TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

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

Compound Number: GSK2140944

Development Phase: I

Effective Date: 05-SEP-2017

Protocol Amendment Number: 02

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N281831_00	2016-JUL-12	Original
2016N281831_01	2017-MAR-16	Amendment No. 1
The purpose of this amendment is to remove the Chinese cohort and introduce a second oral dose for Japanese subjects in Part 2 in a fixed sequence design. Japanese subjects will receive a single 1500-mg dose in Period 1 followed by a single 3000-mg dose in Period 2. Blood and urine samples (Part 2 only) will also be collected for pharmacokinetic analysis of gepotidacin concentrations in Japanese subjects.		
2016N281831_02	2017-SEP-05	Amendment No. 2
The purpose of this amendment is to introduce an additional part to the study (Part 3), and an additional cohort of Japanese subjects will be enrolled in a fixed sequence design. Japanese subjects in the fed state will receive single escalating doses of gepotidacin (1500 mg, 2250 mg, and 3000 mg) in Periods 1, 2, and 3, respectively, or placebo. This amendment provides additional guidelines for managing subjects in Part 3 who experience adverse events of diarrhea.		

SPONSOR SIGNATORY

PPD

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Medical Director
Infectious Disease Medicines Development
and Discovery

05 SEP 2017
Date

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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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(s): IND 111885

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number BTZ117351

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

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 Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY BTZ117351

Rationale

Part 1a is being conducted to evaluate the safety, tolerability, and relative bioavailability of the 2 free base tablet formulations (related compound [RC] and high shear wet granulation [HSWG]) compared with the reference capsule formulation. This will guide which gepotidacin formulation will be used for future pivotal studies and commercialization. Following review of pharmacokinetic (PK), safety, and tolerability data in Part 1a, a decision will be made whether to proceed with the remainder of the study.

Part 1b will assess the effect of food on the pharmacokinetics of the tablet formulation selected from Part 1a. If the relative bioavailability of the tablet formulations are similar to the reference capsule formulation, Part 1b may not be needed, and the results of moderate fat meal evaluated in the RC mesylate tablet from Study BTZ117349 will be used to guide dosing recommendations with food.

Part 2 will evaluate the pharmacokinetics, safety, and tolerability of 2 different doses of the tablet formulation selected from Part 1a in Japanese subjects. Testing gepotidacin in this specific population will provide PK data and enable future pivotal Phase III studies in Japan.

Part 3 will evaluate the pharmacokinetics, safety, and tolerability of 3 different doses of the tablet formulation selected from Part 1a in Japanese subjects in the fed state. Testing gepotidacin in this specific population will provide PK data under fed conditions and enable future pivotal Phase III studies in Japan.

Objectives/Endpoints

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

Objectives	Endpoints
• To assess dose proportionality following a single 1500-mg (2 × 750 mg) dose, a single 2250-mg (3 × 750 mg) dose, and a single 3000-mg (4 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state	

AE = adverse event; ECG = electrocardiogram; HSWG = high shear wet granulation; RC = related compound.

Overall Design

This is a Phase I, multi-center, single-dose, 3-part study. Parts 1 and 2 are open-label, and Part 3 is a randomized, double-blind, placebo-controlled study. Part 1a is being conducted to evaluate the relative bioavailability of 2 free base tablet formulations of gepotidacin compared with the reference capsule formulation under fasted conditions. Based upon PK, safety and tolerability data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for the remainder of the study. Part 1b will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Part 2 will evaluate pharmacokinetics of 2 different doses of the selected tablet formulation in Japanese subjects under fasted conditions. Part 3 will evaluate pharmacokinetics of 3 single escalating doses of the selected tablet formulation in Japanese subjects in the fed state.

Part 1a: Relative Bioavailability

Part 1a is a 3-period, cross-over study that will assess the relative bioavailability of a single 1500-mg dose of gepotidacin in 2 free base tablet formulations (2 × 750 mg RC and HSWG tablets) compared with the reference capsule formulation of gepotidacin (3 × 500-mg capsules). Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA).

Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations. Blood and urine samples will be collected up to approximately 48 hours after dosing.

Part 1b (Optional): Food Effect

Part 1b is a 2-period, cross-over study and will evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation selected from Part 1a. If both formulations of the free base tablet exhibit similar bioavailability to the capsule formulation, then the results of the moderate fat meal evaluated in the RC mesylate tablet formulation from Study BTZ117349 will be used to guide dosing recommendations with food.

Subjects will participate in 2 treatment periods and blood samples will be collected for PK analysis of gepotidacin concentrations. Blood samples will be collected up to approximately 48 hours after dosing.

Part 2: Pharmacokinetics in Japanese Subjects

Part 2 is a 2-period, fixed-sequence study and will evaluate the pharmacokinetics of a single dose of 1500 mg followed by a single dose of 3000 mg gepotidacin tablet formulation selected from Part 1a in a cohort of Japanese subjects under fasted conditions.

Subjects will participate in 2 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations. Blood and urine samples will be collected up to approximately 48 hours after dosing.

Part 3: Pharmacokinetics in Japanese Subjects - Fed State

Part 3 is a 3-period, randomized, double-blind, placebo-controlled, fixed-sequence study and will evaluate the safety, tolerability, and pharmacokinetics of single ascending doses of 1500 mg, 2250 mg, and 3000 mg gepotidacin tablet formulation selected from Part 1a or placebo in a cohort of Japanese subjects in the fed state.

Subjects will be stratified by gender in a 1:1 ratio and randomly assigned (10 active: 2 placebo) to receive gepotidacin or placebo. For each period, a sentinel group of up to 4 subjects will be dosed with study drug and evaluated for safety and tolerability prior to dosing the remaining subjects. The adverse event profiles will be reviewed before escalating to the next dose. Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations. Blood and urine samples will be collected up to approximately 48 hours after dosing.

Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic. Subjects will enter the clinic at Check-in (Day –1) before study drug administration (Day 1) and will be enrolled as follows:

Part 1a – Relative Bioavailability:

- Treatment A: Gepotidacin 1500 mg (3 × 500 mg) reference capsules
- Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets
- Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (ABC, CAB, or BCA) to receive a single dose of gepotidacin 1500 mg (2 × 750 mg) RC tablet, 1500 mg (2 × 750 mg) HSWG tablet, or 1500 mg (3 × 500 mg) reference capsule in each period. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

Based on PK, safety, and tolerability data from Part 1a, subjects may be enrolled for the remainder of the study.

Part 1b (Optional) – Food Effect:

- Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets – fasted
- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets – fed

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (DE or ED) and receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted and fed conditions. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Part 2: Pharmacokinetics in Japanese Subjects

- Treatment B or C: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets, respectively
- Treatment F: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets

On Day 1 (Period 1), subjects will receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. On Day 1 of Period 2, subjects will receive a single 3000-mg (4 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Part 3: Pharmacokinetics in Japanese Subjects - Fed State

- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets - fed
- Treatment G: Gepotidacin 2250 mg (3 × 750 mg) RC or HSWG tablets - fed
- Treatment H: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets - fed
- Treatment I: Placebo tablets - fed

Subjects will be stratified by gender in a 1:1 ratio and randomly assigned (10 active: 2 placebo) to receive gepotidacin tablet (RC or HSWG) selected from Part 1a in an ascending manner (Treatments E, G, and H) on Day 1 of Periods 1, 2, and 3, respectively, or placebo. For each period, a sentinel group of up to 4 subjects will be dosed with study drug and evaluated for safety and tolerability prior to dosing the remaining subjects. There will be a washout period of at least 3 days between doses. The adverse event profiles will be reviewed before escalating to the next dose. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all

scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

Type and Number of Subjects

For Part 1a, approximately 27 subjects will be enrolled with approximately 9 subjects in each of the 3 treatment sequences to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation. For Part 1b, approximately 16 subjects will be enrolled with approximately 8 subjects in each of the 2 treatment sequences. For Part 2, approximately 10 Japanese subjects will be enrolled. For Part 3, approximately 12 Japanese subjects (ideally 6 male, 6 female) will be enrolled.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the sponsor in consultation with the investigator.

Analysis

Plasma concentrations of gepotidacin will be analyzed (as data permit) by noncompartmental PK analysis to determine the following PK metrics: area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinite time [AUC(0-∞)], AUC from time 0 to time of last quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax), relative bioavailability of drug (Frel; Part 1a only), terminal phase half-life (t1/2), lag time before observation of drug concentrations in sampled matrix (tlag), and time to first occurrence of Cmax (Tmax). AUC(0-∞) and Cmax following single dose may be used for assessment of dose proportionality (Parts 2 and 3 only).

Urine (Parts 1a, 2, and 3 only) 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)], AUC from time 0 to 12 hours after dosing [AUC(0-12)], AUC from time 0 to 24 hours after dosing [AUC(0-24)], AUC from time 0 to 48 hours after dosing [AUC(0-48)], percentage of the given dose of drug excreted in urine (fe%), and renal clearance of drug (CLr).

Plasma and urine (Parts 1a, 2, and 3 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.

The log-transformed AUC(0-∞), AUC(0-t), and Cmax values for gepotidacin will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed-effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% confidence intervals (CIs) for the differences of interest (RC tablets and HSWG tablets versus capsules) will be constructed

using the residual variance. Point and interval estimates will then be exponentially back-transformed to construct point and 90% CI estimates for the ratios of interest (RC tablets and HSWG tablets versus capsules).

Estimates of within-subject variability for AUC(0-∞), AUC(0-t), and Cmax of gepotidacin will be provided, where:

$$CVw\ (\%) = \mathrm{sqrt}(\exp[MSE] - 1) \times 100$$

and MSE is the residual mean squared error from the model. CVw(%) represents a pooled measure of within-subject variability across regimens.

Distributional assumptions will be assessed by residual plots. Homogeneity of variance will be assessed by plotting the residuals against the predicted values from the model, whilst normality will be examined by normal probability plots. If assumptions are grossly violated, alternative analyses will be considered.

For Parts 2 and 3, dose proportionality of AUC(0-∞) and Cmax will be explored separately and/or pooled together as a single model.

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

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 type II 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

Part 1a is being conducted to evaluate the safety, tolerability, and relative bioavailability of the 2 free base tablet formulations (related compound [RC] and high shear wet granulation [HSWG]) compared with the reference capsule formulation. This will guide which gepotidacin formulation will be used for future pivotal studies and commercialization. Following review of pharmacokinetic (PK), safety, and tolerability data in Part 1a, a decision will be made whether to proceed with the remainder of the study.

Part 1b will assess the effect of food on the pharmacokinetics of the tablet formulation selected from Part 1a. If the relative bioavailability of the tablet formulations are similar to the reference capsule formulation, Part 1b may not be needed, and the results of moderate fat meal evaluated in the RC mesylate tablet from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food.

Part 2 will evaluate the pharmacokinetics, safety, and tolerability of 2 different doses of the tablet formulation selected from Part 1a in Japanese subjects. Testing gepotidacin in this specific population will provide PK data and enable future pivotal Phase III studies in Japan.

Part 3 will evaluate the pharmacokinetics, safety, and tolerability of 3 different doses of the tablet formulation selected from Part 1a in Japanese subjects in the fed state. Testing gepotidacin in this specific population will provide PK data under fed conditions and enable future pivotal Phase III studies in Japan.

2.2. Brief Background

Gepotidacin has been administered to healthy subjects in 7 Phase I studies and 2 Phase II studies. 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. Additional details can be found in the Investigator's Brochure (IB; GlaxoSmithKline Document Number CM2010/00033/04).

3. OBJECTIVES AND ENDPOINTS

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

Objectives	Endpoints
Part 3 • To assess the safety and tolerability of a single 1500-mg (2 × 750 mg) dose, a single 2250-mg (3 × 750 mg) dose, and a single 3000-mg (4 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state • To assess dose proportionality following a single 1500-mg (2 × 750 mg) dose, a single 2250-mg (3 × 750 mg) dose, and a single 3000-mg (4 × 750 mg) dose of gepotidacin tablets (RC or HSWG) selected from Part 1a in Japanese subjects in the fed state	

AE = adverse event; ECG = electrocardiogram; HSWG = high shear wet granulation; RC = related compound.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I, multi-center, single-dose, 3-part study. Parts 1 and 2 are open-label, and Part 3 is a randomized, double-blind, placebo-controlled study. Part 1a is being conducted to evaluate the relative bioavailability of 2 free base tablet formulations of gepotidacin compared with the reference capsule formulation under fasted conditions. Based upon PK, safety, and tolerability data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for the remainder of the study. Part 1b will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Part 2 will evaluate pharmacokinetics of 2 different doses of the selected tablet formulation in Japanese subjects under fasted conditions. Part 3 will evaluate pharmacokinetics of 3 single escalating doses of the selected tablet formulation in Japanese subjects in the fed state.

Part 1a: Relative Bioavailability

Part 1a is a 3-period, cross-over study that will assess the relative bioavailability of a single 1500-mg dose of gepotidacin in 2 free base tablet formulations (2 × 750 mg RC and HSWG tablets) compared with the reference capsule formulation of gepotidacin (3 × 500-mg capsules). Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA). See the study schematic in Table 1 for more details.

Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 9). Blood and urine samples will be collected up to approximately 48 hours after dosing.

Table 1 Part 1a Relative Bioavailability Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.
[a] 1500 mg single dose given as 3 × 500-mg capsules (Treatment A; reference formulation)
[b] 1500 mg single dose given as 2 × 750-mg RC (Treatment B) or HSWG (Treatment C) tablets

Part 1b (Optional): Food Effect

Part 1b is a 2-period, cross-over study and will evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation selected from Part 1a. If both formulations of the free base tablet exhibit similar bioavailability to the capsule formulation, then the results of the moderate fat meal evaluated in the RC mesylate tablet formulation from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food. See the study schematic in Table 2 for more details.

Subjects will participate in 2 treatment periods and blood samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 9). Blood samples will be collected up to approximately 48 hours after dosing.

Table 2 Part 1b Food Effect Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.
[a] 1500 mg single dose given as 2 × 750 mg tablets fasted (Treatment D) and fed (Treatment E)

Part 2: Pharmacokinetics in Japanese Subjects

Part 2 is a 2-period, fixed-sequence study and will evaluate the pharmacokinetics of a single dose of 1500 mg followed by a single dose of 3000 mg gepotidacin tablet formulation selected from Part 1a in a cohort of Japanese subjects under fasted conditions. See the study schematic in Table 3 for more details.

Subjects will participate in 2 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 9). Blood and urine samples will be collected up to approximately 48 hours after dosing.

Table 3 Part 2 Pharmacokinetic Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.
[a] 1500 mg single dose given as 2 × 750-mg RC (Treatment B) or HSWG (Treatment C) tablets; 3000 mg single dose given as 4 × 750-mg RC or HSWG tablets (Treatment F)

Part 3: Pharmacokinetics in Japanese Subjects - Fed State

Part 3 is a 3-period, randomized, double-blind, placebo-controlled, fixed-sequence study and will evaluate the safety, tolerability, and pharmacokinetics of single ascending doses of 1500 mg, 2250 mg, and 3000 mg gepotidacin tablet formulation selected from Part 1a or placebo in a cohort of Japanese subjects in the fed state. See the study schematic in Table 4 for more details.

Table 4 Part 3 Pharmacokinetic Study Design Schematic - Fed State

Treatment	Fixed-sequence					Follow-up
RC, HSWG, or placebo tablet - fed[a]	Period 1	Wash-out At least 3 days	Period 2	Wash-out At least 3 days	Period 3	5 to 7 days after final dose
Sequence 7	E or I		G or I		H or I	

HSWG = high shear wet granulation; RC = related compound.
[a] 1500 mg single dose given as 2 × 750-mg RC or HSWG (Treatment E) tablets – fed; 2250 mg single dose given as 3 × 750-mg RC or HSWG (Treatment G) tablets – fed; 3000 mg single dose given as 4 × 750-mg RC or HSWG (Treatment H) tablets – fed; or placebo (Treatment I) tablets – fed

Subjects will be stratified by gender in a 1:1 ratio and randomly assigned (10 active: 2 placebo) to receive gepotidacin or placebo. For each period, a sentinel group of up to 4 subjects will be dosed with study drug and evaluated for safety and tolerability prior to dosing the remaining subjects. The adverse event profiles will be reviewed before escalating to the next dose. Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 9). Blood and urine samples will be collected up to approximately 48 hours after dosing.

4.2. Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic. Subjects will enter the clinic at Check-in (Day –1) before study drug administration (Day 1) and will be enrolled as follows:

Part 1a – Relative Bioavailability:

- Treatment A: Gepotidacin 1500 mg (3 × 500 mg) reference capsules
- Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets
- Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (ABC, CAB, or BCA) to receive a single dose of gepotidacin 1500 mg (2 × 750 mg) RC tablet, 1500 mg (2 × 750 mg) HSWG tablet, or 1500 mg (3 × 500 mg) reference capsule in each period. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

Based on PK, safety, and tolerability data from Part 1a, subjects may be enrolled for the remainder of the study.

Part 1b (Optional) – Food Effect:

- Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets – fasted
- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets – fed

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (DE or ED) and receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted and fed conditions. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Part 2: Pharmacokinetics in Japanese Subjects

- Treatment B or C: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets, respectively
- Treatment F: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets

On Day 1 (Period 1), subjects will receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. On Day 1 of Period 2, subjects will receive a single 3000-mg (4 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. There will be a washout period of at least 3 days between doses.

Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Part 3: Pharmacokinetics in Japanese Subjects - Fed State

- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets - fed
- Treatment G: Gepotidacin 2250 mg (3 × 750 mg) RC or HSWG tablets - fed
- Treatment H: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets - fed
- Treatment I: Placebo tablets - fed

On Day 1 (Period 1), subjects will be stratified by gender in a 1:1 ratio and randomly assigned (10 active: 2 placebo) to receive gepotidacin tablet (RC or HSWG) selected from Part 1a in an ascending manner (Treatments E, G, and H) on Day 1 of Periods 1, 2, and 3, respectively, or placebo. For each period, a sentinel group of up to 4 subjects will be dosed with study drug and evaluated for safety and tolerability prior to dosing the remaining subjects. There will be a washout period of at least 3 days between doses. The adverse event profiles will be reviewed before escalating to the next dose. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

4.3. Type and Number of Subjects

For Part 1a, approximately 27 subjects will be enrolled with approximately 9 subjects in each of the 3 treatment sequences to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation. For Part 1b, approximately 16 subjects will be enrolled with approximately 8 subjects in each of the 2 treatment sequences. For Part 2, approximately 10 Japanese subjects will be enrolled. For Part 3, approximately 12 Japanese subjects (ideally 6 male, 6 female) will be enrolled.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the sponsor in consultation with the investigator.

4.4. Design Justification

The study design for Part 1a is commonly used when evaluating relative bioavailability of a drug entity in subjects. It is based on recommendations given in the US Food and Drug Administration (FDA) draft guidance for industry, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations [DHHS, 2014].

The study design for Part 1b is commonly used when evaluating the effect of food on a drug entity in subjects. It is based on recommendations given in the US FDA draft guidance for industry, Food-Effect Bioavailability and Fed Bioequivalence Studies [DHHS, 2002].

The study design for Part 2 is commonly used when evaluating pharmacokinetics of a drug entity in subjects from different ethnic groups. The fixed-sequence design allows for dosing of a lower dose followed by a higher dose within a subject and requires fewer subjects for PK evaluation compared with a parallel cohort. Pharmacokinetic data obtained from this group would satisfy regulatory guidelines and provide dosing recommendations for future Phase III studies in Japanese subjects.

The study design for Part 3 is commonly used when evaluating pharmacokinetics of a drug entity in subjects from different ethnic groups. The fixed-sequence design allows for dosing of a lower dose followed by escalating doses within a subject and requires fewer subjects for PK evaluation compared with a parallel cohort. The fed state will evaluate whether food improves tolerability at higher doses of gepotidacin. Pharmacokinetic data obtained from this group would satisfy regulatory guidelines and provide dosing recommendations under fed conditions for future Phase III studies in Japanese subjects.

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 1500-mg dose of gepotidacin is considered to be the likely dose used for future Phase III studies and will be evaluated in all parts of this study. The 3000-mg dose of gepotidacin will be evaluated in Parts 2 and 3 of this study to evaluate PK, safety, and tolerability for planned use in future Phase III studies. The 2250-mg dose of gepotidacin will be evaluated in Part 3 of this study as an intermediate dose that may have utility for future Phase III studies. Selection of dose and dosing frequency for this study is justified based on observed safety and PK data following oral single (100 to 3000 mg) and repeat twice daily (400 to 2300 mg) and 3 times daily (1500 to 2000 mg) capsule doses in healthy subjects in Studies BTZ114595 and BTZ116778, and single 1500-mg doses of the capsule and RC tablet formulations in Study BTZ117349. The 1500-mg dose (PK data for Study BTZ116778 [Table 5] and Study BTZ117349 [Table 6]) and 3000-mg dose (PK for Study BTZ114595 [Table 7]) achieve the projected therapeutic target plasma concentration and will be evaluated in all parts of the study. A moderate fat meal should only have a minimal effect on PK after administration of the tablet formulation since only a minimal food effect on PK was previously observed in Studies BTZ114595 and BTZ117349 [Table 6].

Table 5 Selected PK Parameters of Gepotidacin After Single and Repeat BID Dose of 1500 mg Orally (Study BTZ116778)

	AUC(0-∞)[a] (µg.hr/mL)	Cmax (µg/mL)[a]	Tmax (hr)[b]	t1/2 (hr)[a]
Single Dose PK [Day 1] (N=12)	20.1 (21.5%)	4.08 (40.3%)	2.0 [1.5 – 4.0]	12.0 (17.9%)
	AUC(0-12)[a] (µg.hr/mL)	**Cmax[1] (µg/mL)[a]**	**Tmax (hr)[b]**	**Ro[a]**
Repeat BID Dose PK [Day 14] (N=12)	22.4 (29.6%)	5.41 (31.1%)	2.0 [1.5 – 4.0]	1.30 (34.9%)

BID = twice daily, CVb% = percent coefficient of variation, PK = pharmacokinetic, Ro = accumulation ratio.
[a] Geometric mean (CVb%) [range]
[b] Median [range]

Table 6 Selected Gepotidacin PK Parameters After Single Dose Oral Capsule and Tablet Administration Under Fasted and Fed Conditions (Study BTZ117349)

	Gepotidacin 1500-mg Capsule/Fasted (N=15)	Gepotidacin 1500 mg RC Tablet/Fasted (N=14)	Gepotidacin 1500 mg RC Tablet/Fed (N=13)
AUC(0-∞) (µg.hr/mL)[a]	13.6 (28.8%)	15.8 (20.3%)	16.9 (16.2%)
Cmax (µg/mL)[a]	3.77 (58.1%)	4.37 (24.7%)	3.73 (29.1%)
Tmax (hr)[b]	1.5 (0.5 – 6.0)	1.75 (1.0 – 3.0)	3.0 (1.5 – 4.0)
t1/2 (hr)[c]	12.1 (27.3)	11.8 (19.2)	11.7 (18.6)

CVb% = percent coefficient of variation, PK = pharmacokinetic.
[a] Geometric mean (CVb%)
[b] Median [range]
[c] Arithmetic mean (CVb%)

Table 7 Selected Gepotidacin PK Parameters After Single Oral Capsule Administration of 3000 mg (Study BTZ114595)

	AUC(0-∞) (µg.hr/mL)[a]	Cmax (µg/mL)[a]	Tmax (hr)[b]	t1/2 (hr)[b]
Single Dose PK [Day 1] (N=6)	33.1 (31.5%)	9.03 (36.0%)	1.25 [1.00 – 2.00]	10.8 [8.66 – 13.90]

CVb% = percent coefficient of variation, PK = pharmacokinetic.
[a] Geometric mean (CVb%)
[b] Median [range]

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with gepotidacin can be found in the IB (GlaxoSmithKline Document Number CM2010/00033/04).

Section 4.6.1 outlines the risk assessment and mitigation strategy for this study (GlaxoSmithKline Document Number 2013N174977).

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product Gepotidacin		
Gastrointestinal (GI) Effects	Lower GI effects (soft stools, flatulence, and diarrhea) are the most common GI-associated adverse events (AEs) reported in human subjects dosed with gepotidacin. Additional events of heme + stool have been observed. In the Phase I studies, out of approximately 400 healthy subjects who have received gepotidacin, *Clostridium difficile* has been reported in 8 subjects. In an acute bacterial skin and skin structure infection study of 122 patients from 13 sites in the USA, the most frequently reported AEs were in the GI system including diarrhea, nausea, and abdominal cramping (see GlaxoSmithKline Document Number 2015N243789_00 Study ID BTZ116704). Events were usually mild in severity with fewer of moderate severity. No patients experienced severe GI AEs and none withdrew due to GI AEs.	Exclusion criterion and close monitoring of clinical parameters and AEs will be conducted to mitigate and assess GI effects. Subjects 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 product and will be followed as appropriate until resolution of the AE. For Part 3, subjects experiencing Grade 3 or Grade 4 diarrhea will be managed as described in Table 8
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 beats per minute to 10 beats per minute 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. The 1500 mg oral dose yields a Cmax of 4.8 µg/mL with predicted ΔΔQTcF (90% CI) of 7.5 msec (6.8 to 8.3 msec) compared with that observed after the therapeutic 1,000 mg intravenous (IV) dose (Cmax of 7.3 µg/mL) administered in the thorough QTc study.	Exclusion criteria, oral dosing of capsule and tablet formulations will have lower Cmax compared with IV doses in the thorough QTc study, 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 (including dizziness, abdominal pain, salivary hypersecretion, hot flush, diarrhea, fatigue, and nausea). 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.
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 GlaxoSmithKline Document Number 2014N198291_00 Study ID 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 GlaxoSmithKline Document Number 2015N243789_00 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, 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 (GlaxoSmithKline Document Number CM2010/00033/04).

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 subjects between 18 and 64 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy 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. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the investigator feels and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 3. Additional inclusion criteria for Japanese subjects (Parts 2 and 3): • The subject was a non-naturalized Japanese citizen and held a Japanese passport. • The subject had 2 Japanese parents and 4 Japanese grandparents who were all

non-naturalized Japanese citizens, as confirmed by interview.

- The subject had been living outside of Japan for up to 10 years as confirmed by interview.

WEIGHT
4. Body weight: • Subjects in Part 1a and Part 1b: ≥50 kg and body mass index (BMI) within the range 19 and 32 kg/m^2, inclusive. • Japanese subjects (Parts 2 and 3): ≥50 kg and BMI within the range 18 and 32 kg/m^2, inclusive.

SEX
5. 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 spontaneous amenorrhea (in questionable cases a blood sample with simultaneous follicle-stimulating hormone [FSH] 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 postmenopausal status prior to study enrollment. b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (Appendix 7) from 30 days prior to the first dose of study medication and until completion of the Follow-up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
6. 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 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, renal, 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. Corrected QT (QTc) >450 msec. 4. Use of a systemic antibiotic within 30 days of Screening. 5. Within 2 months before Screening, either a confirmed history of *Clostridium difficile* diarrhea infection or a past positive *Clostridium difficile* toxin test. 6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 7. History of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinic uses heparin to maintain intravenous cannula patency).

CONCOMITANT MEDICATIONS
8. 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.

RELEVANT HABITS
9. History of regular alcohol consumption within 6 months of screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full strength beer, 470 mL of light beer, 30 mL of spirits, or 100 mL of wine.

10. Urinary cotinine level indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months before screening.

CONTRAINDICATIONS

11. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

12. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
13. Female subject has a positive pregnancy test result or is lactating at Screening or upon admission to the clinic.
14. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN)
15. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. Urinalysis positive for blood without other cause identified.
17. A positive pre-study drug/alcohol screen.
18. A positive test for human immunodeficiency virus (HIV) antibody.
19. Subject has clinically significant abnormal findings in serum chemistry, hematology, or urinalysis results obtained at Screening or Day –1.
20. 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.
21. Previous exposure to gepotidacin within 12 months prior to the first dosing day.
22. Exclusion criteria for screening and baseline 12-lead ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<40 and >100 beats per minute	<50 and >100 beats per minute
PR interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcB or QTcF interval	>450 msec	
QTcB = corrected QT interval using Bazett's formula, QTcF = corrected QT interval using Fridericia's formula.		

- Evidence of previous myocardial infarction (does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, atrioventricular block [second degree or higher], Wolf-Parkinson-White syndrome), sinus pauses >3 seconds, non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats) or any significant arrhythmia which, in the opinion of the principal investigator and GSK medical monitor, will interfere with the safety of the individual subject.

23. 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).
24. Subject is unable to comply with all study procedures, in the opinion of the investigator.
25. 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 demographics, screen failure details, eligibility criteria, and serious AEs (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 site 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 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 site 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 ≥3 × ULN

For details of the required assessments if a subject meets the above criteria, refer to Appendix 2, Liver Chemistry Stopping Criteria.

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 QTcF, then the QTcF 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 non-protocol 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 bulleted criterion below will be withdrawn from the study:

- QTc >500 msec
- Increase from baseline of QTc >60 msec

For subjects with underlying bundle branch block, the following discontinuation criteria will be used instead:

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 diarrhea 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.

For Part 3, subjects who experience diarrhea should also be evaluated using the guidelines detailed in Table 8

Table 8 Part 3 Management of Gastrointestinal Symptoms - Diarrhea

Diarrhea	Treatment Strategy
Grade 1	Initiate supportive care including loperamide.
Grade 2	Initiate supportive care including loperamide. Consider discontinuation of subject from the study upon discussion with medical monitor.
Grades 3 or 4	Above plus consider IV hydration, hospital admission and prophylactic antibiotics as appropriate. Withhold study drug(s) until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxis. Discontinue subject from the study upon discussion with medical monitor.

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) capsule	Gepotidacin (GSK2140944B) RC tablet	Gepotidacin (GSK2140944B) HSWG tablet	Placebo tablet
Formulation description:	Immediate release capsules containing gepotidacin (mesylate salt) and inactive formulation excipients	Immediate release tablets containing gepotidacin (free base) and inactive formulation excipients	Immediate release tablets containing gepotidacin (free base) and inactive formulation excipients	Immediate release tablets containing only inactive formulation excipients
Dosage form:	Capsule	Tablet	Tablet	Tablet
Unit dose strength/ Dosage level:	500 mg/ 1500 mg (3 × 500 mg)	750 mg/ 1500 mg (2 × 750 mg) 2250 mg (3 × 750 mg) 3000 mg (4× 750 mg)	750 mg/ 1500 mg (2 × 750 mg)	Not applicable
Route of Administration:	Oral	Oral	Oral	Oral
Dosing instructions:	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing capsules.	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing tablets.	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing tablets.	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing tablets.
Physical description:	Pink Gelatin size 00 capsule with no identifying markings containing slightly agglomerated pale yellow to grayish yellow to yellowish gray powder.	A capsule-shape white film-coated tablet with no identifying markings.	An oval shape white film-coated tablet with no identifying markings.	A capsule-shape white film-coated tablet with no identifying markings.
Manufacturer/ Source of procurement:	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline

6.2. Treatment Assignment

Subjects in Part 1a will be assigned to a treatment sequence to receive gepotidacin (GSK2140944) capsules, RC tablets, and HSWG tablets in accordance with the randomization schedule generated by PPD before the start of the study, using validated internal software. Based upon PK, safety, and tolerability data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for the remainder of the study. Subjects in Part 1b will be assigned to a treatment sequence to receive the selected tablet formulation under fasted and fed conditions. Japanese subjects in Part 2 will receive 2 different doses of the selected tablet formulation. Japanese subjects in Part 3 will be stratified by gender in a 1:1 ratio and randomized (10 active: 2 placebo) to receive the selected tablet formulation in a fixed sequence or placebo under fed conditions.

A description of each regimen for all study parts is provided in the table below:

Part	Treatment Code	Treatment
1a	A	Gepotidacin 1500 mg (3 × 500 mg) capsules
1a	B	Gepotidacin 1500 mg (2 × 750 mg) RC tablets
1a	C	Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets
1b	D	Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets – fasted
1b	E	Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets – fed
2	B or C	Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets, respectively
2	F	Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets
3	E	Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets – fed
3	G	Gepotidacin 2250 mg (3 × 750 mg) RC or HSWG tablets – fed
3	H	Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets – fed
3	I	Placebo tablets - fed

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.

6.4. Blinding

Parts 1 and 2 will be an open-label study.

Part 3 will be a double-blind (sponsor unblinded) study. The subjects will be completely blinded and the site staff will be blinded to subject-specific treatment assignment. The GSK study team will be unblinded at the aggregate level for decision making throughout the study (e.g. to support dose escalations and use of Bayesian predictive techniques).

Where possible, the GSK/clinical research organization personnel will not have access to subject-specific treatment assignment so as to not potentially introduce bias in discussions with the study site. The pharmacokineticists, statisticians, programmers, and data managers, however, will need access to subject randomization during the course of the study for analysis purposes to support dose adjustments and escalations. Other GSK staff may be included in discussions around dose adjustments and progression if it is deemed necessary and relevant by the above mentioned GSK study team members.

During dosing of a specific cohort, the investigator or treating physician may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the GSK medical monitor or appropriate GSK study personnel before unblinding the subject's treatment assignment. If this is impractical, the investigator must notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the electronic data capture system. *In this situation, the subject will be withdrawn from further treatment if the subject's treatment code is unblinded by the investigator or treating physician.* The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the electronic data capture system. GSK's Global Clinical Safety and Pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to the investigator in accordance with local regulations and/or GSK policy.

During the dose escalation safety review, the GSK clinical team and the investigator will review safety data in a blinded aggregate form. In the event of concern over a potential safety signal, the GSK clinical team and the investigator may review unblinded treatment assignments for the purposes of safety review and dose selection without study interruption. If a safety signal is determined to indicate findings in subjects who received gepotidacin, the findings will be escalated for assessment by the GSK safety team and actions taken as appropriate including review of study for possible halting of further dosing.

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

No special preparation of study treatment is required.

- 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. Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

6.8. Treatment of Study Treatment Overdose

Gepotidacin (all parts) or placebo (Part 3 only) 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.

GlaxoSmithKline 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 volunteers are eligible for study participation.

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 (and/or pummelos, exotic citrus fruits, or grapefruit hybrids) from 7 days prior to the first dose of study medication until after the final dose.

For Parts 1a and 2, subjects will fast from food and drink (except water) for at least 10 hours before dosing on Day 1 of each period. For the fed group of the food effect evaluation in Part 1b, study drug will be administered within 30 minutes after the completion of a moderate fat meal. For Part 3, study drug (gepotidacin or placebo) will be administered within 30 minutes after the completion of a standard Japanese meal.

Fasting requirements may be modified, relaxed, or removed based on emerging safety, tolerability, and PK data from Part 1a. If fasting requirements are removed, then Part 1b may be conducted as a single-period study with drug administered only under fed conditions. In the event that the formulation tested for Part 1b is not tolerated in the fasting state, subjects may receive the formulation with a meal after consultation with the sponsor and investigator.

6.10.2. Caffeine, Alcohol, and Tobacco

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.

Use of tobacco products is not allowed from 3 months before Screening until after the final Follow-up visit.

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

Hormonal contraceptives and/or acetaminophen, at doses of ≤2 grams/day are permitted for use. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

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

6.11.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), 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.

Since gepotidacin is known to have some prolongation of QTc, any drugs known to increase QTc interval should be avoided when treating an AE.

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 Table (Table 9), 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 Table (Table 9).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    5. 12-lead ECG
    6. vital signs
    7. 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.
- 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 Table

Table 9 Time and Events Table: All Parts

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

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

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

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

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

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

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

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

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

[g] Urine collection intervals (Parts 1a, 2, and 3 only) for subjects include 0 (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.

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

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

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 Table (Table 9). 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 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 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 Table (Table 9).
- 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 not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about 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 non-serious 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 related to study treatment (even for noninterventional post marketing 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.

GlaxoSmithKline has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GlaxoSmithKline 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 a 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 the Follow-up visit.

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 heart rate. Body temperature and respiratory rate will be collected at Screening only.

7.3.5. Electrocardiogram

Triplicate 12-lead ECGs will be measured in semi-supine position after 5 minutes rest and obtained at least 5 minutes apart on Day –1. Single 12-lead ECGs will be measured in semi-supine position after 5 minutes rest at all other time points during the study 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 stopping 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 10, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Table (Table 9). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center 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 site by the laboratory responsible for the assessments.

If additional non-protocol 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, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 10.

Table 10 Protocol-Required Safety 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	Aspartate aminotransferase	Total and direct bilirubin
Creatinine	Sodium	Alanine aminotransferase	Total protein
Glucose	Calcium	Alkaline phosphatase	Albumin
Creatine kinase	Bicarbonate	Chloride	
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests			
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), cotinine, and drug screen (via serum, urine, or saliva) to include, at a minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines).			
Fecal occult blood test and stool cultures as appropriate for gastrointestinal adverse events (Appendix 8)			

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

[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

Blood samples for PK analysis of gepotidacin will be collected at the time points indicated in the Time and Events Table (Table 9). 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

Pharmacokinetic urine samples for the analysis of gepotidacin (Parts 1a, 2, and 3 only) will be collected at the time points listed in the Time and Events Table (Table 9). 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. Sample Analysis

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

7.5. Genetics

Depending on the clinical study results, 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 Table (Table 9). 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

All statistical analyses will be performed by PPD using SAS (SAS Institute Inc., Cary, North Carolina, USA), version 9.2 or higher. Pharmacokinetic parameters will be calculated using Phoenix WinNonlin (Certara USA Inc., Princeton, New Jersey, USA), version 6.2.1 or higher.

Before database lock, a reporting and analysis plan (RAP) will be issued as a separate document, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described in a RAP addendum and justified in the final integrated clinical study report.

9.1. Hypotheses

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

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Sample size is largely based on feasibility; however, some justification is provided below.

Part 1a – Relative Bioavailability:

The sample size of 24 PK parameter population subjects will be used based on feasibility to address the objectives of Part 1a of the study.

There are no estimates for the coefficient of variation (CV) of HSWG for any PK parameters. An assumed CV of 27.5% for a PK parameter implies that the sample size of 24 PK parameter evaluable subjects will provide at least 80% power to demonstrate equivalence of the PK parameter. Equivalence is demonstrated when 90% confidence interval (CI) for the ratio of Test:Reference of the PK parameter will be within 0.8 to 1.25 following log transformation.

Two different test formulations are being used in this study. No adjustment for pre-planned multiple comparisons are made.

The total sample size of 27 subjects (9 subjects in 3 sequences) will be randomized to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation.

Part 1b – Food Effect:

A sample size of 16 subjects will be randomized (8 per sequence) based on feasibility to address the objectives of Part 1b of the study.

This sample size will ensure equivalence (as specified in sample size assumption in Part 1a) with 80% power with an assumed CV of 22%.

Part 2 – Pharmacokinetics:

A sample size of approximately 10 subjects will be used in Part 2 based on feasibility to address the objectives of Part 2 of the study.

Part 3 – Pharmacokinetics - Fed State:

A sample size of 12 subjects (ideally 6 male, 6 female) will be randomized (10 active: 2 placebo) based on feasibility to address the objectives of Part 3 of the study.

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, standard deviation (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 1 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 by the study team after completing Part 1a of the study to select the formulation for Part 1b, Part 2, and Part 3, and also to

determine if the effect of food on the selected formulation needs to be studied (Part 1b). At the time of finalization of Protocol Amendment 1, Part 1b is no longer needed based on data from Part 1a. The team will review unblinded data from Part 1a of this open-label study to select the appropriate formulation.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Pharmacokinetic Analyses

Plasma and urine 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 (AUC) from time 0 (predose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of the last quantifiable concentration
Cmax	Maximum observed concentration
Frel	Relative bioavailability of drug, calculated as: $[AUC(0-\infty)_{tablet}]/[AUC(0-\infty)_{capsule}]$ (Part 1a only)
t1/2	Terminal phase half-life
tlag	Lag time before observation of drug concentrations in sampled matrix
Tmax	Time to first occurrence of Cmax

Urine (Parts 1a, 2, and 3 only):

Ae total	Total unchanged drug (total amount of drug excreted in urine), calculated by adding all the fractions of drug collected over all the allotted time intervals
Ae(t1-t2)	Amount of drug excreted in urine in time intervals of 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
AUC(0-12)	Area under the concentration-time curve from time 0 (predose) to 12 hours after dosing
AUC(0-24)	Area under the concentration-time curve from time 0 (predose) to 24 hours after dosing
AUC(0-48)	Area under the concentration-time curve from time 0 (predose) to 48 hours after dosing
fe%	Percentage of the given dose of drug excreted in urine, calculated as: $fe\% = (Ae\ total/Dose) \times 100$
CLr	Renal clearance of drug, calculated as: Ae total/AUC(0-t)

Plasma (all subjects) and urine (Parts 1a, 2, and 3 only) concentrations 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 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 will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed-effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% CIs for the differences of interest (RC tablets and HSWG tablets versus capsules) will be constructed using the residual variance. Point and interval estimates will then be exponentially back-transformed to construct point and 90% CI estimates for the ratios of interest (RC tablets and HSWG tablets versus capsules).

Estimates of within-subject variability for AUC(0-∞), AUC(0-t), and Cmax of gepotidacin will be provided, where:

$$CVw\ (\%) = \mathrm{sqrt}(\exp[MSE] - 1) \times 100$$

and MSE is the residual mean squared error from the model. CVw(%) represents a pooled measure of within-subject variability across regimens.

Distributional assumptions will be assessed by residual plots. Homogeneity of variance will be assessed by plotting the residuals against the predicted values from the model, whilst normality will be examined by normal probability plots. If assumptions are grossly violated, alternative analyses will be considered.

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

For Parts 2 and 3, dose proportionality of AUC(0-∞) and Cmax will be explored separately and/or pooled together as a single model based on dose normalized parameters (log transformed parameters) using reference dose. The lower dose group (1500 mg) would be chosen as the reference dose.

The dose proportionality of AUC(0-∞) and Cmax will be summarized by descriptive statistics (including 90% confidence interval).

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

9.4.2. Secondary Analyses

Safety Analyses

The following safety evaluations will be performed:

- Monitoring for AEs
- Changes in routine clinical laboratory parameters including serum chemistry, hematology, 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 (systolic and diastolic 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 will be defined as any AEs, regardless of relationship to investigational product, that occur after the dose of investigational product. All AEs 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. Listings for the subsets of SAEs and treatment-related SAEs will be provided. The number of 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 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 >500 msec or increase in QTc from the baseline ECG of ≥60 msec, will be summarized by group.

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 site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Council for 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 Site 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 1 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
AUC	area under the plasma concentration-time curve
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 the last quantifiable concentration
BMI	body mass index
CI	confidence interval
CLr	renal clearance of drug
Cmax	maximum observed concentration
CV	coefficient of variation
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
fe%	percentage of the given dose of drug excreted in urine
Frel	relative bioavailability of drug
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HSWG	high shear wet granulation
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury
msec	millisecond
PK	pharmacokinetic
QTc	corrected QT interval; the measure of time between the start of the Q wave and the end of the T wave
QTcB	corrected QT interval using Bazett's formula

QTcF	corrected QT interval using Fridericia's formula
RAP	reporting and analysis plan
RC	related compound
SAE	serious adverse event
SD	standard deviation
SRM	Study Reference Manual
t1/2	terminal phase half-life
tlag	lag time before observation of drug concentrations in sampled matrix
Tmax	time to first occurrence of Cmax
ULN	upper limit of normal

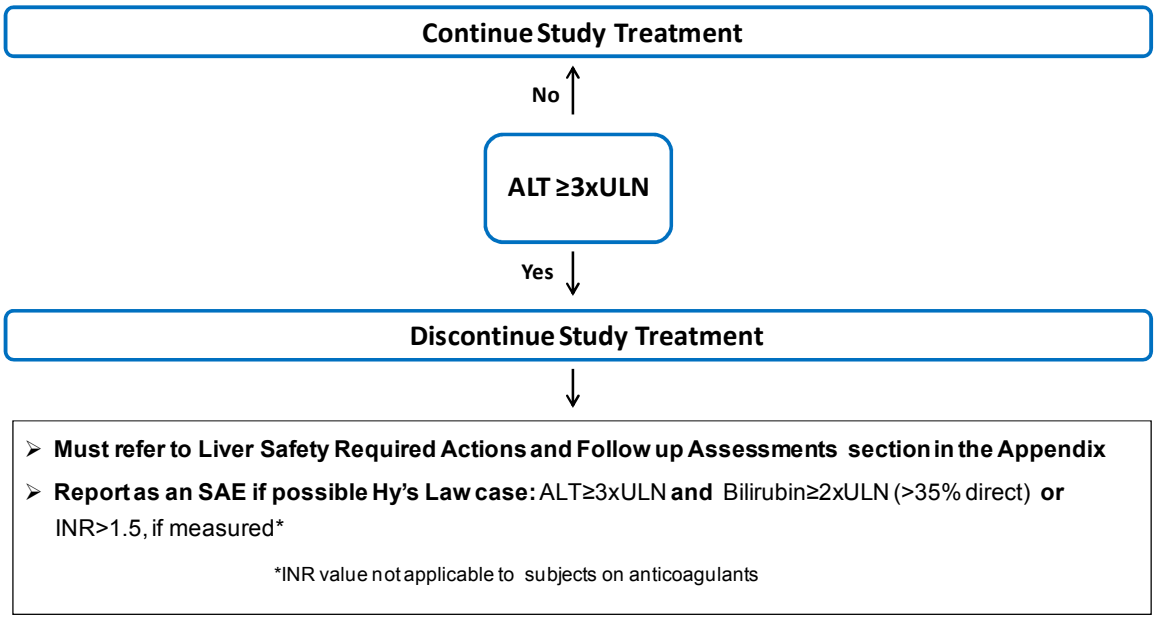
Trademark Information

Trademarks of the GlaxoSmithKline group of companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
Phoenix WinNonlin
SAS

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

Genetics – Background

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.

Genetic Research Objectives and Analyses

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 informed consent form. 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, clinical 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 conditions 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 (SAE) is defined as any untoward medical occurrence that, at any dose:

c. Results in death

d. 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.

e. 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.

f. 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, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

g. Is a congenital anomaly/birth defect

h. 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

i. Is associated with liver injury and 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 INR measurement is obtained, the value is to be recorded on the SAE form.

12.5.3. Recording of Adverse Events and Serious Adverse Events

Adverse Events and Serious Adverse Event 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 CRF
- 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 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.

12.5.4. 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 Division of Microbiology 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.

12.5.5. Reporting of Serious Adverse Events to GSK

Serious adverse event 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, National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the Division of AIDs and modified to better meet the needs of participants in DMID 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; mm Hg = millimeters of mercury; 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
Diarrhea	Mild or transient; 3 to 4 loose stools/day or mild diarrhea lasting <1 week	Moderate or persistent; 5 to 7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; 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. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2), 2009].

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.

1. 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.
2. 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

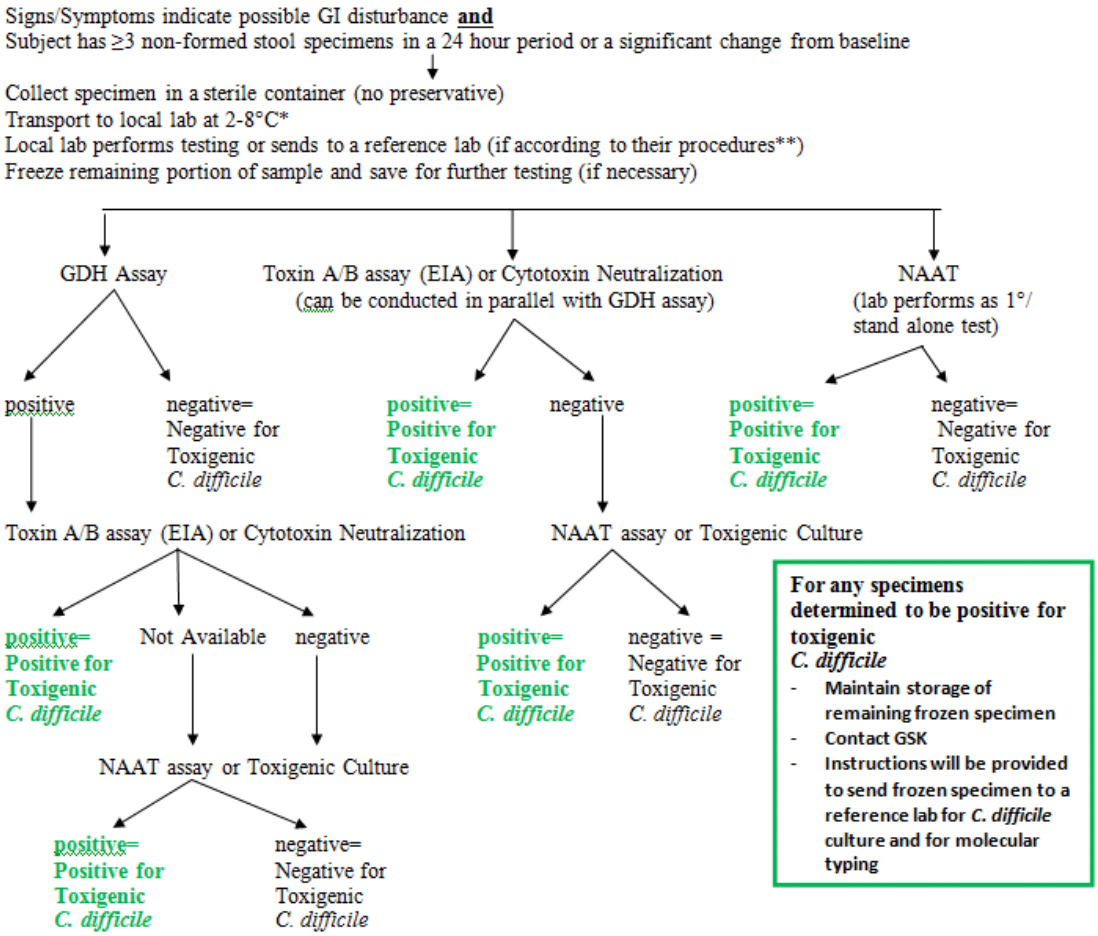
Subjects who experience diarrhea or enteritis should be evaluated with additional fecal occult blood tests and stool cultures as deemed appropriate by the investigator. Any subject with a positive fecal occult blood test should be referred to a gastroenterologist for further evaluation at the discretion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

Subjects who experience an AE of diarrhea 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: Protocol Changes

Protocol Amendment 1

Where the Amendment Applies

To the site participating in Part 2 of BTZ117351

Summary of Amendment Changes With Rationale

The Chinese cohort will be removed from Part 2 of this study since PK data obtained from Chinese subjects living abroad would not satisfy regulatory requirements in China. Japanese subjects in Part 2 will receive a single 1500 mg oral dose followed by a single 3000 mg oral dose of gepotidacin selected from Part 1a in a fixed-sequence design. The inclusion of a 3000-mg dose will be to assess the PK, safety, and tolerability of a higher dose that is intended for future Phase III studies. Blood and urine samples (Part 2 only) will also be collected for PK analysis of gepotidacin concentrations in Japanese subjects.

Minor formatting and administrative changes are also made for clarity.

Protocol Amendment 2

Where the Amendment Applies

To the site participating in Part 3 of BTZ117351

Summary of Amendment Changes With Rationale

An additional part to the study (Part 3) was added, and an additional cohort of Japanese subjects will be enrolled in a fixed sequence design. This additional part was added based on tolerability results from 3000 mg in the fasted state during Part 2. Japanese subjects in the fed state will receive single escalating doses of gepotidacin (1500 mg, 2250 mg, and 3000 mg) in Periods 1, 2, and 3, respectively, or placebo. This amendment also provides additional guidelines for managing subjects in Part 3 who experience adverse events of diarrhea.

Formatting, grammatical, and administrative changes are also made for clarity.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase I, Multi-Center, Open-Label, Single-Dose, 2-Part Study to Evaluate the Relative Bioavailability of Three Formulations in Healthy Subjects, Food Effect on Tablet Formulation in Healthy Subjects, and Pharmacokinetics of Gepotidacin (GSK2140944) in Japanese Subjects

Compound Number: GSK2140944

Development Phase: I

Effective Date: 16-MARCH -2017

Protocol Amendment Number: 1

Author (s):

GSK Authors: PPD (Clinical Pharmacology Modeling and Simulation), PPD (ID, Medicines Discovery and Development), PPD (Clinical Statistics), and PPD (Projects Clinical Platforms and Sciences)

PPD Authors: PPD (Pharmacokineticist), PPD (Biostatistician), and PPD (Medical Writer)

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N281831_00	2016-JUL-12	Original
2016N281831_01	2017-MAR-16	Amendment No. 1
The purpose of this amendment is to remove the Chinese cohort and introduce a second oral dose for Japanese subjects in Part 2 in a fixed sequence design. Japanese subjects will receive a single 1500-mg dose in Period 1 followed by a single 3000-mg dose in Period 2. Blood and urine samples (Part 2 only) will also be collected for pharmacokinetic analysis of gepotidacin concentrations in Japanese subjects.		

SPONSOR SIGNATORY

PPD

PPD

Etienne Dumont, MD
Medical Director
Infectious Disease Medicines
Development and Discovery

16 MAR 2017
Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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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(s): IND 111885

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number BTZ117351

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

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 Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY BTZ117351

Rationale

Part 1a is being conducted to evaluate the safety, tolerability, and relative bioavailability of the 2 free base tablet formulations (related compound [RC] and high shear wet granulation [HSWG]) compared with the reference capsule formulation. This will guide which gepotidacin formulation will be used for future pivotal studies and commercialization. Following review of pharmacokinetic (PK) and safety data in Part 1a, a decision will be made whether to proceed with Parts 1b and 2.

Part 1b will assess the effect of food on the pharmacokinetics of the tablet formulation selected from Part 1a. If the relative bioavailability of the tablet formulations are similar to the reference capsule formulation, Part 1b may not be needed, and the results of moderate fat meal evaluated in the RC mesylate tablet from Study BTZ117349 (see GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food.

Part 2 will evaluate the pharmacokinetics, safety, and tolerability of 2 different doses of the tablet formulation selected in Part 1a in Japanese subjects. Testing gepotidacin in this specific population will provide PK data and enable future pivotal Phase III studies in Japan.

Objectives/Endpoints

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

AE = adverse event; ECG = electrocardiogram; HSWG = high shear wet granulation; RC = related compound.

Overall Design

This is a Phase I, multi-center, open-label, single-dose, 2-part study. Part 1a is being conducted to evaluate the relative bioavailability of 2 free base tablet formulations of gepotidacin compared with the reference capsule formulation under fasted conditions. Based upon safety and PK data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for Parts 1b and 2. Part 1b will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Part 2 will evaluate pharmacokinetics of 2 different doses of the formulation selected from Part 1a in Japanese subjects under fasted conditions.

Part 1a: Relative Bioavailability

Part 1a is a 3-period, cross-over study that will assess the relative bioavailability of a single 1500-mg dose of gepotidacin in 2 free base tablet formulations (2 × 750 mg RC and HSWG tablets) compared with the reference capsule formulation of gepotidacin (3 × 500-mg capsules). Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA).

Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations. Blood and urine samples will be collected up to approximately 48 hours after dosing.

Part 1b (Optional): Food Effect

Part 1b is a 2-period, cross-over study and will evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation (selected in Part 1a). If both formulations of the free base tablet exhibit similar bioavailability to the capsule formulation, then the results of the moderate fat meal evaluated in the RC mesylate tablet formulation from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food.

Subjects will participate in 2 treatment periods and blood samples will be collected for PK analysis of gepotidacin concentrations. Blood samples will be collected up to approximately 48 hours after dosing.

Part 2: Pharmacokinetics in Japanese Subjects

Part 2 is a 2-period, fixed-sequence study and will evaluate the pharmacokinetics of a single dose of 1500 mg followed by a single dose of 3000 mg gepotidacin tablet formulation (RC or HSWG tablet) in a cohort of Japanese subjects under fasted conditions. A decision will be made whether to use the RC tablet formulation or the HSWG tablet formulation based upon the safety and PK data obtained from Part 1a.

Subjects will participate in 2 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations. Blood and urine samples will be collected up to approximately 48 hours after dosing.

Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic. Subjects will enter the clinic at Check-in (Day –1) before study drug administration (Day 1) and will be enrolled as follows:

Part 1a – Relative Bioavailability:

- Treatment A: Gepotidacin 1500 mg (3 × 500 mg) reference capsules
- Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets

- Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (ABC, CAB, or BCA) to receive a single dose of gepotidacin 1500 mg (2 × 750 mg) RC tablet, 1500 mg (2 × 750 mg) HSWG tablet, or 1500 mg (3 × 500 mg) reference capsule in each period. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

Based on PK, safety, and tolerability data from Part 1a, subjects for Parts 1b (food effect) and 2 (Japanese subjects) may be enrolled.

Part 1b (Optional) – Food Effect:

- Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted
- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (DE or ED) and receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted and fed conditions. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Part 2: Pharmacokinetics in Japanese Subjects

- Treatment B or C: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets, respectively
- Treatment F: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets selected from Part 1a

On Day 1 of Period 1, subjects will receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. On Day 1 of Period 2, subjects will receive a single 3000-mg (4 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Type and Number of Subjects

For Part 1a, approximately 27 subjects will be enrolled with approximately 9 subjects in each of the 3 treatment sequences to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation. For Part 1b, approximately 16 subjects will be enrolled with approximately 8 subjects in each of the 2 treatment sequences. For Part 2, approximately 10 Japanese subjects will be enrolled.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the sponsor in consultation with the investigator.

Analysis

Plasma concentrations of gepotidacin will be analyzed (as data permit) by noncompartmental PK analysis to determine the following PK metrics: area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinite time [AUC(0-∞)], AUC from time 0 to time of last quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax), relative bioavailability of drug (Frel; Part 1a only), terminal phase half-life (t1/2), lag time before observation of drug concentrations in sampled matrix (tlag), and time to first occurrence of Cmax (Tmax). AUC(0-∞) and Cmax following single dose may be used for assessment of dose proportionality (Part 2 only).

Urine (Parts 1a and 2 only) 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)], AUC from time 0 to 12 hours after dosing [AUC(0-12)], AUC from time 0 to 24 hours after dosing [AUC(0-24)], AUC from time 0 to 48 hours after dosing [AUC(0-48)], percentage of the given dose of drug excreted in urine (fe%), and renal clearance of drug (CLr).

Plasma and urine (Parts 1a and 2 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.

The log-transformed AUC(0-∞), AUC(0-t), and Cmax values for gepotidacin will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed-effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% confidence intervals (CIs) for the differences of interest (RC tablets and HSWG tablets versus capsules) will be constructed using the residual variance. Point and interval estimates will then be exponentially back-transformed to construct point and 90% CI estimates for the ratios of interest (RC tablets and HSWG tablets versus capsules).

Estimates of within-subject variability for AUC(0-∞), AUC(0-t), and Cmax of gepotidacin will be provided, where:

$$CVw\ (\%) = \mathrm{sqrt}(\exp[MSE] - 1) \times 100$$

and MSE is the residual mean squared error from the model. CVw(%) represents a pooled measure of within-subject variability across regimens.

Distributional assumptions will be assessed by residual plots. Homogeneity of variance will be assessed by plotting the residuals against the predicted values from the model, whilst normality will be examined by normal probability plots. If assumptions are grossly violated, alternative analyses will be considered.

Dose proportionality of AUC(0-∞) and Cmax will be assessed in Part 2.

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

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 type II 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

Part 1a is being conducted to evaluate the safety, tolerability, and relative bioavailability of the 2 free base tablet formulations (related compound [RC] and high shear wet granulation [HSWG]) compared with the reference capsule formulation. This will guide which gepotidacin formulation will be used for future pivotal studies and commercialization. Following review of pharmacokinetic (PK) and safety data in Part 1a, a decision will be made whether to proceed with Parts 1b and 2.

Part 1b will assess the effect of food on the pharmacokinetics of the tablet formulation selected from Part 1a. If the relative bioavailability of the tablet formulations are similar to the reference capsule formulation, Part 1b may not be needed, and the results of moderate fat meal evaluated in the RC mesylate tablet from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food.

Part 2 will evaluate the pharmacokinetics, safety, and tolerability of 2 different doses of the tablet formulation selected in Part 1a in Japanese subjects. Testing gepotidacin in this specific population will provide PK data and enable future pivotal Phase III studies in Japan.

2.2. Brief Background

Gepotidacin has been administered to healthy subjects in 7 Phase I studies and 2 Phase II studies. 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. Additional details can be found in the Investigator's Brochure (IB; GlaxoSmithKline Document Number CM2010/00033/04).

3. OBJECTIVES AND ENDPOINTS

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

AE = adverse event; ECG = electrocardiogram; HSWG = high shear wet granulation; RC = related compound.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I, multi-center, open-label, single-dose, 2-part study. Part 1a is being conducted to evaluate the relative bioavailability of 2 free base tablet formulations of gepotidacin compared with the reference capsule formulation under fasted conditions. Based upon safety and PK data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for Parts 1b and 2. Part 1b will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Part 2 will evaluate pharmacokinetics of 2 different doses of the formulation selected from Part 1a in Japanese subjects under fasted conditions.

Part 1a: Relative Bioavailability

Part 1a is a 3-period, cross-over study that will assess the relative bioavailability of a single 1500-mg dose of gepotidacin in 2 free base tablet formulations (2 × 750 mg RC and HSWG tablets) compared with the reference capsule formulation of gepotidacin (3 × 500-mg capsules). Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA). See the study schematic in Table 1 for more details.

Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 7). Blood and urine samples will be collected up to approximately 48 hours after dosing.

Table 1 Part 1a Relative Bioavailability Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.
[a] 1500 mg single dose given as 3 × 500-mg capsules (Treatment A; reference formulation)
[b] 1500 mg single dose given as 2 × 750-mg RC (Treatment B) or HSWG (Treatment C) tablets

Part 1b (Optional): Food Effect

Part 1b is a 2-period, cross-over study and will evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation (selected in Part 1a). If both formulations of the free base tablet exhibit

similar bioavailability to the capsule formulation, then the results of the moderate fat meal evaluated in the RC mesylate tablet formulation from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food. See the study schematic in Table 2 for more details.

Subjects will participate in 2 treatment periods and blood samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 7). Blood samples will be collected up to approximately 48 hours after dosing.

Table 2 Part 1b Food Effect Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.

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

Part 2: Pharmacokinetics in Japanese Subjects

Part 2 is a 2-period, fixed-sequence study and will evaluate the pharmacokinetics of a single dose of 1500 mg followed by a single dose of 3000 mg gepotidacin tablet formulation (RC or HSWG tablet) in a cohort of Japanese subjects under fasted conditions. A decision will be made whether to use the RC tablet formulation or the HSWG tablet formulation based upon the safety and PK data obtained from Part 1a. See the study schematic in Table 3 for more details.

Subjects will participate in 2 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 7). Blood and urine samples will be collected up to approximately 48 hours after dosing.

Table 3 Part 2 Pharmacokinetic Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.

[a] 1500 mg single dose given as 2 × 750-mg RC (Treatment B) or HSWG (Treatment C) tablets; 3000 mg single dose given as 4 × 750-mg RC or HSWG tablets (Treatment F)

4.2. Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic. Subjects will enter the clinic at Check-in (Day –1) before study drug administration (Day 1) and will be enrolled as follows:

Part 1a – Relative Bioavailability:

- Treatment A: Gepotidacin 1500 mg (3 × 500 mg) reference capsules
- Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets
- Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (ABC, CAB, or BCA) to receive a single dose of gepotidacin 1500 mg (2 × 750 mg) RC tablet, 1500 mg (2 × 750 mg) HSWG tablet, or 1500 mg (3 × 500 mg) reference capsule in each period. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

Based on PK, safety, and tolerability data from Part 1a, subjects for Parts 1b (food effect) and 2 (Japanese subjects) may be enrolled.

Part 1b (Optional) – Food Effect:

- Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted
- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (DE or ED) and receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted and fed conditions. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Part 2: Pharmacokinetics in Japanese Subjects

- Treatment B or C: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets, respectively
- Treatment F: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets selected from Part 1a

On Day 1 of Period 1, subjects will receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. On Day 1 of Period 2, subjects will receive a single 3000-mg (4 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

4.3. Type and Number of Subjects

For Part 1a, approximately 27 subjects will be enrolled with approximately 9 subjects in each of the 3 treatment sequences to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation. For Part 1b, approximately 16 subjects will be enrolled with approximately 8 subjects in each of the 2 treatment sequences. For Part 2, approximately 10 Japanese subjects will be enrolled.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the sponsor in consultation with the investigator.

4.4. Design Justification

The study design for Part 1a is commonly used when evaluating relative bioavailability of a drug entity in subjects. It is based on recommendations given in the US Food and Drug Administration (FDA) draft guidance for industry, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations [DHHS, 2014].

The study design for Part 1b is commonly used when evaluating the effect of food on a drug entity in subjects. It is based on recommendations given in the US FDA draft guidance for industry, Food-Effect Bioavailability and Fed Bioequivalence Studies [DHHS, 2002].

The study design for Part 2 is commonly used when evaluating pharmacokinetics of a drug entity in subjects from different ethnic groups. The fixed-sequence design allows for dosing of a lower dose followed by a higher dose within a subject and requires fewer subjects for PK evaluation compared with a parallel cohort. Pharmacokinetic data obtained from this group would satisfy regulatory guidelines and provide dosing recommendations for future Phase III studies in Japanese subjects.

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 1500-mg dose of gepotidacin is considered to be the likely dose used for future Phase III studies and will be evaluated in all parts of this study. The 3000-mg dose of gepotidacin will be evaluated in Part 2 of this study to evaluate PK, safety, and tolerability for planned use in future Phase III studies. Selection of dose and dosing frequency for this study is justified based on observed safety and PK data following oral single (100 to 3000 mg) and repeat twice daily (400 to 2300 mg) and 3 times daily (1500 to 2000 mg) capsule doses in healthy subjects in Studies BTZ114595 and BTZ116778, and single 1500-mg doses of the capsule and RC tablet formulations in Study BTZ117349. The 1500-mg dose (PK data for Study BTZ116778 [Table 4] and Study BTZ117349 [Table 5]) and 3000-mg dose (PK for Study BTZ114595 [Table 6]) achieve the projected therapeutic target plasma concentration and will be evaluated in all parts of the study. A moderate fat meal should only have a minimal effect on PK after administration of the tablet formulation since only a minimal food effect on PK was previously observed in Studies BTZ114595 and BTZ117349 [Table 5].

Table 4 Selected PK Parameters of Gepotidacin After Single and Repeat BID Dose of 1500 mg Orally (Study BTZ116778)

	AUC(0-∞)[a] (µg.hr/mL)	Cmax (µg/mL)[a]	Tmax (hr)[b]	t1/2 (hr)[a]
Single Dose PK [Day 1] (N=12)	20.1 (21.5%)	4.08 (40.3%)	2.0 [1.5 – 4.0]	12.0 (17.9%)
	AUC(0-12)[a] (µg.hr/mL)	**Cmax[1] (µg/mL)[a]**	**Tmax (hr)[b]**	**Ro[a]**
Repeat BID Dose PK [Day 14] (N=12)	22.4 (29.6%)	5.41 (31.1%)	2.0 [1.5 – 4.0]	1.30 (34.9%)

BID = twice daily, CVb% = percent coefficient of variation, PK = pharmacokinetic, Ro = accumulation ratio.
[a] Geometric mean (CVb%) [range]
[b] Median [range]

Table 5 Selected Gepotidacin PK Parameters After Single Dose Oral Capsule and Tablet Administration Under Fasted and Fed Conditions (Study BTZ117349)

	Gepotidacin 1500-mg Capsule/Fasted (N=15)	Gepotidacin 1500 mg RC Tablet/Fasted (N=14)	Gepotidacin 1500 mg RC Tablet/Fed (N=13)
AUC(0-∞)[a] (µg.hr/mL)	13.6 (28.8%)	15.8 (20.3%)	16.9 (16.2%)
Cmax (µg/mL)[a]	3.77 (58.1%)	4.37 (24.7%)	3.73 (29.1%)
Tmax (hr)[b]	1.5 (0.5 – 6.0)	1.75 (1.0 – 3.0)	3.0 (1.5 – 4.0)
t1/2 (hr)[c]	12.1 (27.3)	11.8 (19.2)	11.7 (18.6)

CVb% = percent coefficient of variation, PK = pharmacokinetic.
[a] Geometric mean (CVb%)
[b] Median [range]
[c] Arithmetic mean (CVb%)

Table 6 Selected Gepotidacin PK Parameters After Single Oral Capsule Administration of 3000 mg (Study BTZ114595)

	AUC(0-∞)[a] (µg.hr/mL)	Cmax (µg/mL)[a]	Tmax (hr)[b]	t1/2 (hr)[b]
Single Dose PK [Day 1] (N=6)	33.1 (31.5%)	9.03 (36.0%)	1.25 [1.00 – 2.00]	10.8 [8.66 – 13.90]

CVb% = percent coefficient of variation, PK = pharmacokinetic.
[a] Geometric mean (CVb%)
[b] Median [range]

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with gepotidacin can be found in the IB (GlaxoSmithKline Document Number CM2010/00033/04).

Section 4.6.1 outlines the risk assessment and mitigation strategy for this study (GlaxoSmithKline Document Number 2013N174977).

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product Gepotidacin		
Gastrointestinal (GI) Effects	Lower GI effects (soft stools, flatulence, and diarrhea) are the most common GI-associated adverse events (AEs) reported in human subjects dosed with gepotidacin. Additional events of heme + stool have been observed. In the Phase I studies, out of approximately 400 healthy subjects who have received gepotidacin, *Clostridium difficile* has been reported in 8 subjects. In an acute bacterial skin and skin structure infection study of 122 patients from 13 sites in the USA, the most frequently reported AEs were in the GI system including diarrhea, nausea, and abdominal cramping (see GlaxoSmithKline Document Number 2015N243789_00 Study ID BTZ116704). Events were usually mild in severity with fewer of moderate severity. No patients experienced severe GI AEs and none withdrew due to GI AEs.	Exclusion criterion and close monitoring of clinical parameters and AEs will be conducted to mitigate and assess GI effects. Subjects 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 product 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 beats per minute to 10 beats per minute 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. The 1500 mg oral dose yields a Cmax of 4.8 µg/mL with predicted ΔΔQTcF (90% CI) of 7.5 msec (6.8 to 8.3 msec) compared with that observed after the therapeutic 1,000 mg intravenous (IV) dose (Cmax of 7.3 µg/mL) administered in the thorough QTc study.	Exclusion criteria, oral dosing of capsule and tablet formulations will have lower Cmax compared with IV doses in the thorough QTc study, 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 (including dizziness, abdominal pain, salivary hypersecretion, hot flush, diarrhea, fatigue, and nausea). 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.
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 GlaxoSmithKline Document Number 2014N198291_00 Study ID 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 GlaxoSmithKline Document Number 2015N243789_00 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, 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 (GlaxoSmithKline Document Number CM2010/00033/04).

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 subjects between 18 and 64 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy 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. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the investigator feels and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 3. Additional inclusion criteria for Japanese subjects (Part 2): • The subject was a non-naturalized Japanese citizen and held a Japanese passport. • The subject had 2 Japanese parents and 4 Japanese grandparents who were all

non-naturalized Japanese citizens, as confirmed by interview.

- The subject had been living outside of Japan for up to 10 years as confirmed by interview.

WEIGHT
4. Body weight: • Subjects in Part 1a and Part 1b: ≥50 kg and body mass index (BMI) within the range 19 and 32 kg/m^2, inclusive. • Japanese subjects (Part 2): ≥50 kg and BMI within the range 18 and 32 kg/m^2, inclusive.

SEX
5. 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 spontaneous amenorrhea (in questionable cases a blood sample with simultaneous follicle-stimulating hormone [FSH] 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 postmenopausal status prior to study enrollment. b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (Appendix 7) from 30 days prior to the first dose of study medication and until completion of the Follow-up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
6. 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 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, renal, 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. Corrected QT (QTc) >450 msec. 4. Use of a systemic antibiotic within 30 days of Screening. 5. Within 2 months before Screening, either a confirmed history of *Clostridium difficile* diarrhea infection or a past positive *Clostridium difficile* toxin test. 6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 7. History of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinic uses heparin to maintain intravenous cannula patency).

CONCOMITANT MEDICATIONS
8. 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.

RELEVANT HABITS
9. History of regular alcohol consumption within 6 months of screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full strength beer, 470 mL of light beer, 30 mL of spirits, or 100 mL of wine.

10. Urinary cotinine level indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months before screening.

CONTRAINDICATIONS

11. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

12. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
13. Female subject has a positive pregnancy test result or is lactating at Screening or upon admission to the clinic.
14. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN)
15. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. Urinalysis positive for blood without other cause identified.
17. A positive pre-study drug/alcohol screen.
18. A positive test for human immunodeficiency virus (HIV) antibody.
19. Subject has clinically significant abnormal findings in serum chemistry, hematology, or urinalysis results obtained at Screening or Day –1.
20. 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.
21. Previous exposure to gepotidacin within 12 months prior to the first dosing day.
22. Exclusion criteria for screening and baseline 12-lead ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<40 and >100 beats per minute	<50 and >100 beats per minute
PR interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcB or QTcF interval	>450 msec	
QTcB = corrected QT interval using Bazett's formula, QTcF = corrected QT interval using Fridericia's formula.		

- Evidence of previous myocardial infarction (does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, atrioventricular block [second degree or higher], Wolf-Parkinson-White syndrome), sinus pauses >3 seconds, non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats) or any significant arrhythmia which, in the opinion of the principal investigator and GSK medical monitor, will interfere with the safety of the individual subject.

23. 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).
24. Subject is unable to comply with all study procedures, in the opinion of the investigator.
25. 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 demographics, screen failure details, eligibility criteria, and serious AEs (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 site 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 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 site 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 ≥3 × ULN

For details of the required assessments if a subject meets the above criteria, refer to Appendix 2, Liver Chemistry Stopping Criteria.

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 QTcF, then the QTcF 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 non-protocol 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 bulleted criterion below will be withdrawn from the study:

- QTc >500 msec
- Increase from baseline of QTc >60 msec

For subjects with underlying bundle branch block, the following discontinuation criteria will be used instead:

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 diarrhea 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) capsule	Gepotidacin (GSK2140944B) RC tablet	Gepotidacin (GSK2140944B) HSWG tablet
Formulation description:	Immediate release capsules containing gepotidacin (mesylate salt) and inactive formulation excipients	Immediate release tablets containing gepotidacin (free base) and inactive formulation excipients	Immediate release tablets containing gepotidacin (free base) and inactive formulation excipients
Dosage form:	Capsule	Tablet	Tablet
Unit dose strength/ Dosage level:	500 mg/ 1500 mg (3 × 500 mg)	750 mg/ 1500 mg (2 × 750 mg)	750 mg/ 1500 mg (2 × 750 mg)
Route of Administration:	Oral	Oral	Oral

	Study Treatment		
Dosing instructions:	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing capsules.	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing tablets.	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing tablets.
Physical description:	Pink Gelatin size 00 capsule with no identifying markings containing slightly agglomerated pale yellow to grayish yellow to yellowish gray powder.	A capsule-shape white film-coated tablet with no identifying markings.	An oval shape white film-coated tablet with no identifying markings.
Manufacturer/Source of procurement:	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline

6.2. Treatment Assignment

Subjects in Part 1a will be assigned to a treatment sequence to receive gepotidacin (GSK2140944) capsules, RC tablets, and HSWG tablets in accordance with the randomization schedule generated by PPD before the start of the study, using validated internal software. Subjects in Part 1b will be assigned to a treatment sequence to receive gepotidacin RC or HSWG tablets under fasted and fed conditions.

A description of each regimen for Parts 1 and 2 is provided in the table below:

Part	Treatment Code	Treatment
1a	A	Treatment A: Gepotidacin 1500 mg (3 × 500 mg) capsules
1a	B	Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets
1a	C	Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets
1b	D	Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted
1b	E	Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed
2	B or C	Treatment B or C: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets, respectively
2	F	Treatment F: Gepotidacin 3000 mg (4 × 750 mg) RC or HSWG tablets selected from Part 1a

Subjects in Part 2 will receive 2 different doses of the tablet formulation (RC or HSWG) selected based on PK, safety, and tolerability data from Part 1a.

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.

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

No special preparation of study treatment is required.

- 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. Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

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.

GlaxoSmithKline 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 electronic case report form (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 volunteers are eligible for study participation.

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 (and/or pummelos, exotic citrus fruits, or grapefruit hybrids) from 7 days prior to the first dose of study medication until after the final dose.

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

Fasting requirements may be modified, relaxed, or removed based on emerging safety, tolerability, and PK data from Part 1a. If fasting requirements are removed, then Part 1b may be conducted as a single-period study with drug administered only under fed conditions. In the event that the formulation tested for Part 1b is not tolerated in the fasting state, subjects may receive the formulation with a meal after consultation with the sponsor and investigator.

6.10.2. Caffeine, Alcohol, and Tobacco

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.

Use of tobacco products is not allowed from 3 months before Screening until after the final Follow-up visit.

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

Hormonal contraceptives and/or acetaminophen, at doses of ≤2 grams/day are permitted for use. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

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

6.11.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), 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.

Since gepotidacin is known to have some prolongation of QTc, any drugs known to increase QTc interval should be avoided when treating an AE.

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 Table (Table 7), 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 Table (Table 7).

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.
- 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 Table

Table 7 Time and Events Table: Parts 1a, 1b, and 2

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

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

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

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

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

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

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

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

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

[g] Urine collection intervals (Parts 1a and 2 only) for subjects include 0 (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.

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

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

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 Table (Table 7). 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 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 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 Table (Table 7).
- 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 not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about 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 non-serious 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 related to study treatment (even for noninterventional post marketing 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.

GlaxoSmithKline has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GlaxoSmithKline 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 a 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 the Follow-up visit.

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 heart rate. Body temperature and respiratory rate will be collected at Screening only.

7.3.5. Electrocardiogram

Triplicate 12-lead ECGs will be measured in semi-supine position after 5 minutes rest and obtained at least 5 minutes apart on Day –1. Single 12-lead ECGs will be measured in semi-supine position after 5 minutes rest at all other time points during the study 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 stopping 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 8, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Table (Table 7). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center 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 site by the laboratory responsible for the assessments.

If additional non-protocol 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, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 8.

Table 8 Protocol-Required Safety 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	Aspartate aminotransferase	Total and direct bilirubin
Creatinine	Sodium	Alanine aminotransferase	Total protein
Glucose	Calcium	Alkaline phosphatase	Albumin
Creatine kinase	Bicarbonate	Chloride	
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests			
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), cotinine, and drug screen (via serum, urine, or saliva) to include, at a minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines).			
Fecal occult blood test and stool cultures as appropriate for gastrointestinal adverse events (Appendix 8)			

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

[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

Blood samples for PK analysis of gepotidacin will be collected at the time points indicated in the Time and Events Table (Table 7). 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

Pharmacokinetic urine samples for the analysis of gepotidacin (Parts 1a and 2 only) will be collected at the time points listed in the Time and Events Table (Table 7). 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. Sample Analysis

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

7.5. Genetics

Depending on the clinical study results, 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 Table (Table 7). 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

All statistical analyses will be performed by PPD using SAS (SAS Institute Inc., Cary, North Carolina, USA), version 9.2 or higher. Pharmacokinetic parameters will be calculated using Phoenix WinNonlin (Certara USA Inc., Princeton, New Jersey, USA), version 6.2.1 or higher.

Before database lock, a reporting and analysis plan (RAP) will be issued as a separate document, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described in a RAP addendum and justified in the final integrated clinical study report.

9.1. Hypotheses

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

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Sample size is largely based on feasibility, however some justification is provided below.

Part 1a – Relative Bioavailability:

The sample size of 24 PK parameter population subjects will be used based on feasibility to address the objectives of Part 1a of the study.

There are no estimates for the coefficient of variation (CV) of HSWG for any PK parameters. An assumed CV of 27.5% for a PK parameter implies that the sample size of 24 PK parameter evaluable subjects will provide at least 80% power to demonstrate equivalence of the PK parameter. Equivalence is demonstrated when 90% confidence interval (CI) for the ratio of Test:Reference of the PK parameter will be within 0.8 to 1.25 following log transformation.

Two different test formulations are being used in this study. No adjustment for pre-planned multiple comparisons are made.

The total sample size of 27 subjects (9 subjects in 3 sequences) will be randomized to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation.

Part 1b – Food Effect:

A sample size of 16 subjects will be randomized (8 per sequence) based on feasibility to address the objectives of Part 1b of the study.

This sample size will ensure equivalence (as specified in sample size assumption in Part 1a) with 80% power with an assumed CV of 22%.

Part 2 – Pharmacokinetics:

A sample size of approximately 10 subjects will be used in Part 2 based on feasibility to address the objectives of Part 2 of the study.

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, standard deviation (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 1 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 by the study team after completing Part 1a of the study to select the formulation for Part 1b, and Part 2, and also to determine if the effect of food on the selected formulation needs to be studied (Part 1b). At the time of finalization of the amendment, Part 1b is no longer needed based on data from Part 1a. The team will review unblinded data from Part 1a of this open-label study to select the appropriate formulation.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Pharmacokinetic Analyses

Plasma and urine 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 (AUC) from time 0 (predose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of the last quantifiable concentration
Cmax	Maximum observed concentration
Frel	Relative bioavailability of drug, calculated as: $[AUC(0-\infty)_{tablet}]/[AUC(0-\infty)_{capsule}]$ (Part 1a only)
t1/2	Terminal phase half-life
tlag	Lag time before observation of drug concentrations in sampled matrix
Tmax	Time to first occurrence of Cmax

Urine (Parts 1a and 2 only):

Ae total	Total unchanged drug (total amount of drug excreted in urine), calculated by adding all the fractions of drug collected over all the allotted time intervals
Ae(t1-t2)	Amount of drug excreted in urine in time intervals of 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
AUC(0-12)	Area under the concentration-time curve from time 0 (predose) to 12 hours after dosing
AUC(0-24)	Area under the concentration-time curve from time 0 (predose) to 24 hours after dosing
AUC(0-48)	Area under the concentration-time curve from time 0 (predose) to 48 hours after dosing
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)

Plasma (all subjects) and urine (Parts 1a and 2 only) concentrations 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 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 will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed-effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% CIs for the differences of interest (RC tablets and HSWG tablets versus capsules) will be constructed using the residual variance. Point and interval estimates will then be exponentially back-transformed to construct point and 90% CI estimates for the ratios of interest (RC tablets and HSWG tablets versus capsules).

Estimates of within-subject variability for AUC(0-∞), AUC(0-t), and Cmax of gepotidacin will be provided, where:

$$CVw\ (\%) = \text{sqrt}(\exp[MSE] - 1) \times 100$$

and MSE is the residual mean squared error from the model. CVw(%) represents a pooled measure of within-subject variability across regimens.

Distributional assumptions will be assessed by residual plots. Homogeneity of variance will be assessed by plotting the residuals against the predicted values from the model, whilst normality will be examined by normal probability plots. If assumptions are grossly violated, alternative analyses will be considered.

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

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

Dose Proportionality (Part 2 only)

Dose proportionality of AUC(0-∞) and Cmax will be explored based on dose normalized parameters (log transformed parameters) using reference dose. The lower dose group (1500 mg) would be chosen as the reference dose.

The dose proportionality of AUC(0-∞) and Cmax will be summarized by descriptive statistics (including 90% confidence interval).

9.4.2. Secondary Analyses

Safety Analyses

The following safety evaluations will be performed:

- Monitoring for AEs

- Changes in routine clinical laboratory parameters including serum chemistry, hematology, 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 (systolic and diastolic 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 will be defined as any AEs, regardless of relationship to investigational product, that occur after the dose of investigational product. The treatment-emergent AEs 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 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 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 >500 msec or increase in QTc from the baseline ECG of ≥60 msec, will be summarized by group.

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 site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Council for 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 Site 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 1 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
AUC	area under the plasma concentration-time curve
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 the last quantifiable concentration
BMI	body mass index
CI	confidence interval
CLr	renal clearance of drug
Cmax	maximum observed concentration
CV	coefficient of variation
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
fe%	percentage of the given dose of drug excreted in urine
Frel	relative bioavailability of drug
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HSWG	high shear wet granulation
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury
msec	millisecond
PK	pharmacokinetic
QTc	corrected QT interval; the measure of time between the start of the Q wave and the end of the T wave
QTcB	corrected QT interval using Bazett's formula

QTcF	corrected QT interval using Fridericia's formula
RAP	reporting and analysis plan
RC	related compound
SAE	serious adverse event
SD	standard deviation
SRM	Study Reference Manual
t1/2	terminal phase half-life
tlag	lag time before observation of drug concentrations in sampled matrix
Tmax	time to first occurrence of Cmax
ULN	upper limit of normal

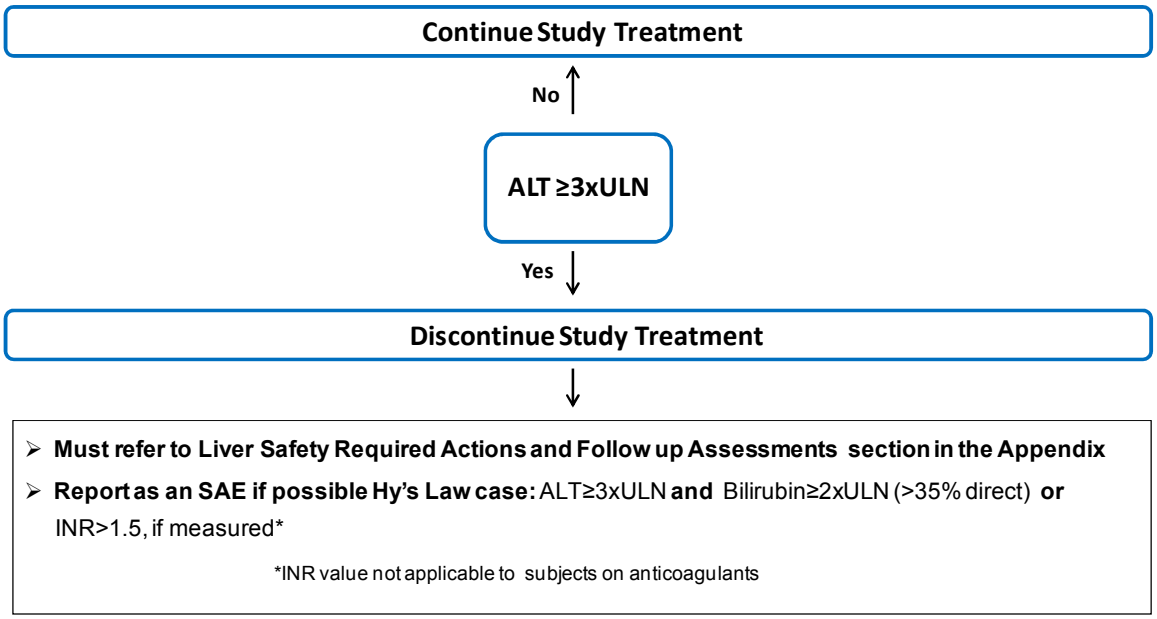
Trademark Information

Trademarks of the GlaxoSmithKline group of companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
Phoenix WinNonlin
SAS

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

Genetics – Background

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.

Genetic Research Objectives and Analyses

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 informed consent form. 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, clinical 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 conditions 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 (SAE) 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, diarrhea, 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 INR measurement is obtained, the value is to be recorded on the SAE form.

12.5.3. Recording of Adverse Events and Serious Adverse Events

Adverse Events and Serious Adverse Event 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 CRF
- 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 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.

12.5.4. 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 Division of Microbiology 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.

12.5.5. Reporting of Serious Adverse Events to GSK

Serious adverse event 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, National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the Division of AIDs and modified to better meet the needs of participants in DMID 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; mm Hg = millimeters of mercury; 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
Diarrhea	Mild or transient; 3 to 4 loose stools/day or mild diarrhea lasting <1 week	Moderate or persistent; 5 to 7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; 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. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2), 2009].

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

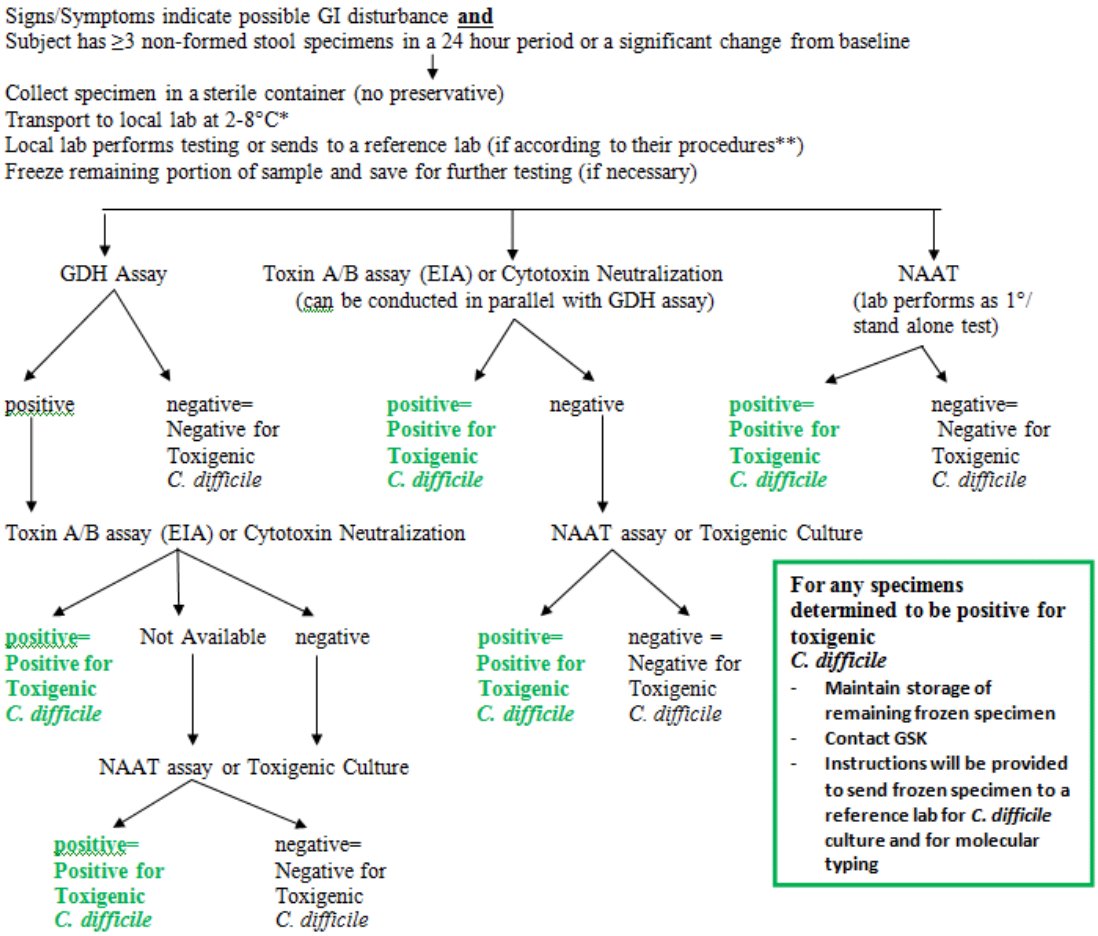
Subjects who experience diarrhea or enteritis should be evaluated with additional fecal occult blood tests and stool cultures as deemed appropriate by the investigator. Any subject with a positive fecal occult blood test should be referred to a gastroenterologist for further evaluation at the discretion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

Subjects who experience an AE of diarrhea 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: Protocol Changes

Protocol Amendment 1

Where the Amendment Applies

To the site participating in Part 2 of BTZ117351

Summary of Amendment Changes With Rationale

The Chinese cohort will be removed from Part 2 of this study since PK data obtained from Chinese subjects living abroad would not satisfy regulatory requirements in China. Japanese subjects in Part 2 will receive a single 1500 mg oral dose followed by a single 3000 mg oral dose of gepotidacin selected from Part 1a in a fixed-sequence design. The inclusion of a 3000-mg dose will be to assess the PK, safety, and tolerability of a higher dose that is intended for future Phase III studies. Blood and urine samples (Part 2 only) will also be collected for PK analysis of gepotidacin concentrations in Japanese subjects.

Minor formatting and administrative changes are also made for clarity.

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A Phase I, Multi-Center, Open-Label, Single-Dose, 2-Part Study to Evaluate the Relative Bioavailability of Three Formulations in Healthy Subjects, Food Effect on Tablet Formulation in Healthy Subjects, and Pharmacokinetics of Gepotidacin (GSK2140944) in Japanese and Chinese Subjects

Compound Number: GSK2140944

Development Phase I

Effective Date: 12-JUL-2016

Authors:

GSK Authors: PPD (Clinical Pharmacology Modeling and Simulation), PPD (ID, Medicines Discovery and Development), PPD (Clinical Statistics), and PPD (Projects Clinical Platforms and Sciences).

PPD Authors: PPD (Pharmacokineticist), PPD (Biostatistician), and PPD (Medical Writer)

SPONSOR SIGNATORY:

PPD

12 JULY 2016

Etienne Dumont, MD
Medical Director
Infectious Disease Medicines Development and Discovery

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor and SAE Contact Information	PPD MD	Safety Hotline: PPD	PPD	PPD	PPD 929 N Front St Wilmington, NC 28401
Secondary Medical Monitor	PPD MD	Safety Hotline: PPD	PPD	PPD	PPD 7551 Metro Center Austin, Texas 78744

Sponsor Legal Registered Address:

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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(s): 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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY BTZ117351

Rationale

Part 1a is being conducted to evaluate the safety, tolerability, and relative bioavailability of the 2 free base tablet formulations (related compound [RC] and high shear wet granulation [HSWG]) compared to the reference capsule formulation. This will guide which gepotidacin formulation will be used for future pivotal studies and commercialization. Following review of pharmacokinetic (PK) and safety data in Part 1a, a decision will be made whether to proceed with Parts 1b and 2.

Part 1b will assess the effect of food on the pharmacokinetics of the tablet formulation selected from Part 1a. If the relative bioavailability of the tablet formulations are similar to the reference capsule formulation, Part 1b may not be needed, and the results of moderate fat meal evaluated in the RC mesylate tablet from Study BTZ117349 (see GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food.

Part 2a will evaluate the pharmacokinetics of the tablet formulation selected in Part 1a in Japanese subjects. Part 2b will evaluate the pharmacokinetics of the tablet formulation selected in Part 1a in Chinese subjects. Testing gepotidacin in these specific populations will provide PK data and enable future pivotal Phase III studies in the respective countries.

Objectives/Endpoints

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

AE = adverse event; ECG = electrocardiogram; HSWG = high shear wet granulation; RC = related compound.

Overall Design

This is a Phase I, multi-center, open-label, single-dose, 2-part study. Part 1a is being conducted to evaluate the relative bioavailability of 2 free base tablet formulations of gepotidacin compared to the reference capsule formulation under fasted conditions. Based upon safety and PK data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for Parts 1b and 2. Part 1b will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Part 2 will evaluate pharmacokinetics in Japanese subjects (Part 2a) under

fasted conditions, and pharmacokinetics in Chinese subjects (Part 2b) under fasted conditions.

Part 1a: Relative Bioavailability

Part 1a is a 3-period, cross-over study that will assess the relative bioavailability of a single 1500-mg dose of gepotidacin in 2 free base tablet formulations (2 × 750 mg RC and HSWG tablets) compared with the reference capsule formulation of gepotidacin (3 × 500-mg capsules). Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA).

Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations. Blood and urine samples will be collected up to approximately 48 hours after dosing.

Part 1b (Optional): Food Effect

Part 1b is a 2-period, cross-over study and will evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation (selected in Part 1a). If both formulations of the free base tablet exhibit similar bioavailability to the capsule formulation, then the results of the moderate fat meal evaluated in the RC mesylate tablet formulation from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349 will be used to guide dosing recommendations with food.

Subjects will participate in 2 treatment periods and blood samples will be collected for PK analysis of gepotidacin concentrations. Blood samples will be collected up to approximately 48 hours after dosing.

Parts 2a and 2b: Pharmacokinetics in Japanese and Chinese Subjects

Parts 2a and 2b will evaluate the pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation (RC or HSWG tablet) in a cohort of Japanese (Part 2a) and Chinese subjects (Part 2b) under fasted conditions. A decision will be made whether to use the RC tablet formulation or the HSWG tablet formulation based upon the safety and PK data obtained from Part 1a.

Subjects will receive study drug on Day 1 and blood samples will be collected for PK analysis of gepotidacin concentrations. Blood samples will be collected up to approximately 48 hours after dosing.

Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic. Subjects will enter the clinic at Check-in (Day –1) before study drug administration (Day 1) and will be enrolled as follows:

Part 1a – Relative Bioavailability:

- Treatment A: Gepotidacin 1500 mg (3 × 500 mg) reference capsules
- Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets
- Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (ABC, CAB, or BCA) to receive a single dose of gepotidacin 1500 mg (2 × 750 mg) RC tablet, 1500 mg (2 × 750 mg) HSWG tablet, or 1500 mg (3 × 500 mg) reference capsule in each period. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

- Based on PK, safety, and tolerability data from Part 1a, subjects for Parts 1b (food effect), 2a (Japanese subjects), and 2b (Chinese subjects) may be enrolled.

Part 1b (Optional) – Food Effect:

- Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted
- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (DE or ED) and receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted and fed conditions. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Parts 2a and 2b: Pharmacokinetics in Japanese and Chinese Subjects

On Day 1, subjects will receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. Subjects will remain in the clinical research unit from Day –1 until Day 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 38 days.

Type and Number of Subjects

For Part 1a, approximately 27 subjects will be enrolled with approximately 9 subjects in each of the 3 treatment sequences to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation. For Part 1b, approximately 16 subjects will be enrolled with approximately 8 subjects in each of the 2 treatment sequences. For Parts 2a and 2b, 12 Japanese and 12 Chinese subjects will be enrolled, respectively.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the sponsor in consultation with the investigator.

Analysis

Plasma concentrations of gepotidacin will be analyzed (as data permit) by noncompartmental PK analysis to determine the following PK metrics: area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinite time [AUC(0-∞)], AUC from time 0 to time of last quantifiable concentration [AUC(0-t)], maximum observed concentration (Cmax), relative bioavailability of drug (Frel; Part 1a only), terminal phase half-life (t1/2), lag time before observation of drug concentrations in sampled matrix (tlag), and time to first occurrence of Cmax (Tmax).

Urine (Part 1a only) 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)], AUC from time 0 to 12 hours after dosing [AUC(0-12)], AUC from time 0 to 24 hours after dosing [AUC(0-24)], AUC from time 0 to 48 hours after dosing [AUC(0-48)], percentage of the given dose of drug excreted in urine (fe%), and renal clearance (CLr).

Plasma and urine (Part 1a 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.

The log-transformed AUC(0-∞), AUC(0-t), and Cmax values for gepotidacin will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% confidence intervals (CIs) for the differences of interest (RC tablets and HSWG tablets versus capsules) will be constructed using the residual variance. Point and interval estimates will then be exponentially back-transformed to construct point and 90% CI estimates for the ratios of interest (RC tablets and HSWG tablets versus capsules).

Estimates of within-subject variability for AUC(0-∞), AUC(0-t), and Cmax of gepotidacin will be provided, where:

$$CVw\ (\%) = \mathrm{sqrt}(\exp[MSE] - 1) \times 100$$

and MSE is the residual mean squared error from the model. CVw(%) represents a pooled measure of within-subject variability across regimens.

Distributional assumptions will be assessed by residual plots. Homogeneity of variance will be assessed by plotting the residuals against the predicted values from the model, whilst normality will be examined by normal probability plots. If assumptions are grossly violated, alternative analyses will be considered.

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

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 type II 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

Part 1a is being conducted to evaluate the safety, tolerability, and relative bioavailability of the 2 free base tablet formulations (related compound [RC] and high shear wet granulation [HSWG]) compared to the reference capsule formulation. This will guide which gepotidacin formulation will be used for future pivotal studies and commercialization. Following review of pharmacokinetic (PK) and safety data in Part 1a, a decision will be made whether to proceed with Parts 1b and 2.

Part 1b will assess the effect of food on the pharmacokinetics of the tablet formulation selected from Part 1a. If the relative bioavailability of the tablet formulations are similar to the reference capsule formulation, Part 1b may not be needed, and the results of moderate fat meal evaluated in the RC mesylate tablet from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349) will be used to guide dosing recommendations with food.

Parts 2a will evaluate the pharmacokinetics of the tablet formulation selected in Part 1a in Japanese subjects. Part 2b will evaluate the pharmacokinetics of the tablet formulation selected in Part 1a in Chinese subjects. Testing gepotidacin in these specific populations will provide PK data and enable future pivotal Phase III studies in the respective countries.

2.2. Brief Background

Gepotidacin has been administered to healthy subjects in 7 Phase I studies and 2 Phase II studies. 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. Additional details can be found in the Investigator's Brochure (IB; GlaxoSmithKline Document Number CM2010/00033/03) and supplement to the IB (GlaxoSmithKline Document Number 2016N275883_00).

3. OBJECTIVES AND ENDPOINTS

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

AE = adverse event; ECG = electrocardiogram; HSWG = high shear wet granulation; RC = related compound.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I, multi-center, open-label, single-dose, 2-part study. Part 1a is being conducted to evaluate the relative bioavailability of 2 free base tablet formulations of gepotidacin compared to the reference capsule formulation under fasted conditions. Based upon safety and PK data obtained from Part 1a, a decision will be made whether to use the free base RC or HSWG tablet formulation for Parts 1b and 2. Part 1b will evaluate the bioavailability of the selected tablet formulation under fasted and fed conditions. Part 2 will evaluate pharmacokinetics in Japanese subjects (Part 2a) under fasted conditions, and pharmacokinetics in Chinese subjects (Part 2b) under fasted conditions.

Part 1a: Relative Bioavailability

Part 1a is a 3-period, cross-over study that will assess the relative bioavailability of a single 1500-mg dose of gepotidacin in 2 free base tablet formulations (2 × 750 mg RC and HSWG tablets) compared with the reference capsule formulation of gepotidacin (3 × 500-mg capsules). Each subject will receive all 3 treatments according to their assigned treatment sequence based on a Latin square design (ABC, CAB, or BCA). See the study schematic in Table 1 for more details.

Subjects will participate in 3 treatment periods and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 5). Blood and urine samples will be collected up to approximately 48 hours after dosing.

Table 1 Part 1a Relative Bioavailability Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.
[a] 1500 mg single dose given as 3 × 500-mg capsules (Treatment A; reference formulation)
[b] 1500 mg single dose given as 2 × 750-mg RC (Treatment B) or HSWG (Treatment C) tablets

Part 1b (Optional): Food Effect

Part 1b is a 2-period, cross-over study and will evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single dose of 1500 mg gepotidacin tablet

formulation (selected in Part 1a). If both formulations of the free base tablet exhibit similar bioavailability to the capsule formulation, then the results of the moderate fat meal evaluated in the RC mesylate tablet formulation from Study BTZ117349 (GlaxoSmithKline Document Number 2013N176846_01 Study ID BTZ117349 will be used to guide dosing recommendations with food. See the study schematic in Table 2 for more details.

Subjects will participate in 2 treatment periods and blood samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 5). Blood samples will be collected up to approximately 48 hours after dosing.

Table 2 Part 1b Food Effect Study Design Schematic

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

HSWG = high shear wet granulation; RC = related compound.
[a] 1500 mg single dose given as 2 × 750 mg tablets fasted (Treatment D) and fed (Treatment E)

Parts 2a and 2b: Pharmacokinetics in Japanese and Chinese Subjects

Parts 2a and 2b will evaluate the pharmacokinetics of a single dose of 1500 mg gepotidacin tablet formulation (RC or HSWG tablet) in a cohort of Japanese (Part 2a) and Chinese subjects (Part 2b) under fasted conditions. A decision will be made whether to use the RC tablet formulation or the HSWG tablet formulation based upon the safety and PK data obtained from Part 1a.

Subjects will receive study drug on Day 1 and blood samples will be collected for PK analysis of gepotidacin concentrations according to the Time and Events Table (Table 5). Blood samples will be collected up to approximately 48 hours after dosing.

4.2. Treatment Arms and Duration

Subjects will be screened within 30 days prior to entry to the clinic. Subjects will enter the clinic at Check-in (Day –1) before study drug administration (Day 1) and will be enrolled as follows:

Part 1a – Relative Bioavailability:

- Treatment A: Gepotidacin 1500 mg (3 × 500 mg) reference capsules
- Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets
- Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (ABC, CAB, or BCA) to receive a single dose of gepotidacin 1500 mg (2 × 750 mg) RC tablet,

1500 mg (2 × 750 mg) HSWG tablet, or 1500 mg (3 × 500 mg) reference capsule in each period. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 of Period 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 44 days.

Based on PK, safety, and tolerability data from Part 1a, subjects for Parts 1b (food effect), 2a (Japanese subjects), and 2b (Chinese subjects) may be enrolled.

Part 1b (Optional) – Food Effect:

- Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fasted
- Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1a – fed

On Day 1 (Period 1), subjects will be randomly assigned to a treatment sequence (DE or ED) and receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a under fasted and fed conditions. There will be a washout period of at least 3 days between doses. Subjects will remain in the clinical research unit from Day –1 until Day 3 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 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 41 days.

Parts 2a and 2b: Pharmacokinetics in Japanese and Chinese Subjects

On Day 1, subjects will receive a single 1500-mg (2 × 750 mg) dose of gepotidacin tablet (RC or HSWG) selected from Part 1a. Subjects will remain in the clinical research unit from Day –1 until Day 3 after all scheduled PK and safety assessments have been completed, and will return to the clinic for a Follow-up visit approximately 5 to 7 days after the final dose of study drug. The duration of the study (from Screening to the Follow-up visit) will be approximately 38 days.

4.3. Type and Number of Subjects

For Part 1a, approximately 27 subjects will be enrolled with approximately 9 subjects in each of the 3 treatment sequences to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation. For Part 1b, approximately 16 subjects will be enrolled with approximately 8 subjects in each of the 2 treatment sequences. For Parts 2a and 2b, 12 Japanese and 12 Chinese subjects will be enrolled, respectively.

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the sponsor in consultation with the investigator.

4.4. Design Justification

The study design for Part 1a is commonly used when evaluating relative bioavailability of a drug entity in subjects. It is based on recommendations given in the US Food and Drug Administration (FDA) draft guidance for industry, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations [DHHS, 2014].

The study design for Part 1b is commonly used when evaluating the effect of food on a drug entity in subjects. It is based on recommendations given in the US FDA draft guidance for industry, Food-Effect Bioavailability and Fed Bioequivalence Studies [DHHS, 2002].

The study designs for Parts 2a and 2b are commonly used when evaluating pharmacokinetics of a drug entity in subjects from different ethnic groups. Pharmacokinetic data obtained from these groups would satisfy regulatory guidelines and provide dosing recommendations for future Phase III studies in specific ethnic groups.

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 1500-mg dose of gepotidacin is considered to be the likely dose used for future Phase 3 studies and will be evaluated in all parts of this study. Selection of dose and dosing frequency for this study is justified based on observed safety and PK data following oral single (100 to 3000 mg) and repeat twice daily (400 to 2300 mg) and 3 times daily (1500 to 2000 mg) capsule doses in healthy subjects in Studies BTZ114595 and BTZ116778, and single 1500-mg doses of the capsule and RC tablet formulations in Study BTZ117349. The 1500-mg dose (PK data for Study BTZ116778 [Table 3] and Study BTZ117349 [Table 4]) achieves the projected therapeutic target plasma concentration and will be evaluated in all parts of the study. A moderate fat meal should only have a minimal effect on PK after administration of the tablet formulation since only a minimal food effect on PK was previously observed in Studies BTZ114595 and BTZ117349 [Table 4].

Table 3 Preliminary PK Parameters of Gepotidacin after Single and Repeat BID Dose of 1500 mg Orally (Study BTZ116778)

	AUC(0-∞)[a] (µg.hr/mL)	Cmax (µg/mL)[a]	tmax (hr)[b]	t1/2 (hr)[a]
Single Dose PK [Day 1] (N=12)	20.0 (21.5%) [15.6 – 31.0]	4.08 (40.3%) [2.0 – 6.62]	2.0 [1.5 – 4.0]	11.7 (19.2%) [9.09 – 16.4]
	AUC(0-12)[a] (µg.hr/mL)	**Cmax[1] (µg/mL)[a]**	**tmax (hr)[b]**	**Ro[a]**
Repeat BID Dose PK [Day 14] (N=12)	22.4 (29.5%) [15.8 – 39.9]	5.41 (31.1%) [3.61 – 8.09]	2.0 [1.5 – 4.0]	1.30 (34.9%) [0.59 – 1.89]

BID = twice daily, CVb% = percent coefficient of variation, PK = pharmacokinetic, Ro = accumulation ratio.
[a] Geometric mean (CVb%) [range]
[b] Median [range]

Table 4 Selected Gepotidacin PK Parameters After Single Dose Oral Capsule and Tablet Administration Under Fasted and Fed Conditions (Study BTZ117349)

	Gepotidacin 1500-mg Capsule/Fasted (N=15)	Gepotidacin 1500 mg RC Tablet/Fasted (N=15)	Gepotidacin 1500 mg RC Tablet/Fed (N=15)
AUC(0-∞)[a] (µg.hr/mL)	13.6 (28.8%)	15.8 (20.3%)	16.9 (16.2%)
Cmax (µg/mL)[a]	3.77 (58.1%)	4.37 (24.7%)	3.73 (29.1%)
tmax (hr)[b]	1.5 (0.5 – 6.0)	1.75 (1.0 – 3.0)	3.0 (1.5 – 4.0)
t1/2 (hr)[c]	12.1 (27.3)	11.8 (19.2)	11.7 (18.6)

CVb% = percent coefficient of variation, PK = pharmacokinetic.
[a] Geometric mean (CVb%)
[b] Median [range]
[c] Arithmetic mean (CVb%)

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with gepotidacin can be found in the IB(GlaxoSmithKline Document Number CM2010/00033/03) and supplement to the IB (GlaxoSmithKline Document Number 2016N275883_00).

Section 4.6.1 outlines the risk assessment and mitigation strategy for this study (GlaxoSmithKline Document Number 2013N174977).

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product Gepotidacin		
Gastrointestinal (GI) Effects	Lower GI effects (soft stools, flatulence, and diarrhea) are the most common GI-associated adverse events (AEs) reported in human subjects dosed with gepotidacin. Additional events of heme + stool have been observed. In the Phase I studies, out of approximately 400 healthy subjects who have received gepotidacin, *C. difficile* has been reported in 8 subjects. In an acute bacterial skin and skin structure infection study of 122 patients from 13 sites in the USA, the most frequently reported AEs were in the GI system including diarrhea, nausea, and abdominal cramping (see GlaxoSmithKline Document Number 2015N243789_00 Study ID BTZ116704). Events were usually mild in severity with fewer of moderate severity. No patients experienced severe GI AEs and none withdrew due to GI AEs.	Exclusion criterion and close monitoring of clinical parameters and AEs will be conducted to mitigate and assess GI effects. Subjects 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 product 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 beats per minute to 10 beats per minute 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. The 1500 mg oral dose yields a Cmax of 4.8 µg/mL with predicted ΔΔQTcF (90% CI) of 7.5 msec (6.8 to 8.3 msec) compared to that observed after the therapeutic 1,000 mg intravenous dose	Exclusion criteria, oral dosing of capsule and tablet formulations will have lower Cmax compared to IV doses in the thorough QTc study, 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	(Cmax of 7.3 µg/mL) administered in the thorough QTc study.	
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 (including dizziness, abdominal pain, salivary hypersecretion, hot flush, diarrhea, fatigue and nausea). 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.
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 GlaxoSmithKline Document Number 2014N198291_00 Study ID 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 GlaxoSmithKline Document Number 2015N243789_00 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, 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 (GlaxoSmithKline Document Number CM2010/00033/03) and supplement to the IB (GlaxoSmithKline Document Number 2016N275883_00).

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 subjects between 18 and 64 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by the investigator based on medical history, clinical laboratory results (serum chemistry, hematology, urinalysis, and serology), vital sign measurements, 12-lead ECG results, and physical examination findings. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the investigator feels and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 3. Additional inclusion criteria for Japanese subjects (Part 2a only): • The subject was a non-naturalized Japanese citizen and held a Japanese passport. • The subject had 2 Japanese parents and 4 Japanese grandparents who were all non-naturalized Japanese citizens, as confirmed by interview.

- The subject had been living outside of Japan for up to 10 years as confirmed by interview.

4. Additional inclusion criteria for Chinese subjects (Part 2b only):
   - The subject was a non-naturalized Chinese citizen and held a Chinese passport.
   - The subject had 2 Chinese parents and 4 Chinese grandparents who were all non-naturalized Chinese citizens, as confirmed by interview.
   - The subject had been living outside of China for up to 10 years as confirmed by interview.

WEIGHT

5. Body weight:
   - Subjects in Part 1a and Part 1b: ≥50 kg and body mass index (BMI) within the range 19 and 32 kg/m^2, inclusive.
   - Japanese and Chinese subjects (Part 2a and Part 2b): ≥50 kg and BMI within the range 18 and 32 kg/m^2, inclusive.

SEX

6. 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. Non-reproductive potential defined as:
   - Pre-menopausal 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 spontaneous amenorrhea (in questionable cases a blood sample with simultaneous follicle-stimulating hormone (FSH) 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 one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (Appendix 7) from 30 days prior to the first dose of study

medication and until completion of the Follow-up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.
INFORMED CONSENT
7. 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 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, renal, 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. Corrected QT (QTc) >450 msec. 4. Use of a systemic antibiotic within 30 days of Screening. 5. Within 2 months before Screening, either a confirmed history of *Clostridium difficile* diarrhea infection or a past positive *Clostridium difficile* toxin test. 6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 7. History of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinic uses heparin to maintain intravenous cannula patency).

CONCOMITANT MEDICATIONS
8. 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.

RELEVANT HABITS
9. History of regular alcohol consumption within 6 months of screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full strength beer, 470 mL of light beer,

30 mL of spirits, or 100 mL of wine.

10. Urinary cotinine level indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months before screening.

CONTRAINDICATIONS

11. History of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

12. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
13. Female subject has a positive pregnancy test result or is lactating at Screening or upon admission to the clinic.
14. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN)
15. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. Urinalysis positive for blood without other cause identified.
17. A positive pre-study drug/alcohol screen.
18. A positive test for human immunodeficiency virus antibody.
19. Subject has clinically significant abnormal findings in serum chemistry, hematology, or urinalysis results obtained at Screening or Day –1.
20. 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.
21. Previous exposure to gepotidacin within 12 months prior to the first dosing day.
22. Exclusion criteria for screening and baseline 12-lead ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<40 and >100 beats per minute	<50 and >100 beats per minute
PR interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcB or QTcF interval	>450 msec	
QTcB = corrected QT interval using Bazett's formula, QTcF = corrected QT interval using Fridericia's formula.		

- Evidence of previous myocardial infarction (does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, atrioventricular block [second degree or higher], Wolf-Parkinson-White syndrome), sinus pauses >3 seconds, non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats) or any significant arrhythmia which, in the opinion of the principal investigator and GSK medical monitor, will interfere with the safety of the individual subject.

23. 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).
24. Subject is unable to comply with all study procedures, in the opinion of the investigator.
25. 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 demographics, screen failure details, eligibility criteria, and serious AEs (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 site 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 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 site 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 ≥3 × ULN

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 QTcF, then the QTcF 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 non-protocol 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 bulleted criterion below will be withdrawn from the study:

- QTc >500 msec
- Increase from baseline of QTc >60 msec

For subjects with underlying bundle branch block, the following discontinuation criteria will be used instead:

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 diarrhea 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) capsule	Gepotidacin (GSK2140944B) RC tablet	Gepotidacin (GSK2140944B) HSWG tablet
Formulation description:	Immediate release capsules containing gepotidacin (mesylate salt) and inactive formulation excipients	Immediate release tablets containing gepotidacin (free base) and inactive formulation excipients	Immediate release tablets containing gepotidacin (free base) and inactive formulation excipients
Dosage form:	Capsule	Tablet	Tablet
Unit dose strength/ Dosage level:	500 mg/ 1500 mg (3 × 500 mg)	750 mg/ 1500 mg (2 × 750 mg)	750 mg/ 1500 mg (2 × 750 mg)
Route of Administration:	Oral	Oral	Oral
Dosing instructions:	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing capsules.	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing tablets.	Dose with 240 mL of water. Up to an additional 100 mL of water may be given to assist in swallowing tablets.

Physical description:	Pink Gelatin size 00 capsule with no identifying markings containing slightly agglomerated pale yellow to grayish yellow to yellowish gray powder.	A capsule-shape white film-coated tablet with no identifying markings.	An oval shape white film-coated tablet with no identifying markings.
Manufacturer/Source of procurement:	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline

6.2. Treatment Assignment

Subjects in Part 1a will be assigned to a treatment sequence to receive gepotidacin (GSK2140944) capsules, RC tablets, and HSWG tablets in accordance with the randomization schedule generated by PPD before the start of the study, using validated internal software. Subjects in Part 1b will be assigned to a treatment sequence to receive gepotidacin RC or HSWG tablets under fasted and fed conditions.

A description of each regimen for Parts 1a and 1b is provided in the table below:

Part	Treatment Code	Treatment
1a	A	Treatment A: Gepotidacin 1500 mg (3 × 500 mg) capsules
1a	B	Treatment B: Gepotidacin 1500 mg (2 × 750 mg) RC tablets
1a	C	Treatment C: Gepotidacin 1500 mg (2 × 750 mg) HSWG tablets
1b	D	Treatment D: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1 – fasted
1b	E	Treatment E: Gepotidacin 1500 mg (2 × 750 mg) RC or HSWG tablets selected from Part 1 – fed

Subjects in Parts 2a, and 2b will receive the tablet formulation (RC or HSWG) selected based on PK, safety, and tolerability data from Part 1a.

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.

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

No special preparation of study treatment is required.

- 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. Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

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 electronic case report form (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 volunteers are eligible for study participation.

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 (and/or pummelos, exotic citrus fruits, or grapefruit hybrids) from 7 days prior to the first dose of study medication until after the final dose.

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

Fasting requirements may be modified, relaxed, or removed based on emerging safety, tolerability, and PK data from Part 1a. If fasting requirements are removed, then Part 1b may be conducted as a single-period study with drug administered only under fed conditions. In the event that the formulation tested for Part 1b is not tolerated in the fasting state, subjects may receive the formulation with a meal after consultation with the sponsor and investigator.

6.10.2. Caffeine, Alcohol, and Tobacco

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.

Use of tobacco products is not allowed from 3 months before Screening until after the final Follow-up visit.

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

Hormonal contraceptives and/or acetaminophen, at doses of ≤2 grams/day is permitted for use. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

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

6.11.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), 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.

Since gepotidacin is known to have some prolongation of QTc, any drugs known to increase QTc interval should be avoided when treating an AE.

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 Table, 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 Table (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.
- 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 Table

Table 5 Time and Events Table: Parts 1a, 1b, 2a, and 2b

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

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

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

[a] The Day –1 visit occurs in Period 1 only. Periods 2 and 3 (Part 1a only) begin on Day 1.

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

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

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

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

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

[g] Urine collection intervals (Part 1a only) for subjects include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours.

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

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

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 Table (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 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 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 Table (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 not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about 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 non serious 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 related to study treatment (even for non-interventional post marketing 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 a 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 the Follow-up visit.

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 heart rate. Body temperature and respiratory rate will be collected at Screening only.

7.3.5. Electrocardiogram

Triplicate 12-lead ECGs will be measured in semi-supine position after 5 minutes rest and obtained at least 5 minutes apart on Day –1. Single 12-lead ECGs will be measured in semi-supine position after 5 minutes rest at all other time points during the study 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 stopping 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 Table (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center 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 site by the laboratory responsible for the assessments.

If additional non-protocol 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, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 6.

Table 6 Protocol Required Safety 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	Aspartate aminotransferase	Total and direct bilirubin
Creatinine	Sodium	Alanine aminotransferase	Total protein
Glucose	Calcium	Alkaline phosphatase	Albumin
Creatine kinase	Bicarbonate	Chloride	
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests			
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), cotinine, and drug screen (via serum, urine, or saliva) to include, at a minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines).			
Fecal occult blood test and stool cultures as appropriate for gastrointestinal adverse events (Appendix 8)			

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

[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

Blood samples for PK analysis of gepotidacin will be collected at the time points indicated in the Time and Events Table (Section 7.1). 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

Pharmacokinetic urine samples for the analysis of gepotidacin (Part 1a only) will be collected at the time points listed in the Time and Events Table (Section 7.1). 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. Sample Analysis

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

7.5. Genetics

Depending on the clinical study results, 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 Table (Table 5). 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

All statistical analyses will be performed by PPD using SAS (SAS Institute Inc., Cary, North Carolina, USA), version 9.2 or higher. Pharmacokinetic parameters will be calculated using Phoenix WinNonlin (Certara USA Inc., Princeton, New Jersey, USA), version 6.2.1 or higher.

Before database lock, a reporting and analysis plan (RAP) will be issued as a separate document, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described in a RAP addendum and justified in the final integrated clinical study report.

9.1. Hypotheses

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

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Sample size is largely based on feasibility, however some justification is provided below.

Part 1a – Relative Bioavailability:

The sample size of 24 PK parameter population subjects will be used based on feasibility to address the objectives of Part 1a of the study.

There are no estimates for the coefficient of variation (CV) of HSWG for any PK parameters. An assumed CV of 27.5% for a PK parameter implies that the sample size of 24 PK parameter evaluable subjects will provide at least 80% power to demonstrate equivalence of the PK parameter. Equivalence is demonstrated when 90% confidence interval (CI) for the ratio of Test:Reference of the PK parameter will be within 0.8 to 1.25 following log transformation.

Two different test formulations are being used in this study. No adjustment for pre-planned multiple comparisons are made.

The total sample size of 27 subjects (9 subjects in 3 sequences) will be randomized to ensure 24 PK parameter evaluable subjects with PK parameter estimates from the reference and at least one test formulation.

Part 1b – Food Effect:

A sample size of 16 subjects will be randomized (8 per sequence) based on feasibility to address the objectives of Part 1b of the study.

This sample size will ensure equivalence (as specified in sample size assumption in Part 1a) with 80% power with an assumed CV of 22%.

Parts 2a and 2b – Pharmacokinetics:

A sample size of approximately 12 subjects will be used in each Part 2a and Part 2b based on feasibility to address the objectives of Part 2a and 2b of the study.

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, standard deviation (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 1 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 by the study team after completing Part 1a of the study to select the formulation for Part 1b, Part 2a, and Part 2b, and also to determine if the effect of food on the selected formulation needs to be studied (Part 1b). The team will review unblinded data from Part 1a of this open-label study to select the appropriate formulation.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Pharmacokinetic Analyses

Plasma and urine 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 (AUC) from time 0 (predose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of the last quantifiable concentration
Cmax	Maximum observed concentration
Frel	Relative bioavailability of drug, calculated as: $[AUC(0-\infty)_{tablet}]/[AUC(0-\infty)_{capsule}]$ (Part 1a only)
t1/2	Terminal phase half-life
tlag	Lag time before observation of drug concentrations in sampled matrix
Tmax	Time to first occurrence of Cmax

Urine (Part 1a only):

Ae total	Total unchanged drug (total amount of drug excreted in urine), calculated by adding all the fractions of drug collected over all the allotted time intervals
Ae(t1-t2)	Amount of drug excreted in urine in time intervals of 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
AUC(0-12)	Area under the concentration-time curve from time 0 (predose) to 12 hours after dosing
AUC(0-24)	Area under the concentration-time curve from time 0 (predose) to 24 hours after dosing
AUC(0-48)	Area under the concentration-time curve from time 0 (predose) to 48 hours after dosing
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)

Plasma (all subjects) and urine (Part 1a only) concentrations 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 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 will be analyzed separately using a mixed effects model as appropriate to the study design, fitting fixed effect terms for sequence, period, and regimen, and treating subject within sequence as a random effect. Point estimates and 90% CIs for the differences of interest (RC tablets and HSWG tablets versus capsules) will be constructed using the residual variance. Point and interval estimates will then be exponentially back-transformed to construct point and 90% CI estimates for the ratios of interest (RC tablets and HSWG tablets versus capsules).

Estimates of within-subject variability for AUC(0-∞), AUC(0-t), and Cmax of gepotidacin will be provided, where:

$$CVw\ (\%) = \mathrm{sqrt}(\exp[MSE] - 1) \times 100$$

and MSE is the residual mean squared error from the model. CVw(%) represents a pooled measure of within-subject variability across regimens.

Distributional assumptions will be assessed by residual plots. Homogeneity of variance will be assessed by plotting the residuals against the predicted values from the model, whilst normality will be examined by normal probability plots. If assumptions are grossly violated, alternative analyses will be considered.

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

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

9.4.2. Secondary Analyses

Safety Analyses

The following safety evaluations will be performed:

- Monitoring for AEs
- Changes in routine clinical laboratory parameters including serum chemistry, hematology, 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 (systolic

and diastolic 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 will be defined as any AEs, regardless of relationship to investigational product, that occur after the dose of investigational product. The treatment-emergent AEs 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 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 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 >500 msec or increase in QTc from the baseline ECG of ≥60 msec, will be summarized by group.

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 site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Council for 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 Site 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 1 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
AUC	area under the plasma concentration-time curve
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 the last quantifiable concentration
BMI	body mass index
CI	confidence interval
CLr	renal clearance of drug
Cmax	maximum observed concentration
CV	coefficient of variation
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
fe%	percentage of the given dose of drug excreted in urine
Frel	Relative bioavailability of drug
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HSWG	high shear wet granulation
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury
msec	millisecond
PK	pharmacokinetic
QTc	corrected QT interval; the measure of time between the start of the Q wave and the end of the T wave
QTcB	corrected QT interval using Bazett's formula

QTcF	corrected QT interval using the Fridericia formula
RAP	reporting and analysis plan
RC	related compound
SAE	serious adverse event
SD	standard deviation
SRM	Study Reference Manual
t1/2	terminal phase half-life
tlag	lag time before observation of drug concentrations in sampled matrix
Tmax	time to first occurrence of Cmax
ULN	upper limit of normal

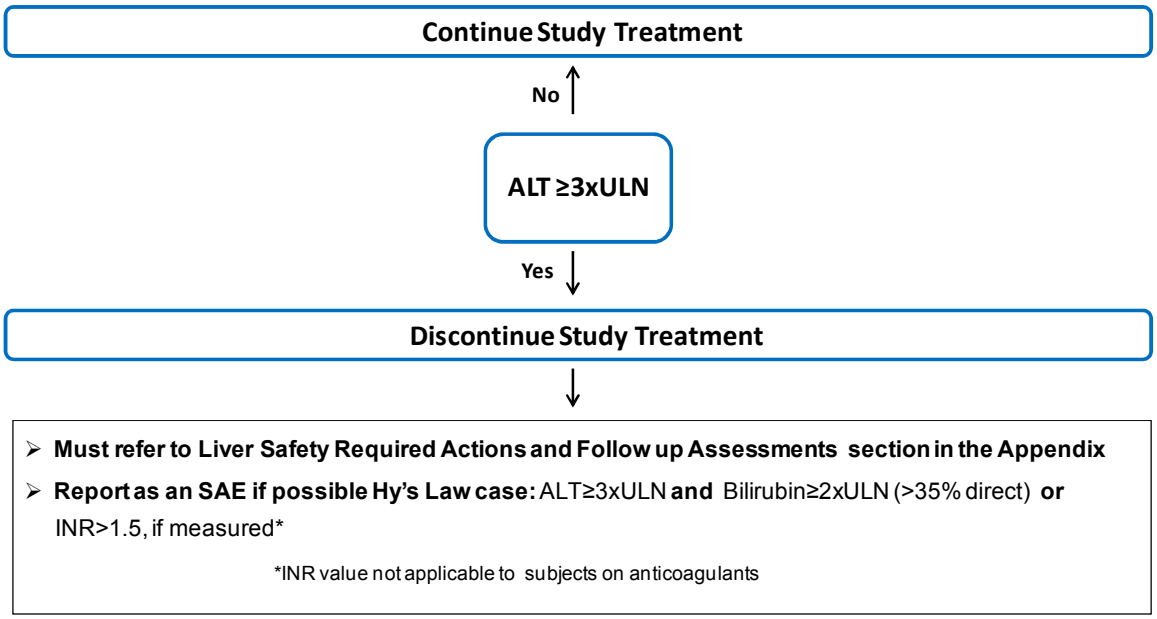
Trademark Information

Trademarks of the GlaxoSmithKline group of companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
Phoenix WinNonlin
SAS

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

Genetics – Background

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.

Genetic Research Objectives and Analyses

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 informed consent form. 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, clinical 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 conditions 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 (SAE) 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, diarrhea, 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 INR measurement is obtained, the value is to be recorded on the SAE form.

12.5.3. Recording of Adverse Events and Serious Adverse Events

Adverse Events and Serious Adverse Event 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 CRF
- 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.

12.5.4. 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 Division of Microbiology 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.

12.5.5. Reporting of Serious Adverse Events to GSK

Serious adverse event 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, National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the Division of AIDs and modified to better meet the needs of participants in DMID 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; mm Hg = millimeters of mercury; 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
Diarrhea	Mild or transient; 3 to 4 loose stools/day or mild diarrhea lasting <1 week	Moderate or persistent; 5 to 7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; 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

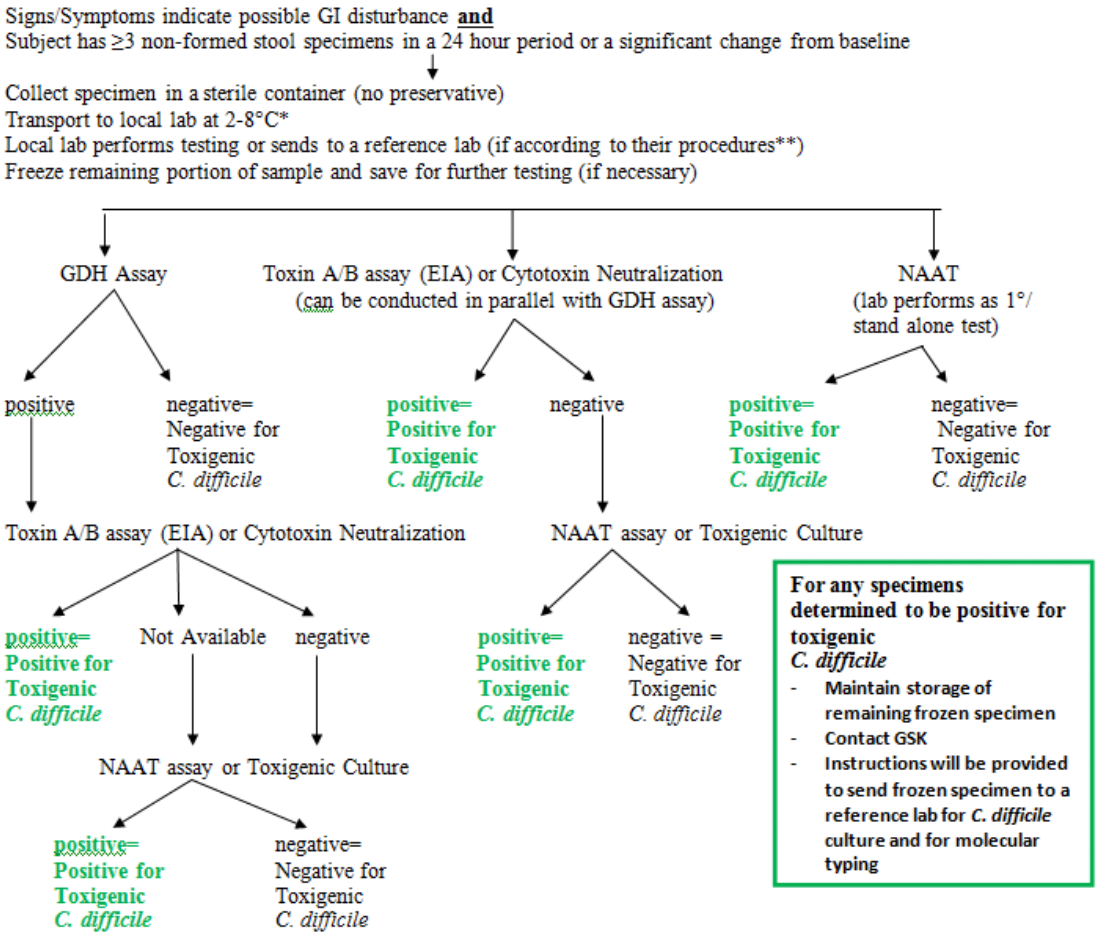
Subjects who experience diarrhea or enteritis should be evaluated with additional fecal occult blood tests and stool cultures as deemed appropriate by the investigator. Any subject with a positive fecal occult blood test should be referred to a gastroenterologist for further evaluation at the discretion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

Subjects who experience an AE of diarrhea 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.