personnel will enroll the subject into the study once a subject has met all eligibility requirements.

At Screening, subjects will be enrolled to the appropriate groups based on the classification as defined in the FDA 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 (or ESRD) will be assigned to a study group based on their eGFR calculated using the isotope dilution mass spectrometry-traceable Modification of Diet in Renal Disease formula as follows:

- eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine) – 1.154 × (age) – 0.203 × (0.742 if female) × (1.212 if African American)

In addition, subjects with normal renal function will be classified based on estimated Clcr by the Cockcroft-Gault equation.

CLcr in mL/min is estimated from a spot serum creatinine (mg/dL) determination using the following formula:

- Clcr (mL/min) = [140 − age (years)] × weight (kg) ÷ 72 × serum creatinine (mg/dL) (× 0.85 for female patients)

Subjects will be given a subject number that will be a unique identifier. Once a subject number has been assigned, the number will not be reused even if the subject withdraws from the study before receiving gepotidacin.

6.3. Planned Dose Adjustments

Planned dose adjustments are not allowed during this study. However, based on emerging data from Part 1 (or Period 1 for Group F), the Part 2 (or Period 2 for Group F) dose may be reduced.

6.4. Blinding

This will be an open-label study.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for the preparation of gepotidacin will be detailed in a Study Specific Technical Agreement/Memo or pharmacy manual which will be accompanied by a Quality Agreement.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are to be reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized clinic staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized clinic staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to clinic staff.
- A Material Safety Data Sheet or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

When subjects are dosed at the clinic, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the clinic staff other than the person administering the study treatment.

Gepotidacin will be administered IV to subjects at the clinic. Administration will be documented in the source documents and reported in the electronic case report form (eCRF).

6.8. Treatment of Study Treatment Overdose

Gepotidacin will be administered at the clinic, thus limiting the risk of overdose. In the unlikely event that an overdose with gepotidacin should occur, the investigator must notify the sponsor promptly. There is no specific antidote for overdose with a bacterial topoisomerase inhibitor such as gepotidacin. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator should:

1. Contact the medical monitor immediately
2. Closely monitor the subject for AEs/SAEs and laboratory abnormalities until gepotidacin can no longer be detected systemically (at least 3 days for gepotidacin)
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on a clinical evaluation of the subject.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy subjects; subjects with mild, moderate, and severe renal impairment; and subjects with ESRD are eligible for study participation.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Meals and Dietary Restrictions

Standard meals will be provided during the study dosing period at specified times.

Subjects will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pummelos, pomegranate juice, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the first dose of study medication until after the final dose.

6.10.2. Caffeine and Alcohol

- Subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours prior to the start of dosing until collection of the final PK sample.
- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final PK sample.

6.10.3. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during the study (e.g., watch television, read).

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

In subjects with normal renal function, acetaminophen at doses of ≤2 grams/day is permitted; and in subjects with renal impairment or ESRD, acetaminophen at doses of ≤2 grams/day is permitted for use with the approval of the investigator. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

Subjects with renal impairment and subjects with ESRD may be taking medications that are considered therapeutic, and these medications should not interfere with the conduct of the study. 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 until completion of the Follow-up Visit.

All concomitant medication use will be documented on the concomitant medication page in the eCRF.

6.11.2. Prohibited Medications and Nondrug Therapies

Subjects with normal renal function, subjects with renal impairment, and subjects with ESRD must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements), unless specified in Section 6.11.1, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the Follow-up Visit, unless, in the opinion of the investigator and Sponsor, the medication will not interfere with the study.

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

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

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Tables, Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
  1. 12-lead ECG
  2. vital signs
  3. blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety and PK assessments, may be altered during the course of the study based on newly available

data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which will be approved by the relevant GSK study team member and then archived in the study sponsor and clinic study files, but this will not constitute a protocol amendment.
- The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Tables

Table 2 Time and Events Table (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.
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 Table 6.

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		
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 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 Table 3 for time points.
Saliva collection for pharmacokinetics[c]			X	X	X		See 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.

Table 3 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.

Table 4 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, "Pharmacokinetics in Patients with Impaired Renal Function" [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 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 Table 5 for time points.
Urine collection for pharmacokinetics			X	X	X			X	X	X		See Table 5 for time points. Subjects may not be able to produce a urine sample.
Dialysate collections for pharmacokinetics			X	X	X							See Table 5 for time points.
AE/SAE review	X	X	←==========							==========→	X	
Concomitant medication review		X	←==========					==========		→	X	

Footnotes continued on the next page.

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.

Table 5 Safety and Pharmacokinetic 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.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at Screening.

The following demographic parameters will be captured: year of birth, sex, race, and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Tables (Section 7.1). Additional time points for safety tests such as vital signs, physical exams and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events and Serious Adverse Events

The definitions of an AE or an SAE can be found in Appendix 5.

The investigator and their designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting Adverse Event and Serious Adverse Event information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs and SAEs will be collected from the time informed consent is obtained until the follow-up contact (see Section 7.3.1.3) at the time points specified in the Time and Events Tables (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.3.1.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken to not introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about an AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.3.1.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to GSK of SAEs and nonserious AEs related to study treatment (even for noninterventional postmarketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of dosing and until 7 days post-last dose.

- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

7.3.3. Physical Exams

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

7.3.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure, and pulse rate. Baseline body temperature and respiratory rate will be collected at Screening only.

7.3.5. Electrocardiogram

- Single 12-lead ECGs will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 6, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Tables (Section 7). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, clinic number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the clinic by the laboratory responsible for the assessments.

If additional nonprotocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Hematology, serum chemistry, urinalysis, and additional parameters to be tested are listed in Table 6.

Table 6 Laboratory Assessments

Hematology			
Platelet Count	RBC Indices:	WBC count with Differential:	
RBC Count	MCV	Neutrophils	
Hemoglobin	MCH	Lymphocytes	
Hematocrit	MCHC	Monocytes	
		Eosinophils	
		Basophils	
Serum Chemistry[a]			
Blood urea nitrogen	Potassium	AST	Total and direct bilirubin
Creatinine	Sodium	ALT	Total protein
Glucose	Calcium	Alkaline phosphatase	Albumin
Creatine kinase			
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests			
eGFR (Section 6.2)			
Clcr (Section 6.2)			
Hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus			
Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only)			
Serum test for human chorionic gonadotropin (as needed in women of childbearing potential)			
Alcohol (via urine, blood alcohol, or breathalyzer test) and drug screen (via serum, urine, or saliva) to include, at a minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines).			

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 5.4.1 and Appendix 3.

All laboratory tests with values that are considered clinically significantly abnormal during participation should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

The PK blood samples for the analysis of gepotidacin will be collected at the time points listed in Section 7.1, Time and Events Tables. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

For each sample, 3 mL of blood will be drawn via an indwelling catheter and/or direct venipuncture into tubes containing ethylenediaminetetraacetate anticoagulant. Details of PK blood sample processing, storage, and shipping procedures are provided in the SRM.

7.4.2. Urine Sample Collection

The PK urine samples for the analysis of gepotidacin will be collected at the time points listed in Section 7.1, Time and Events Tables. The actual date and time of each urine sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK urine sample processing, storage, and shipping procedures are provided in the SRM.

7.4.3. Saliva Sample Collection

The PK saliva samples for parent analysis of gepotidacin will be collected from subjects in Part 1 at the time points listed in Section 7.1, Time and Events Tables. The timing of saliva samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK saliva sample collection, processing, storage, and shipping procedures are provided in the SRM.

7.4.4. Dialysate Sample Collection

The PK dialysate samples for analysis of gepotidacin will be collected at the time points listed in Section 7.1, Time and Events Tables (Table 4 and Table 5; Group F only). The timing of dialysate samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK dialysate sample collection, processing, storage, and shipping procedures are provided in the SRM.

7.4.5. Sample Analysis

Plasma, urine, saliva, and dialysate analysis will be performed under the control of PTS-DMPK/Scinovo, GSK, the details of which will be included in the SRM. Concentrations of gepotidacin will be determined in plasma, urine, saliva, and dialysate samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Since plasma protein binding of gepotidacin is low (33%), only total drug concentrations will be reported for the PK analysis.

Once the plasma, urine, saliva, and dialysate have been analyzed for gepotidacin, any remaining plasma, urine, saliva, and dialysate may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo, GSK protocol.

7.5. Optional Pharmacokinetic Markers

With the subject's consent, if a kidney or bladder tissue sample is collected for a nonstudy purpose, excess tissue may be collected during this study and may be used for the purposes of measuring drug concentrations of gepotidacin.

7.6. Genetics

Depending on the clinical study results, optional exploratory pharmacogenomics analyses may be performed to examine the potential relationship between genetic variants and clinical endpoints.

The pharmacogenomics samples will be collected according to the Time and Events Tables (Table 2 and Table 4). Information regarding genetic research is included in Appendix 4.

8. DATA MANAGEMENT

- For this study, subject data will be entered via an eCRF into Oracle Clinical Remote Data Capture System. Subject data will be available for viewing through access to the Oracle Clinical Remote Data Capture System. Data provided from other sources will be received, reconciled, combined, and transferred to GSK at predetermined time points.

- Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity and quality of the data (e.g., removing errors and inconsistencies in the data). Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and a validated medication dictionary, GSKDrug.

- The eCRFs (including queries and audit trails) will be sent at the end of the study in electronic format to GSK to be retained. Each investigator will receive a copy of their site specific data in the same format to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. 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.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

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.

9.2.2. Sample Size Re-estimation or Adjustment

Not applicable.

9.3. Data Analysis Considerations

In general, descriptive summaries will include number of subjects (n), mean, SD, median, minimum, and maximum for continuous variables; and percent for categorical variables. Summaries will present data by group, and where appropriate, by assessment time.

9.3.1. Analysis Populations

The **Safety Population** will consist of all subjects who receive at least 1 dose of study drug and have at least one postdose safety assessment.

The **PK Population** will consist of all subjects who received at least 1 dose of gepotidacin and have evaluable PK data for gepotidacin.

The **PK Parameter Population** will consist of all subjects in the PK Population, for whom valid and evaluable PK parameters were derived. This population will be used in the assessment and characterization of PK parameters.

9.3.2. 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).

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Pharmacokinetic Analyses

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

Plasma:

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
CL	Systemic clearance
Cmax	Maximum observed concentration
λz	Terminal-phase rate constant
t1/2	Terminal phase half life
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

Urine:

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
fe%	Percentage of the given dose of drug excreted in urine, calculated as: fe% = (Ae total/Dose) × 100
CLr	Renal clearance of drug, calculated as: Ae total/AUC(0-t)

Dialysate (Subjects with ESRD on dialysis; Group F subjects in Part 2):

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 (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)
CL_D	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)

Plasma concentrations (all subjects), urine concentrations, and dialysate concentrations (Group F) of gepotidacin and the associated PK parameters will be listed, and summary statistics (n, mean, median, standard deviation [SD], minimum, maximum, and coefficient of variation [CV]) will be presented by day and treatment. Mean and individual plasma concentration versus time profiles will be presented graphically on linear and semilogarithmic scales.

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. 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 will be presented.

Linear regression analysis will be used to evaluate the relationships between estimated renal function and relevant PK parameters (e.g., AUC, Cmax, and CL). If the data permit the 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.

If the appropriate number of subjects with severe renal impairment and/or subjects with ESRD not on dialysis cannot be enrolled, or their eGFR values cluster at the higher end of the range, the PK profiles in subjects with ESRD on hemodialysis may be modeled to understand the pharmacokinetics for the other groups of subjects with renal impairment at the lower end of the range (<15 mL/min/1.73 m^2), as well as for subjects with ESRD not on hemodialysis.

Detailed descriptions of the analyses in this study will be presented in the Reporting and Analysis Plan (RAP).

9.4.2. Secondary Analyses

9.4.2.1. Safety Analyses

The following safety evaluations will be performed:

- Monitoring for AEs
- Changes in routine clinical laboratory parameters including hematology, serum chemistry, and urinalysis
- Clinically significant changes in vital sign measurements or physical examination findings
- Changes in 12-lead ECG measurements

Safety endpoints will include AEs, clinical laboratory results (serum chemistry [including liver function parameters], hematology, and urinalysis), vital sign measurements (blood pressure and heart rate), 12-lead ECG measurements, and physical examination findings.

All safety data will be presented in the data listings. Subject demographics, medical history, and prior and concomitant medications will be summarized by group using descriptive statistics. For continuous variables, these summaries will include sample size, mean, median, SD, minimum, and maximum.

For categorical variables, the summaries will include frequencies and corresponding percentages. No inferential hypothesis testing will be performed on the safety variables.

Adverse events will be coded using the MedDRA classification system. Treatment-emergent AEs (TEAEs) will be defined as any AEs, regardless of relationship to investigational product, that occur after the dose of investigational product. The TEAEs will be summarized by group at AE onset for the overall number of AEs and the percentage of subjects who experience them. The total number of AEs will be summarized by group and overall. The AEs will be further summarized by severity and relationship to the study drug. If relationship information is missing, the AE will be considered treatment related. Listings for the subsets of SAEs and treatment-related SAEs will be provided. The number of AEs leading to discontinuation and SAEs will be summarized. The incidence of AEs will also be summarized by system organ class and preferred term.

Clinical laboratory results, vital sign measurements (systolic and diastolic blood pressure and heart rate), and 12-lead ECG results will be summarized by actual values and change from baseline. Clinical laboratory values that are outside of the reference ranges will be flagged and evaluated for clinical significance by the investigator. Any ECG abnormalities, including but not limited to a QTc interval >500 msec or increase in QTc from the Screening ECG of ≥60 msec, will be summarized by group. Physical examination findings will be listed.

Detailed descriptions of the analyses in this study will be presented in the RAP.

9.4.3. Other Analyses

9.4.3.1. Exploratory Analyses

Saliva (subjects in Part 1 only):

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
CL	Systemic clearance
Cmax	Maximum observed concentration
λz	Terminal-phase rate constant
t1/2	Terminal phase half life
Tmax	Time to first occurrence of Cmax
Vz	Volume of distribution of the terminal phase

Saliva concentrations (subjects in Part 1 only; as data permit) of gepotidacin and the associated PK parameters will be listed, and summary statistics (n, mean, median, SD, minimum, maximum, and CV) will be presented by day and treatment. Mean and individual saliva concentration versus time profiles will be presented graphically on linear and semilogarithmic scales.

An exploratory analysis will be performed to explore the relationship between saliva and plasma concentrations. Natural log-transformed saliva gepotidacin concentrations versus the natural log-transformed plasma gepotidacin concentrations will be plotted and a regression line will be fitted. A similar analysis will also be performed for the AUC(0-∞), AUC(0-t), and Cmax.

Detailed descriptions of the analyses in this study will be presented in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a clinic, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- Obtaining signed informed consent.
- Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to the IRB/IEC).
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study.
- The IRB/IEC, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP and GSK/PPD procedures, GSK/PPD monitors will contact the clinic prior to the start of the study to review the following with the clinic staff: the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK/PPD requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK/PPD will monitor the study and clinic activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the clinic records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit, or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Clinic Closure

- Upon completion or premature discontinuation of the study, the GSK/PPD monitor will conduct clinic closure activities with the investigator or clinic staff, as appropriate, in accordance with applicable regulations including GCP, and GSK/PPD standard operating procedures.
- GSK/PPD reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. For multi-center studies, this can occur at one or more or at all clinics.
- If GSK/PPD determines such action is needed, GSK/PPD will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK/PPD will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK/PPD will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK/PPD will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all clinic study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in

conjunction with an assessment of the facility, supporting systems, and relevant clinic staff.

- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK/PPD will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that clinic for the study, as dictated by any institutional requirements or local laws or regulations, GSK/PPD standards/procedures, and/or institutional requirements.
- The investigator must notify GSK/PPD of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the clinic.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	adverse event
Ae total	total unchanged drug
Ae (t1-t2)	amount of drug excreted in urine in a time interval
ALT	alanine aminotransferase
Arem	amount of drug removed by hemodialysis
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 (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	area under the plasma concentration-time curve
AUC(0-∞)	area under the concentration-time curve from time 0 to infinity
AUC(0-t)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t)
AUC(t0-t1)	Partial area under the curve estimated from predialyzer samples collected from start of dialysis (t0) to end of dialysis (t1)
bpm	beats per minute
CI	confidence interval
CL	systemic clearance
Clcr	creatinine clearance
CL_D	dialysis clearance
CLr	renal clearance
Cmax	maximum observed concentration
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomular filtration rate
ESRD	end-stage renal disease
FDA	United States Food and Drug Administration
fe%	percentage of the given dose of drug excreted in urine

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)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GSK	GlaxoSmithKline
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury
msec	millisecond
PBPK	physiologically-based pharmacokinetic
PK	pharmacokinetic
QTc	corrected QT interval; the measure of time between the start of the Q wave and the end of the T wave
QTcF	corrected QT interval using the Fridericia formula
RAP	Reporting and Analysis Plan
SAE	serious adverse event
SRM	Study Reference Manual
t1/2	terminal phase half life
Tmax	time to first occurrence of Cmax
ULN	upper limit of normal
Vss	volume of distribution at steady-state of parent drug
Vz	volume of distribution of the terminal phase

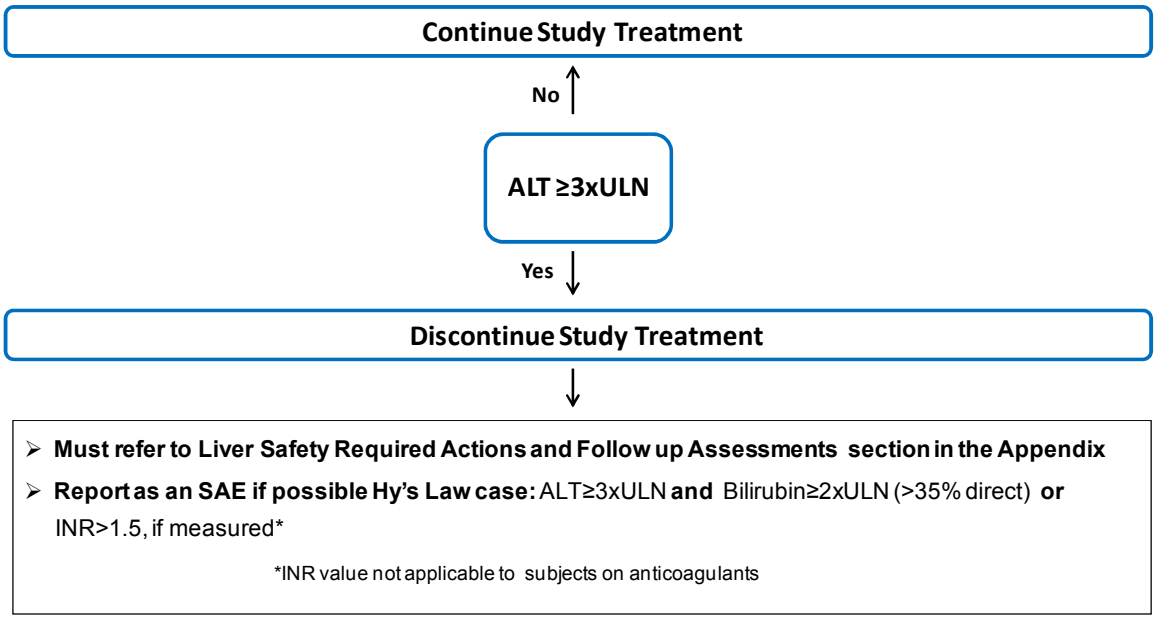
Trademark Information

Trademarks of the GlaxoSmithKline group of companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
SimCYP

12.2. Appendix 2: Liver Chemistry Stopping Criteria

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver safety required actions and follow-up assessments section can be found in Appendix 3.

12.3. Appendix 3: Liver Safety Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA guidance, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," [DHHS, 2009].

Phase I Liver Chemistry Stopping Criteria and Required Follow-up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥3 × ULN

If ALT ≥3 × ULN AND bilirubin[a,b] ≥2 × ULN (>35% direct bilirubin) or INR >1.5, report as an SAE.

See additional actions and follow-up assessments listed below.</td></tr>
<tr><th colspan="2">Required Actions and Follow-up Assessments Following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the Liver Event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[b]
• Perform liver event follow-up assessments
• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)

MONITORING:

If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within 24 hours
• Monitor subjects twice weekly until liver chemistries resolve, stabilize, or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT ≥3 × ULN AND bilirubin <2 × ULN and INR ≤1.5:</td><td>• Viral hepatitis serology[c]
• Serum creatine phosphokinase and lactate dehydrogenase.
• Fractionate bilirubin, if total bilirubin ≥2 × ULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

If ALT ≥3 × ULN AND bilirubin ≥ 2 × ULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 to 72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize, or return to within baseline	globulins). • Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form; GSK = GlaxoSmithKline; IgM = Immunoglobulin M; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3 × ULN **and** bilirubin ≥2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

[b] All events of ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN **and** INR >1.5, if INR measured, which may indicate severe liver injury (possible "Hy's Law"), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.

[c] Includes: hepatitis A IgM antibody; hepatitis B surface antigen and hepatitis B Core Antibody (IgM); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody.

12.4. Appendix 4: Genetic Research

Genetic Research Objectives and Analyses

Naturally occurring genetic variation may contribute to interindividual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine, and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including gepotidacin or any concomitant medicines

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for DNA extraction. A blood sample is collected at the baseline visit, after the subject has provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or clinic staff. Coded samples do not carry personal identifiers (such as a name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers), will only use samples collected from the study for the purpose stated in this protocol and in the ICF. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research, in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the clinic study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.

- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the clinic files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately, and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, serum chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.5.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room, or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥3 × ULN and total bilirubin* ≥2 × ULN (>35% direct), **or**
- ALT ≥3 × ULN and INR** >1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3 × ULN and total bilirubin ≥ 2 × ULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If an INR measurement is obtained, the value is to be recorded on the SAE Form.

12.5.3. Definition of Cardiovascular Events

Cardiovascular Events Definition:

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

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.5.4. Recording of Adverse Events and Serious Adverse Events

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.5.5. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study according to the US National Institute of Allergy and Infectious Diseases DMID criteria for toxicity assessment (Appendix 6).

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 12.5.2).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts, evidence, or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.5.6. Reporting of Serious Adverse Events to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for greater than 24 hours, the clinic will use the paper SAE data collection tool and fax it to the medical monitor or the SAE coordinator.
- The clinic will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given clinic, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data.
- If a clinic receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been

taken off-line, the clinic can report this information on a paper SAE form or to the medical monitor or the SAE coordinator by telephone.

- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment

ESTIMATING SEVERITY GRADE: For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (<48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs: ANY clinical event deemed by the investigator to be serious or life-threatening should be considered a Grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, and severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS [DAIDs], National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the DAIDs and modified to better meet the needs of participants in Division of Microbiology and Infectious Diseases trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide for Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 to 10.5 mg/dL	8.0 to 9.4 gm/dL	6.5 to 7.9 gm/dL	<6.5 gm/dL
Absolute neutrophil count	1000 to 1500 /mm3	750 to 999 /mm3	500 to 749 /mm3	<500 /mm3
Platelets	75,000 to 99,999 /mm3	50,000 to 74,999 /mm3	20,000 to 49,999 /mm3	<20,000 /mm3
White Blood Cells	11,000 to 13,000 /mm3	13,000 to 15,000 /mm3	15,000 to 30,000 /mm3	>30,000 or <1000 /mm3
% Polymorphonuclear leukocytes + band cells	>80%	90 to 95%	>95%	N/A
Abnormal Fibrinogen	Low: 100 to 200 mg/dL High: 400 to 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL High: N/A	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 to 40 mcg/mL	41 to 50 mcg/mL	51 to 60 mcg/dL	>60 mcg/dL
Prothrombin Time	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 mEq/L	123 to 129 mEq/L	116 to 122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146 to 150 mEq/L	151 to 157 mEq/L	158 to 165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 to 3.4 mEq/L	2.5 to 2.9 mEq/L	2.0 to 2.4 mEq/L or intensive replacement therapy of hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6 to 6.0 mEq/L	6.1 to 6.5 mEq/L	6.6 to 7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55 to 64 mg/dL	40 to 54 mg/dL	30 to 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 to 160 mg/dL	161 to 250 mg/dL	251 to 500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 to 7.8 mg/dL	7.7 to 7.0 mg/dL	6.9 to 6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 to 1.2 mEq/L	1.1 to 0.9 mEq/L	0.8 to 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 to 2.4 mg/dL	1.5 to 1.9 mg/dL or replacement Rx required	1.0 to 1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 to <1.25 × ULN	1.25 to <1.5 × ULN	1.5 to 1.75 × ULN	>1.75 × ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 to <1.5 × ULN	1.5 to <2.0 × ULN	2.0 to 3.0 × ULN	>3.0 × ULN
Blood urea nitrogen	1.25 to 2.5 × ULN	2.6 to 5 × ULN	5.1 to 10 × ULN	>10 × ULN
Hyperuricemia (uric acid)	7.5 to 10.0 mg/dL	10.1 to 12.0 mg/dL	12.1 to 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 to 1.5 × ULN	1.6 to 3.0 × ULN	3.1 to 6.0 × ULN	>6 × ULN or dialysis required

Rx = therapy; ULN = upper limit of normal.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Aspartate aminotransferase	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.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac rhythm	N/A	Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required	Unstable dysrhythmia; hospitalization and treatment required
Hypertension	Transient increase >20 mm Hg; no treatment	Recurrent, chronic increase >20 mm Hg; treatment required	Acute treatment required; outpatient treatment or hospitalization possible	End organ damage or hospitalization required
Hypotension	Transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mmHg systolic BP. No treatment required	Symptoms due to orthostatic hypotension or BP decreased by <20 mmHg systolic; correctable with oral fluid treatment	Requires IV fluids; no hospitalization required	Mean arterial pressure <60 mmHg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion; pain; EKG changes	Tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	Microscopic/occult	Mild, no transfusion	Gross blood loss; 1 to 2 units transfused	Massive blood loss; >3 units transfused

BP = blood pressure; EKG = electrocardiogram; IV = intravenous; N/A = not applicable; Rx = therapy

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient; no treatment	Persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	N/A
Bronchospasm, Acute	Transient; no treatment; FEV_1 70 to 80% of peak flow	Requires treatment; normalizes with bronchodilator; FEV_1 50 to 70% of peak flow	No normalization with bronchodilator; FEV_1 25 to 50% of peak flow; or retractions present	Cyanosis: FEV_1 <25% of peak flow; or intubation necessary
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring oxygen therapy

N/A = not applicable; FEV_1 = forced expiratory volume in 1 second

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	Mild or transient; maintains reasonable intake	Moderate discomfort; intake decreased significantly; some activity limited	No significant intake; requires IV fluids	Hospitalization required
Vomiting	1 episode in 24 hours	2 to 5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	Requiring stool softener or dietary modification	Requiring laxatives	Obstipation requiring manual evacuation or enema	Obstruction or toxic megacolon
Diarrhoea	Mild or transient; 3 to 4 loose stools/day or mild diarrhoea lasting <1 week	Moderate or persistent; 5 to 7 loose stools/day or diarrhoea lasting >1 week	>7 loose stools/day or bloody diarrhoea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization
Oral discomfort/ Dysphagia	Mild discomfort; no difficulty swallowing	Some limits on eating/drinking	Eating/talking very limited; unable to swallow solid foods	Unable to drink fluids; requires IV fluids

IV = intravenous.

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	Slight incoordination dysdiadochokinesis	Intention tremor, dysmetria, slurred speech; nystagmus	Locomotor ataxia	Incapacitated
Psychiatric	Mild anxiety or depression	Moderate anxiety or depression; therapy required; change in normal routine	Severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	Acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle strength	Subjective weakness; no objective symptoms/signs	Mild objective signs/symptoms; no decrease in function	Objective weakness; function limited	Paralysis
Paresthesia (burning, tingling, etc.)	Mild discomfort; no treatment required	Moderate discomfort; non- narcotic analgesia required	Severe discomfort; or narcotic analgesia required with symptomatic improvement	Incapacitating; or not responsive to narcotic analgesia
Neurosensory	Mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision, and/or hearing	Moderate impairment (moderately decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e., upper and lower extremities)	Sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	Mild pain not interfering with function	Moderate pain, analgesics and/or pain interfering with function but not with ADL	Severe paid; pain and/or analgesics interfering with ADL	Disabling pain
Arthritis	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling; interfering with function but not with ADL	Severe pain with inflammation, erythema or joint swelling, and interfering with ADL	Permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	Muscle tenderness (at other than injection site) or with moderate impairment of activity	Severe muscle tenderness with marked impairment of activity	Frank myonecrosis

ADL = activities of daily living.

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	Erythema; pruritus	Diffuse, maculo papular rash, dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15 mm	15 to 30 mm	>30 mm	N/A
Erythema	<15 mm	15 to 30 mm	>30 mm	N/A
Edema	<15 mm	15 to 30 mm	>30 mm	N/A
Rash at injection site	<15 mm	15 to 30 mm	>30 mm	N/A
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching over entire body	N/A

N/A = not applicable.

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic reaction	Pruritus without rash	Localized urticarial	Generalized urticarial; angioedema	Anaphylaxis
Headache	Mild, no treatment required	Transient, moderate; treatment required	Severe; responds to initial narcotic therapy	Intractable; requires repeated narcotic therapy
Fever: oral	37.7 to 38.5°C or 100.0 to 101.5°F	38.6 to 39.5°C or 101.6 to 102.9°F	39.6 to 40.5°C or 103 105°F	>40°C or >105°F
Fatigue	Normal activity reduced <48 hours	Normal activity decreased 25 to 50%; >48 hours	Normal activity decreased >50%; cannot work	Unable to care for self

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential and Collection of Pregnancy Information

12.7.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential

The list does not apply to females of reproductive potential with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the clinic personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable).

Male subjects with female partners of child-bearing potential must comply with the following contraception requirements from 30 days prior to the first dose until completion of the Follow-up Visit.

8. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
9. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system

- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.7.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to GSK as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating:

- Will be withdrawn from the study.
- The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.8. Appendix 8: Follow-up for Gastrointestinal Findings

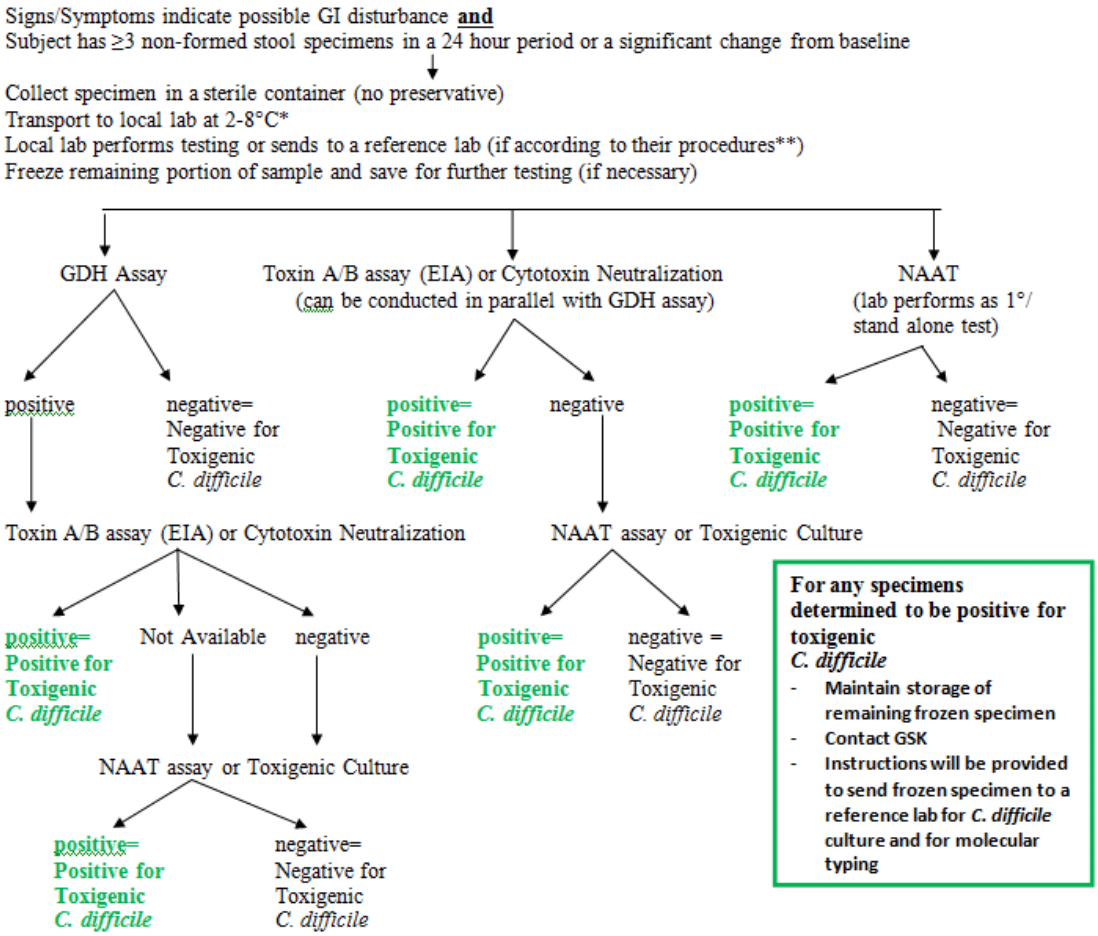
Subjects who experience diarrhoea or enteritis should be evaluated with additional fecal occult blood tests and stool cultures as deemed appropriate by the investigator. Any subject with a positive fecal occult blood test should be referred to a gastroenterologist for further evaluation at the discretion of the investigator.

Subjects who experience an AE of diarrhoea or enteritis should have additional fecal occult blood testing, as well as a routine stool culture performed, which may include the recovery of pathogenic bacteria such as *Salmonella, Shigella*, *Campylobacter*, *Yersinia, Vibrio, Staphylococcus aureus, Escherichia coli* 0157, and enterohemorrhagic *Escherichia coli*.

In addition, if the subject meets the clinical criteria outlined in Appendix 9, *Clostridium difficile* toxin detection should be conducted.

Note: Additional testing is at the discretion of the investigator if it is believed the GI signs/symptoms are due to cholinergic effects and/or if the GI signs/symptoms occur within 24 hours of the infusion.

12.9. Appendix 9: *Clostridium Difficile* Testing Procedure and Algorithm



*If processing and testing cannot be performed within 24 hours, the specimen should be frozen immediately after collection.
**If specimen is sent to a reference laboratory, the procedures to be ordered should follow the same algorithm above.
GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test

12.10. Appendix 10: Country-Specific Requirements

No country-specific requirements exist.

12.11. Appendix 11: Physiologically Based Pharmacokinetic Model Input Parameters

Parameters	Value	References /Resources
Molecular weight	448.5	Investigator Brochure
Compound type	Dibasic	Technical Evidence Document
pKa 1	8.83	Adamantis
pKa 2	6.2	Calculated using Adamantis
cLog P	0.16	Calculated using Adamantis
Fu Plasma	0.67	Study # GlaxoSmithKline Document Number 2013N170240_00
Blood:Plasma ratio	0.95	Study # GlaxoSmithKline Document Number 2012N131922_00
Vdss	1.30	Predicted Full PBPK with addtional organ compartment and Kp scalar 0.7
Additional organ Kp	100	Predicted value of pigmented tissue from QWBA Study # GlaxoSmithKline Document Number 2012N156820_00
CYP3A4 f_m	0.25	
CYP3A4 CL_{int} (μL/min/pmole P450)	0.0434	SimCYP calculation based on CLi.v. of 43 L/hr with measured renal clearance of 16 L/hr with CYP3A4 fm = 0.25
Additional HLM CL_{int} (μl/min/mg protein)	9.00	SimCYP calculation based on CLi.v. of 43 L/hr with measured renal clearance of 16 L/hr with CYP3A4 fm=0.25

CYP = cytochrome 450, Fu = fraction unbound; Vdss = volume of distribution at steady state; Kp = equilibrium partition coefficient of drug; PBPK = physiologically based pharmacokinetic model; QWBA = quantitative whole-body autoradioluminography