TITLE PAGE

Protocol Title: A Phase I, Open-Label, Single-Dose, Two-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function

Protocol Number: BTZ117352

Short Title: Pharmacokinetics Study of Gepotidacin (GSK2140944) in Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function

Compound Number: GSK2140944

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1. SYNOPSIS

Protocol Title: A Phase I, Open-Label, Single-Dose, Two-Part Study to Assess the Pharmacokinetics of Gepotidacin (GSK2140944) in Male and Female Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function

Short Title: Pharmacokinetics Study of Gepotidacin (GSK2140944) in Adult Participants with Varying Degrees of Hepatic Impairment and in Matched Control Participants with Normal Hepatic Function

Rationale:

In a previous absorption, distribution, metabolism, and excretion study for gepotidacin, the mean recovery of radioactivity in urine and feces accounted for approximately 31.2% and 52.5%, respectively, of [^{14}C]-gepotidacin administered as a single oral dose. After oral administration, gepotidacin was eliminated mainly as parent in urine, accounting for approximately 20% of the administered dose. Elimination via metabolism (urine plus feces) accounted for a total of 13% to 19% of the dose.

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

Objectives and Endpoints:

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

Objectives	Endpoints
• To compare the urine PK parameters of a 1500 mg oral dose of gepotidacin in normal healthy participants with participants with mild, moderate, and severe hepatic impairment	• Urine primary PK endpoints include Ae total, fe%, and CLr of gepotidacin, as data permit. Urine secondary PK endpoints include Ae(t1-t2), AUC(0-12), AUC(0-24), and AUC(0-48) of gepotidacin, as data permit
Exploratory	
• To evaluate the saliva PK parameters of a 1500 mg oral dose of gepotidacin in normal healthy participants compared with participants with mild, moderate, and severe hepatic impairment	• Saliva primary PK endpoints include AUC(0-∞) and Cmax of gepotidacin, as data permit. Saliva secondary PK endpoints include AUC(0-t), Tmax, λz, t1/2, CL/F, Vz/F, and saliva to unbound plasma AUC(0-t) and AUC(0-∞) ratios (RAUC) of gepotidacin, as data permit

Overall Design:

This is a Phase I, nonrandomized, open-label, parallel-group, multi-center, two-part study that will evaluate the pharmacokinetics, safety, and tolerability of a single 1500 mg oral dose of gepotidacin in participants with normal hepatic function and in participants with mild, moderate, and severe hepatic impairment. Healthy participants with normal hepatic function will be matched to hepatically impaired participants in terms of gender distribution, age (approximately ±10 years), and body mass index (approximately ±20%).

At Screening, participants will be enrolled to the appropriate groups based on the classification as defined in the Food and Drug Administration Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [DHHS, 2003]. Participants with hepatic impairment will be classified using the Child-Pugh system.

This will be a two-part study, in which PK objectives must be achieved (observed mean values: area under the concentration-time curve [AUC] <48 μg•hr/mL and maximum observed concentration [Cmax] <14 μg/mL); and safety and tolerability will be reviewed before enrolling participants into the next part of the study. In Part 1, participants with moderate hepatic impairment and participants with normal hepatic function will be enrolled. Matching participants with normal hepatic function in Part 1 (Group D) will be enrolled following the completion of all Day 3 assessments of the respective matched hepatically impaired participant.

In Part 2, participants with mild (optional) and severe hepatic impairment and participants with normal hepatic function will be enrolled concurrently based on the PK, safety, and tolerability data of Part 1. Participants with mild hepatic impairment may be studied if there is a significant difference in pharmacokinetics between participants with moderate hepatic impairment and participants with normal hepatic function. Participants with severe hepatic impairment will be studied in Part 2 provided that the PK objectives are achieved in Part 1 (observed mean values in participants with moderate impairment

do not exceed the threshold: AUC <48 μg•hr/mL and Cmax <14 μg/mL). The dose may be adjusted for participants with severe hepatic impairment if either PK parameter is predicted to exceed the threshold. Based on emergent data from Part 1, matching participants with normal hepatic function in Part 2 (Group E) may be enrolled (e.g., if a change in dose is needed or if the demographic data of the mild and/or severe hepatic impairment groups is not well matched to the moderate control data [Group D]).

For participants with normal hepatic function and participants with mild, moderate, and severe hepatic impairment: participants will participate in 1 treatment period and blood, urine, and saliva samples will be collected up to approximately 48 hours after dosing for PK analysis of gepotidacin concentrations.

Number of Participants:

For the target sample size of 8 evaluable participants each in mild, moderate, and severe hepatic impairment groups, the maximum number of evaluable participants in this study is 48 (assuming 24 matching participants with normal hepatic function for the 24 hepatically impaired participants).

Due to the potential difficulty in identifying eligible participants with severe hepatic impairment, the sponsor may stop the study prior to full enrollment in Part 2 provided that a minimum of 6 evaluable participants with severe hepatic impairment have been enrolled.

Treatment Groups and Duration:

Participants will be screened within 30 days prior to entry to the clinic and will be assigned to a study group based on the degree of hepatic impairment using the Child-Pugh classification system:

<u>Part 1:</u>

- Group B: Participants with moderate hepatic impairment (Child-Pugh score 7 to 9)
- Group D: Participants with normal hepatic function

Preliminary PK, safety, and tolerability results from participants in Part 1 will be reviewed before enrolling participants into the next part of the study.

<u>Part 2:</u>

- Group A: Participants with mild hepatic impairment (Child-Pugh score 5 to 6) (optional)
- Group C: Participants with severe hepatic impairment (Child-Pugh score 10 to 15)
- Group E: Participants with normal hepatic function (optional)

Participants in Parts 1 and 2 will enter the clinic at Check-in (Day −1) before study drug administration (Day 1). Participants will receive a single oral dose of study drug as follows: gepotidacin 1500 mg administered as 2 × 750 mg tablets. All participants will be discharged from the clinic on Day 3 after all scheduled PK and safety assessments have

been completed, and will return to the clinic for a Follow-up Visit approximately 10 days (±5 days) after dose administration. The duration of the study (from Screening to the Follow-up Visit) will be approximately 44 days.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Time and Events Table

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

Procedure[1]	**Screening (up to 30 days prior to Day -1)**	**Check-in**	**Treatment Period (Days)**			**Follow-up (10 [±5] days postdose) or Early Termination**	**Notes**
		–1	**1**	**2**	**3**		
HIV antibody, hepatitis B surface antigen, and hepatitis C antibody testing	X						If test has otherwise been performed within 3 months before study drug administration, testing at Screening is not required
Drug and alcohol screen	X	X					See Table 5
Laboratory assessments (include liver chemistries)	X	X		X		X	Including serum chemistry, hematology, and urinalysis. Results from 24 hours after dosing should be available before discharge on Day 3
12-lead ECG	X	X	X	X	X	X	See Table 2 for timing of assessments
Vital signs	X	X	X	X	X	X	Respiratory rate and body temperature collected at Screening only See Table 2 for timing of assessments
Genetic sample		X					Informed consent for optional substudies (e.g., genetics research) must be obtained before collecting a PGx sample. The PGx sample can be collected anytime, but Day −1 is recommended
Study drug administration			X				
Blood collection for pharmacokinetics			X	X	X		See Table 2 for time points
Urine collection for pharmacokinetics			X	X	X		Participants with normal hepatic function and participants with hepatic impairment will have different collection intervals See Table 2 for time points
Saliva collection for pharmacokinetics			X	X	X		See Table 2 for time points
AE/SAE review	X	X	←==========		==========→	X	
Concomitant medication review		X	←==========		==========→	X	

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

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

Table 2 Safety and PK Assessments

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

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

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

3 Urine collection intervals for participants with normal hepatic function (Group D and Group E, if applicable) include 0 (pre-dose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours.

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

- The timing and number of planned study assessments, including: safety and pharmacokinetic 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.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

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

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

3.1. Study Rationale

In a previous absorption, distribution, metabolism, and excretion (ADME) study for gepotidacin (see GSK Document Number 2014N189951_00 Study ID BTZ115774), the mean recovery of radioactivity in urine and feces accounted for approximately 31.2% and 52.5%, respectively, of [^{14}C]-gepotidacin administered as a single oral dose. After oral administration, gepotidacin was eliminated mainly as parent in urine, accounting for approximately 20% of the administered dose. Elimination via metabolism (urine plus feces) accounted for a total of 13% to 19% of the dose.

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

3.2. Background

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

3.3. Benefit/Risk Assessment

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

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) Gepotidacin		
Gastrointestinal (GI) Effects	Lower GI effects (soft stools, flatulence, and diarrhoea) are the most common GI-associated adverse events (AEs) reported in human participants dosed with gepotidacin. In the Phase I studies, out of approximately 400 healthy participants who have received gepotidacin, *Clostridium difficile* has been reported in 8 participants.	Exclusion criterion and close monitoring of clinical parameters and AEs will be conducted to mitigate and assess GI effects. Patients with significant GI symptoms will obtain the appropriate work-up (Appendix 5). Participant evaluation criteria: Participants experiencing Grade 3 or Grade 4 AEs will be followed as appropriate until resolution of the AE (see Section 8.1.3).
Cardiovascular Effects Reversible increase in QT prolongation and a mild increase in heart rate in human participants.	In Study BTZ115775 (see GSK Document Number 2015N227098_00 Study ID BTZ115775), the infusion of gepotidacin at a dose of 1000 mg and 1800 mg over 2 hours caused a mild heart rate effect of approximately 6 bpm to 10 bpm and a QT prolongation, measured as ΔΔQTcF, of 12 msec to 22 msec. The QT prolongation evolved during the infusion and was quickly reversed over 2 hours after the end of the infusion. Blood pressure observations were within normal ranges.	Exclusion criteria, close monitoring of clinical parameters, and AEs will be conducted and stopping criteria will be utilized to mitigate and assess cardiovascular effects. Note: Participants with baseline QTcF interval >450 msec (participant with normal hepatic function) or >480 msec (hepatically impaired participant) will be excluded. Participant monitoring criteria: Participants experiencing a QTcB and/or QTcF >500 msec and/or a change from baseline in QTc >60 msec (see Section 8.1.2).

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 participants have experienced effects consistent with increased cholinergic tone, including central nervous system and GI effects (increased salivation, slurred speech, blurred vision, dizziness, light-headedness, and GI upset). These effects appear to be related to Cmax and are significantly attenuated when Cmax is below 14 µg/mL.	Coadministration of anticholinergics and administration in participants 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 is expected to be below 14 µg/mL in this study.
Rash/Hypersensitivity	A fine, mild, generalized pruritic macular skin rash was seen in 3 of 8 participants following 10 days of dosing 1500 mg 3 times daily (see GSK Document Number 2014N198291_00 Study ID BTZ115198). Rash was reported as an AE for 4 of 122 participants (3%) and consisted of mild, related urticaria; moderate, related rash maculopapular; mild, related rash; mild, related urticaria; and mild, not related arthropod bite (see GSK Document Number 2015N243789_00 Study ID BTZ116704). There has been no other evidence of hypersensitivity in human participants 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. Participant monitoring: Participants will be monitored closely for cutaneous effects throughout the study, and specialist advice will be sought as needed to evaluate any clinically significant finding. Participant evaluation criteria: Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement (see Section 8.1.4).

3.3.2. Benefit Assessment

Since this Phase I study is being conducted in healthy participants with normal hepatic function and in participants with mild, moderate, and severe hepatic impairment, there is no direct clinical benefit to study participants. Participation in this study will contribute to the process of developing new antibiotic therapies in areas of growing unmet need.

3.3.3. 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 participants for the study; the relatively short duration of study drug exposure; and the extent of safety monitoring incorporated into the study.

4. OBJECTIVES AND ENDPOINTS

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

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

5. STUDY DESIGN

5.1. Overall Design

This is a Phase I, nonrandomized, open-label, parallel-group, multi-center, two-part study that will evaluate the pharmacokinetics, safety, and tolerability of a single 1500 mg oral dose of gepotidacin in participants with normal hepatic function and in participants with mild, moderate, and severe hepatic impairment. Healthy participants with normal hepatic function will be matched to hepatically impaired participants in terms of gender distribution, age (approximately ±10 years), and body mass index (BMI; approximately ±20%).

At Screening, participants will be enrolled to the appropriate groups based on the classification as defined in the Food and Drug Administration (FDA) Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [DHHS, 2003]. Participants with hepatic impairment will be classified using the Child-Pugh system. For more details see Section 7.3.

This will be a two-part study, in which PK objectives must achieved (observed mean values: area under the concentration-time curve [AUC] <48 µg•hr/mL and maximum observed concentration [Cmax] <14 µg/mL); and safety and tolerability will be reviewed before enrolling participants into the next part of the study. In Part 1, participants with moderate hepatic impairment and participants with normal hepatic function will be enrolled. Matching participants with normal hepatic function in Part 1 (Group D) will be enrolled following the completion of all Day 3 assessments of the respective matched hepatically impaired participant (see Section 7.3).

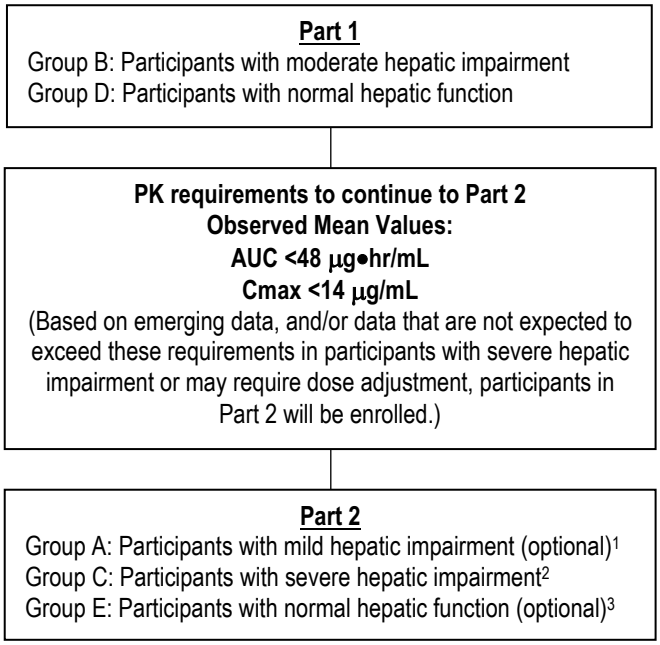
In Part 2, participants with mild (optional) and severe hepatic impairment and participants with normal hepatic function will be enrolled concurrently based on the PK, safety, and tolerability data of Part 1. Participants with mild hepatic impairment may be studied if there is a significant difference in pharmacokinetics between participants with moderate hepatic impairment and participants with normal hepatic function. Participants with severe hepatic impairment will be studied in Part 2 provided that the PK objectives are achieved in Part 1 (observed mean values in participants with moderate impairment do not exceed the threshold: AUC <48 µg•hr/mL and Cmax <14 µg/mL). The dose may be adjusted for participants with severe hepatic impairment if either PK parameter is predicted to exceed the threshold. Based on emergent data from Part 1, matching

participants with normal hepatic function in Part 2 (Group E) may be enrolled (e.g., if a change in dose is needed or if the demographic data of the mild and/or severe hepatic impairment groups is not well matched to the moderate control data [Group D]) (see Section 7.3).

Due to the potential difficulty in identifying eligible participants with severe hepatic impairment, the sponsor may stop the study prior to full enrollment in Part 2 provided that a minimum of 6 evaluable participants with severe hepatic impairment have been enrolled. See the study schematic in Figure 1 for more details.

For participants with normal hepatic function and participants with mild, moderate, and severe hepatic impairment: participants will participate in 1 treatment period and blood, urine, and saliva samples will be collected for PK analysis of gepotidacin concentrations according to the Schedule of Activities (SoA; Section 2). Blood, urine, and saliva samples will be collected up to approximately 48 hours after dosing.

Figure 1 BTZ1117352 Study Schematic



PK = pharmacokinetic

1 Based on emergent data from Part 1, participants with mild hepatic impairment (Group A) may not be enrolled in Part 2 if there is not a significant difference between participants with moderate hepatic impairment and participants with normal hepatic function.

2 If AUC and/or Cmax are predicted to exceed the threshold, the dose may be adjusted for participants with severe hepatic impairment (Group C). Due to the potential difficulty in identifying eligible participants with severe hepatic impairment, the sponsor may stop the study prior to full enrollment in Part 2 provided that a minimum of 6 evaluable participants with severe hepatic impairment have been enrolled.

3 Based on emergent data from Part 1, matching participants with normal hepatic function in Part 2 (Group E) may be enrolled (e.g., if a change in dose is needed or if the demographic data of the mild and/or severe hepatic impairment groups is not well matched to the moderate control data [Group D]).

5.2. Number of Participants

For the target sample size of 8 evaluable participants each in mild, moderate and severe hepatic impairment groups, the maximum the number of evaluable participants in this study is 48 (assuming 24 matching participants with normal hepatic function for the 24 hepatically impaired participants).

Due to the potential difficulty in identifying eligible participants with severe hepatic impairment, the sponsor may stop the study prior to full enrollment in Part 2 provided that a minimum of 6 evaluable participants with severe hepatic impairment have been enrolled.

If participants prematurely discontinue the study, additional replacement participants may be recruited at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the Follow-up Visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

This study design is commonly used when evaluating the pharmacokinetics of a drug entity in participants with impaired hepatic function. It is based on recommendations given in the FDA Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [DHHS, 2003].

Gepotidacin exhibits linear and time-independent pharmacokinetics, which indicates a single-dose study is adequate to achieve study objectives.

In the human ADME study (see report of study BTZ115774), total recovery of radioactivity was approximately 84% (31.2% in urine and 52.5% in feces) after oral administration. Radioactivity was eliminated in higher proportions in feces for oral doses, suggesting hepatic impairment could affect clearance of the parent compound. The absolute oral bioavailability was approximately 44%.

5.5. Dose Justification

The oxidative metabolism of gepotidacin is mediated primarily by cytochrome P450 enzyme 3A4 (CYP3A4). In a clinical drug-drug interaction study when itraconazole (inhibitor of both p-glycoprotein and CYP3A4) was co-administered with gepotidacin, a weak drug-drug interaction (40% increase in Cmax and 50% increase in AUC[0-∞]) was observed (see GSK Document Number 2014N199850_00 Study ID BTZ117349). Therefore, the mean Cmax and AUC following a single oral dose of gepotidacin 1500 mg are not expected to exceed those observed in healthy adult participants who received

gepotidacin 3000 mg (see GSK Document Number 2012N137722_00 Study ID BTZ114595).

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Healthy participants must be in clinically stable health as determined by the investigator based on medical history, clinical laboratory results (serum chemistry, hematology, urinalysis, and serology), vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.
3. Hepatically impaired participants must have chronic (>6 months), stable (no acute episodes of illness within the previous 1 month prior to screening due to deterioration in hepatic function) hepatic insufficiency with features of cirrhosis due to any etiology. Participants must also remain stable throughout the Screening period.
4. Hepatically impaired participants will be classified using the Child-Pugh classification system (see Table 3). Participants must have a Child-Pugh score of 5 to 6 (mild hepatic impairment), 7 to 9 (moderate hepatic impairment), or 10 to 15 (severe hepatic impairment) with known medical history of liver disease (with or without a known history of alcohol abuse) and previous confirmation of liver cirrhosis by liver biopsy or other medical imaging technique (including laparoscopy, computed tomography scan, magnetic resonance imaging, or ultrasonography) associated with unambiguous medical history. If imaging study or biopsy is not available, then the participant should have one of the following:

   i. Physical findings such as hepatomegaly, ascites, palmar erythema, spider angiomata, abdominal venous collaterals, gynecomastia, or other physical manifestations of hepatic disease

   OR

   ii. Laboratory findings: alanine aminotransferase (ALT) or aspartate aminotransferase elevation (> upper limit of normal [ULN]), alkaline phosphatase, or total bilirubin, or international normalized ratio (INR) elevation (>ULN) or an albumin value that is below the lower limit of normal laboratory reference range.

5. Participants with hepatic impairment may be taking medications which, in the opinion of the investigator, are believed to be therapeutic, and these medications should not interfere with the conduct of the study. Participants with hepatic impairment should be on stable regimen of chronic medications for at least 7 days prior to dosing until completion of the Follow-Up Visit.
6. Participants with hepatic impairment must have platelet counts ≥30,000 × 10^9/L of blood and have not had any major bleeding episodes within the past 6 months.

Weight

7. Body weight ≥45 kg and BMI within the range 18.5 to 40 kg/m^2 (inclusive).

Sex

8. Male or female

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 2 of this protocol from Day -1 until completion of the Follow-up Visit.

   b. Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 2), not breastfeeding, and at least one of the following conditions applies:

   i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 2

   OR

   ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 from 30 days prior to study drug administration and until completion of the Follow-up Visit.

Informed Consent

9. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has a clinically significant abnormality in past medical history or at the Screening physical examination (excluding hepatic insufficiency and other related medical conditions within the hepatically impaired populations which should be stable for at least 1 month before study drug administration) that in the investigator's opinion may place the participant at risk or interfere with outcome variables of the study. This includes, but is not limited to, history or current significant cardiac, renal, neurologic, gastrointestinal, respiratory, hematologic, or immunologic disease.

2. Participant 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 participant at risk, in the opinion of the investigator.
3. Female participant has a positive pregnancy test result or is lactating at Screening or upon admission to the clinic.
4. Participant has used a systemic antibiotic within 7 days of Screening.
5. Participant has a confirmed history of *Clostridium difficile* infection or a positive *C. difficile* toxin test within 2 months before Screening.
6. Participant has a history of drug and/or alcohol abuse within 6 months before Screening, as determined by the investigator, or participant has a positive drug screen at Screening or upon admission to the clinic. For participants with hepatic impairment, and a positive drug screen result related to the use of prescription medications is allowed per investigator review and approval, and tetrahydrocannabinol use is allowed per investigator review and approval.
7. History of sensitivity to any of the study drugs, components thereof, or a history of drug or other allergy that, in the opinion of the investigator or GSK medical monitor, contraindicates their participation.
8. History of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinic uses heparin to maintain intravenous cannula patency).

Prior/Concomitant Therapy

9. Participant has used medications known to affect the elimination of serum creatinine (e.g., trimethoprim or cimetidine) or competitors of renal tubular secretion (e.g., probenecid) within 30 days before dosing.
10. Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements), unless specified in Section 7.7.1, within 7 days (or 14 days if the drug is a potential strong enzyme inducer) or 5 half-lives (whichever is longer) prior to study drug administration until completion of the Follow-Up Visit, unless, in the opinion of the investigator and Sponsor, the medication will not interfere with the study. Any exceptions (including participants with hepatic impairment that will be on medications during the study) will be discussed with the sponsor or medical monitor on a case-by-case basis and the reasons will be documented.

Prior/Concurrent Clinical Study Experience

11. Previous exposure to gepotidacin within 12 months prior to study drug administration.
12. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to study drug administration in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the investigational product (whichever is longer).

Diagnostic Assessments

13. Participant with normal hepatic function has presence of hepatitis B surface antigen or positive hepatitis C antibody test result at Screening or within 3 months prior to study drug administration. Participant with hepatic impairment has evidence of recent, acute infection with hepatitis B and/or hepatitis C within preceding 6 months. Hepatically impaired participants with chronic hepatitis B or C (duration >6 months) are eligible for enrolment.
14. A positive test for human immunodeficiency virus antibody.
15. Participant must be able to abstain from alcohol and limit use of nicotine and/or nicotine-containing products (up to 5 cigarettes/day is acceptable for participants with hepatic impairment) for 24 hours before the start of dosing until after collection of the final PK sample. A positive alcohol or cotinine test is not exclusionary for participants with hepatic impairment.
16. Participant has clinically significant abnormal findings in serum chemistry, hematology, or urinalysis results obtained at Screening or Day –1, other than those associated with underlying hepatic conditions or other stable medical conditions consistent with the disease process in participants with hepatic impairment.
17. Participant with normal hepatic function has a baseline corrected QT interval using the Fridericia formula (QTcF) of >450 milliseconds (msec) and participant with hepatic impairment has a baseline QTcF of >480 msec.

Other Exclusions

18. Donation of blood in excess of 500 mL within 12 weeks prior to dosing or participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
19. Participant is unable to comply with all study procedures, in the opinion of the investigator.
20. The participant should not participate in the study, in the opinion of the investigator or Sponsor.

Supplemental Exclusion Criteria for Hepatically Impaired Participants

21. Participants with a pre-existing condition (except hepatic impairment) interfering with normal GI anatomy or motility that could interfere with the absorption, metabolism, and/or excretion of the study drugs. Participants with a history of inflammatory bowel disease should be excluded. Participants with a history of pepticulceration or pancreatitis within the preceding 6 months of screening should be excluded.
22. Participants with any previous GI surgery (except appendectomy or gall bladder removal >3 months prior to Screening) may be enrolled in this study only if, in the opinion of the investigator and the medical monitor, it is not expected to interfere with the study procedures or to pose an additional safety risk to the participant.

23. Participants receiving lactulose who are medically unable to halt lactulose administration from 8 hours before dosing with study drug to 4 hours after dosing with study drug.
24. Participants with clinically active severe encephalopathy (grade 3 or 4 as defined in Table 3) as judged by the investigator or significant central nervous system disease (e.g., dementia or seizures) which the investigator considers will interfere with the informed consent, conduct, completion, or results of this trial or constitutes an unacceptable risk to the participant. Participants with a prior history of severe encephalopathy who are currently treated for this condition will receive the appropriate score for encephalopathy.
25. Participants with estimated creatinine clearance (Clcr) ≤50 mL/min (calculated by the Cockcroft-Gault Formula). If the result calculated by Cockcroft-Gault is between 40 and 50 mL/min, then the site may complete a 24-hour urine collection to more specifically calculate the Clcr. A Clcr value ≤50 mL/min via 24-hour urine collection is also exclusionary.
26. History of gastric or esophageal variceal bleeding within the past 6 months and for which varices have not been adequately treated with medication and/or surgical procedures.
27. Participants with electrolyte imbalance whose serum sodium levels are ≤125 mmol/L; potassium levels are ≤2.5 mmol/L; or calcium levels are ≤6.1 mmol/L.
28. Presence of hepatopulmonary or hepatorenal syndrome.
29. Primary cholestatic liver diseases.
30. History of liver transplantation or participants in the severe hepatic impairment group that are expecting a liver transplant during the study participation period.
31. Participants with signs of active bacterial infection (including active spontaneous bacterial peritonitis).
32. Participants with transjugular intrahepatic portosystemic shunt placement within the past 3 months.
33. Participants with unstable cardiac function or participants with hypertension whose blood pressure that is not well controlled (based on the investigator's discretion).
34. Diabetic participants whose diabetes that is not controlled (based on the investigator's discretion).

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will fast (no food or drink except water) for approximately 8 to 10 hours before dosing and will receive a standard breakfast approximately 30 minutes before dose administration. Participants should consume the breakfast within 30 minutes or less. Standard meals will be provided during the study treatment period at times that do not interfere with study procedures.

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of dosing until after collection of the final PK sample.

6.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants will be instructed to limit use of nicotine and/or nicotine-containing products for 24 hours before the start of dosing until after collection of the final PK sample. Up to 5 cigarettes/day is acceptable.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

For eligibility purposes, clinical laboratory evaluations or vital sign measurements may be repeated once if an abnormal result is observed at the initial reading. Moreover, 12-lead ECG abnormalities may need to be confirmed by repeated measurements. In the event that the participation in the study is delayed and some screening procedures had been performed outside the prescribed screening window, outdated screening procedures can be repeated.

For inclusion and Child-Pugh categorization, clinical laboratory results that are deemed inconsistent with the usual stage of hepatic impairment may be repeated.

Participants who do not qualify based on a reversible medical condition or mild inter-current illness may be re-evaluated after further testing/examination or rescreened after the condition has resolved.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study treatment name:	Gepotidacin
Formulation description:	Immediate-release tablets containing gepotidacin (free base) an inactive formulation excipients
Dosage formulation:	Tablet
Unit dose strength/ Dosage level:	750 mg/ 1500 mg (2 × 750 mg)
Route of administration	Oral
Dosing instructions:	Dose with 240 mL of water in the fed state (within 30 minutes after a standard breakfast). Up to additional 1000 mL of water may be given to assist in swallowing tablets
Physical description:	A capsule-shape, white film-coated tablet with no identifying markings
Manufacturer/ Source of procurement:	GlaxoSmithKline

7.2. Dose Modification

Based on emerging data from Part 1, the dose may be reduced for participants with severe hepatic impairment if either PK parameter is predicted to exceed the threshold (AUC <48 μg•hr/mL and Cmax <14 μg/mL).

7.3. Method of Treatment Assignment

This will be a nonrandomized, open-label study. At Screening, participants will be assigned to a study group based on the degree of hepatic impairment using the Child-Pugh classification system as shown in Table 3.

Table 3 Child-Pugh Classification System

Finding	Points Scored for Each Observed Finding[1]		
	1	2	3
Encephalopathy grade[2]	None	1 or 2	3 or 4 or Participant receiving medication(s) to prevent encephalopathy
Ascites	Absent	Slight	Moderate or Participant receiving medication(s) to control ascites
Serum bilirubin (mg/dL)	<2	2 to 3	>3
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (seconds prolonged) Or Prothrombin time INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

INR = international normalized ratio.

1 For each category (encephalopathy grade, ascites, serum bilirubin, serum albumin, and prothrombin time or prothrombin time INR), points will be assigned based on the participant's condition and the criterion met. The Child-Pugh class will be assigned based on the sum of these points as follows:
Child-Pugh Class A (mild hepatic impairment): 5 to 6 points
Child-Pugh Class B (moderate hepatic impairment): 7 to 9 points
Child-Pugh Class C (severe hepatic impairment): 10 to 15 points

2 Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity

In Part 1, participants with moderate hepatic impairment (Group B) will be enrolled as they become eligible for the study and receive their allocated participant numbers in the order in which they are enrolled. Healthy participants with normal hepatic function (Group D) will be matched to the participants with moderate hepatic impairment in terms of gender distribution, age (±10 years), and BMI (±20%) and will be enrolled following the completion of all Day 3 assessments of the respective matched hepatically impaired participant.

In Part 2, participants with mild (optional) and severe hepatic impairment (Groups A and C, respectively) will be enrolled concurrently as they become eligible for the study and receive their allocated participant numbers in the order in which they are enrolled within their respective groups. Based on emergent data from Part 1, healthy participants with normal hepatic function in Part 2 (Group E) may be enrolled (e.g., if a change in dose is needed [see Section 7.2] or if the demographic data [gender, age, and BMI] of the mild and/or severe hepatic impairment groups is not well matched to the moderate control data [Group D]). Enrollment of healthy participants with normal hepatic function in Part 2 will be performed in the same manner as Part 1.

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

7.4. Blinding

This will be an open-label study.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site 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 labeled storage conditions with access limited to the investigator and authorized site staff.
3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (SRM).
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet (MSDS)/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.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the clinic staff.
- When participants 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 participant identification will be confirmed at the time of dosing by a member of the clinic staff other than the person administering the study treatment. Clinic personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Permitted Therapy

In healthy participants with normal hepatic function, acetaminophen at doses of ≤ 2 grams/day is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

Participants with hepatic impairment may be taking medications which, in the opinion of the investigator, are believed to be therapeutic, and these medications should not interfere with the conduct of the study. Participants with hepatic impairment should be on stable regimen of chronic medications for at least 7 days prior to study drug administration until completion of the Follow-Up Visit.

Hormonal replacement medications for postmenopausal women and hormonal contraceptives are allowed.

7.7.2. Prohibited Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements), unless specified in Section 7.7.1, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to study drug administration until completion of the Follow-Up Visit, unless, in the opinion of the investigator and GSK, the medication will not interfere with the study.

Participants with hepatic impairment are prohibited from receiving lactulose from 8 hours before dosing with study drug until 4 hours after dosing with study drug.

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.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy participants and participants with mild, moderate, and severe hepatic impairment are eligible for study participation.

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

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Evaluation Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Although stopping criteria for continued dosing of investigational product are not applicable for single dose studies, if participants are found to have values consistent with usual stopping parameters, it is appropriate to institute evaluation and monitoring criteria according to standard GSK criteria. Therefore, liver function tests should be evaluated according to stopping criteria and work up instituted if defined parameters are reached.

The following liver chemistry evaluation criterion will be applied for healthy participants:

- ALT ≥3 × ULN

Liver safety required actions and follow-up assessments can be found in Appendix 4.

8.1.2. QTc Evaluation Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on corrected QT interval using the Fridericia formula (QTcF), then QTcF must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *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 participant who develops either of the bulleted criteria below will be monitored, as appropriate:

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

For participants with underlying **bundle branch block**, follow the QTc evaluation criteria listed below:

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

See the SoA for data to be collected at the time of early withdrawal and follow-up and for any further evaluations that need to be completed.

8.1.3. Gastrointestinal Evaluation Criteria

Participants 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, participants who experience diarrhoea or enteritis should be evaluated with additional fecal occult blood tests and stool cultures as deemed appropriate by the investigator as outlined in Appendix 5 and Appendix 6.

8.1.4. Rash/Hypersensitivity Evaluation Criteria

A participant 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).

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

Efficacy will not be evaluated in this study.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 7.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the Follow-Up Visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the Follow-Up Visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the electronic case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 7. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 7.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant 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?”

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 3.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 7.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until completion of the Follow-up Visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 2.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

There is only one dose of study medication administered during this study, and it is administered at the clinic; therefore, overdoses are not anticipated. There is no specific antidote for overdose with a bacterial topoisomerase inhibitor.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until gepotidacin can no longer be detected systemically (at least 3 days).
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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, 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).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

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

9.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained in a semi-supine position after 5 minutes rest as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc evaluation criteria and additional QTc readings that may be necessary. Electrocardiograms should be obtained prior to any vital sign measurements or blood draws scheduled on the same assessment day.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Appendix 8 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during the treatment period until completion of the Follow-up Visit should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 8, must be conducted in accordance with the laboratory manual and the SoA.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection

The PK blood samples for the analysis of gepotidacin will be collected at the time points listed in the SoA (Section 2). 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.

9.5.2. Urine Sample Collection

The PK urine samples for the analysis of gepotidacin will be collected at the time points listed in the SoA (Section 2). 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.

9.5.3. Saliva Sample Collection

The PK saliva samples for analysis of gepotidacin will be collected at the time points listed in the SoA (Section 2). The timing of saliva samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

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

9.5.4. Sample Analysis

Plasma, urine, and saliva analyses will be performed under the control of GSK Platform Technologies and Science (PTS), the details of which will be included in the SRM. Concentrations of gepotidacin will be determined in plasma, urine, and saliva 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. However, in order to derive the saliva to unbound plasma AUC(0-t) and AUC(0-∞) ratios, a correction factor of 0.67 will be applied to the total plasma AUCs of gepotidacin.

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

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

A 6-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 9 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

The target sample size of 8 evaluable participants with normal hepatic function and 8 evaluable hepatically impaired participants in each group was chosen based on feasibility, to address the objectives of the study. This sample size also complies with FDA guideline in a reduced study design involving control participants and moderate hepatic impairment patients.

The between-participant coefficient of variations (CVb%) of PK parameters from the 1500 mg oral tablet on Day 1 in BTZ117351 study were 23.4%, 22.9%, and 43.6% for the AUC(0-t), AUC(0-∞), and Cmax respectively.

For a CVb% of 23.4%, 22.9%, and 43.6%, and a sample size of 8 participants with normal hepatic function and 8 participants with moderate hepatic impairment, it is estimated that the upper limits of the 90% confidence interval (CI) for the ratio of PK

parameters of hepatically impaired participants to normal participants are 22.5%, 22.0%, and 44.4% above the corresponding point estimates for the ratios of AUC(0-t), AUC(0-∞), and Cmax, respectively.

For the target sample size of 8 evaluable participants each in mild, moderate and severe hepatic impairment groups, the maximum the number of evaluable participants in this study is 48 (assuming 24 matching participants with normal hepatic function for the 24 hepatically impaired participants).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
PK Population	All participants who received at least 1 dose of gepotidacin and have evaluable PK data for gepotidacin
PK Parameter Population	All participants 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.
Safety	All participants who receive at least 1 dose of study drug and have at least 1 postdose safety assessment

10.3. Statistical Analyses

10.3.1. 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 from time 0 (predose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of last quantifiable concentration
Cmax	Maximum observed concentration
λz	Terminal-phase rate constant
t1/2	Terminal phase half life
Tmax	Time to first occurrence of Cmax
tlag	Lag time
CL/F	Apparent oral clearance

Vz/F	Apparent volume of distribution

Urine:

Ae total	Total unchanged drug (total amount of drug excreted in urine), calculated by adding all the fractions of drug collected over all the allotted time intervals
Ae(t1-t2)	Amount of drug excreted in urine in a time intervals for predose, 0 to 6, 6 to 12, 12 to 24, or 24 to 36, and 36 to 48 hours after dosing for participants with hepatic impairment; and predose, 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours for participants with normal hepatic function
fe%	Percentage of the given dose of drug excreted in urine, calculated as: fe% = (Ae total/Dose) × 100
CLr	Renal clearance of drug, calculated as: Ae total/AUC(0-t)
AUC(0-12)	Area under the concentration-time curve from time 0 (predose) to 12 hours
AUC(0-24)	Area under the concentration-time curve from time 0 (predose) to 24 hours
AUC(0-48)	Area under the concentration-time curve from time 0 (predose) to 48 hours

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

The natural log-transformed plasma AUC(0-∞) and Cmax values for gepotidacin in the hepatic impairment groups and normal hepatic function groups will be compared using an analysis of variance. Geometric mean ratios between hepatic impairment groups and normal hepatic function groups, and 90% CIs for the ratios of AUC(0-∞) and Cmax for gepotidacin will be presented.

The natural log-transformed urine AUC(0-48) and non-transformed CLr values for gepotidacin in the hepatic impairment groups and normal hepatic function groups will be compared using an analysis of variance. Geometric mean ratios between hepatic impairment groups and normal hepatic function groups, and 90% CIs for the ratios of AUC(0-48) and least square mean difference between hepatic impairment groups and normal hepatic function groups, and 90% CIs for the difference of CLr for gepotidacin will be presented.

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

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

All AEs and all drug-related AEs will be listed. The incidence of AEs will be summarized by system organ class and preferred term for each group and overall. Separate summaries will be provided for AEs by overall frequency, study drug-related AEs, and common (≥5%) AEs. Serious AEs will be summarized and listed and AEs leading to withdrawal from the study will be listed. Listings for liver AEs, cardiovascular AEs, and rash/hypersensitivity AEs will be produced where an event has occurred. Cardiovascular-related medical conditions will be summarized.

Actual values and change from baseline for clinical chemistry and hematology results will be summarized by visit. A separate summary for urinalysis (dipstick) results will be generated. Clinical chemistry, hematology, and urinalysis toxicities of Grade 3 or higher and all clinical chemistry, hematology, and urinalysis data for participants with toxicities of Grade 3 or higher will be presented in data listings.

Twelve-lead ECG findings and changes from baseline in 12-lead ECG values will be summarized. Abnormal 12-lead ECG findings, all 12-lead ECG data for participants with abnormal ECG findings will be listed. In addition, all quantitative ECG values of potential clinical importance, and all ECG values for participants with any value of potential clinical importance will be listed. The frequency of maximum postdose value and change from baseline ECG parameter corrected QTc interval data will be summarized.

Change from baseline for vital sign measurements will be summarized by group and time point. Vital signs of potential clinical importance and all vital signs for participants with potential clinical importance values will be presented in data listings.

Liver monitoring/stopping events, medical conditions for participants with a liver stopping event, alcohol intake at onset of liver event, plasma concentration data for participants with a liver stopping event, liver biopsy details, and liver imaging details will be listed where an event has occurred.

No inferential hypothesis testing will be performed on the safety variables. No formal statistical analysis of safety data will be performed.

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

10.3.3. Other Analyses

Saliva:

AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of last quantifiable concentration
Cmax	Maximum observed concentration
λz	Terminal-phase rate constant
t1/2	Terminal phase half life

Tmax	Time to first occurrence of Cmax
CL/F	Apparent oral clearance
Vz/F	Apparent volume of distribution
RAUC(0-t)	The ratio of the AUC(0-t) observed in saliva relative to the unbound AUC(0-t) in plasma, calculated as: RAUC(0-t) = AUC(0-t) saliva/unbound AUC(0-t) plasma
RAUC(0-∞)	The ratio of the AUC(0-∞) observed in saliva relative to the unbound AUC(0-∞) in plasma, calculated as: RAUC(0-∞) = AUC(0-∞) saliva/AUC(0-∞) plasma

Saliva 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 time point and group. Mean and individual saliva concentration versus time profiles will be presented graphically on linear and semilogarithmic scales.

The natural log-transformed saliva AUC(0-∞) and Cmax values for gepotidacin in the hepatic impairment groups and normal hepatic function groups will be compared using an analysis of variance. Geometric mean ratios between hepatic impairment groups and normal hepatic function groups, and 90% CIs for the ratios of AUC(0-∞) and Cmax for gepotidacin will be presented.

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

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

10.3.4. Interim Analyses

Preliminary plasma PK, safety, and tolerability results from participants in Part 1 will be reviewed by the sponsor before enrolling participants into the next part of the study. Please see Section 10.3.1 for details about the estimation of PK parameters.

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

The RAP will describe the planned interim analyses in greater detail.

11. REFERENCES

Bax BD, Chan PF, Eggleston DS, Fosberry A, Gentry DR, Gorrec F, et al. Type IIA topoisomerase inhibition by a new class of antibacterial agents. *Nature*. 2010;466(7309):935-40.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. [28 screens]. Available from: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm174090.pdf

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

GlaxoSmithKline Document Number 2012N137722_00 Study ID BTZ114595. A randomized, single blind, placebo controlled study to evaluate safety, tolerability, and pharmacokinetics of single escalating oral doses of GSK2140944 in healthy adult subjects. 2012.

GlaxoSmithKline Document Number 2014N189951_00 Study ID BTZ115774. An open-label, non-randomized, two-period, cross-over, mass balance study to investigate the recovery, excretion and pharmacokinetics of ^{14}C-GSK2140944 administered as a single intravenous and single oral dose to healthy adult male subjects. 2014.

GlaxoSmithKline Document Number 2014N198291_00 Study ID BTZ115198. A two part study to evaluate safety, tolerability, and pharmacokinetics of single and repeat IV doses of GSK2140944 in healthy adult subjects. 2014.

GlaxoSmithKline Document Number 2014N199850_00 Study ID BTZ117349. A single-center, three-part, open label study to evaluate the relative bioavailability of two formulations, food effect, and interaction with itraconazole following single dose of GSK2140944 in healthy subjects and effect of food on safety, tolerability, and pharmacokinetics following multiple doses of GSK2140944 in healthy elderly subjects. 2015.

GlaxoSmithKline Document Number 2015N227098_00 Study ID BTZ115775: Population pharmacokinetic-pharmacodynamic analysis of a Phase I, randomized, double-blinded, placebo- and moxifloxacin-controlled, 4-period crossover study to evaluate the effect of GSK2140944 on cardiac conduction as assessed by 12-lead electrocardiogram in healthy volunteers. 2015.

GlaxoSmithKline Document Number 2015N243789_00 Study ID BTZ116704. A Phase II, randomized, two-part, multicenter, dose-ranging study in adult subjects evaluating the safety, tolerability, and efficacy of GSK2140944 in the treatment of subjects with suspected or confirmed gram-positive acute bacterial skin and skin structure infections. 2015.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of acetaminophen-protein adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 2009; 37(8):1779-84.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

λz	terminal-phase rate constant
AChE	acetylcholinesterase
ADME	absorption, distribution, metabolism, and excretion
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 concentration-time curve
AUC(0-∞)	area under the concentration-time curve from time 0 to infinity
AUC(0-t)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t)
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Clcr	creatinine clearance
CL/F	apparent oral clearance
CLr	renal clearance
Cmax	maximum observed concentration
CSR	Clinical Study Report
CVb%	between-participant coefficient of variation
CYP3A4	cytochrome P450 enzyme 3A4
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
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury
MSDS	Material Safety Data Sheet
msec	millisecond
NIAID	National Institute of Allergy and Infectious Disease
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 the Bazett formula
QTcF	corrected QT interval using the Fridericia formula
RAP	Reporting and Analysis Plan
RAUC(0-∞)	ratio of the AUC(0-∞) observed in saliva relative to the unbound AUC(0-∞) in plasma
RAUC(0-t)	ratio of the AUC(0-t) observed in saliva relative to the unbound AUC(0-t) in plasma
SAE	serious adverse event
SoA	schedule of activities
SRM	Study Reference Manual
t1/2	terminal phase half life
Tmax	time to first occurrence of Cmax
ULN	upper limit of normal
Vz/F	apparent volume of distribution
WOCPB	women of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal 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 before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 4 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 4.

Table 4 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [1] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[2] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[2] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[2] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:
1. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

2. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and until the Follow-up Visit.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum or urine pregnancy test at Screening and admission to the clinic
- Additional pregnancy testing will be performed at the Follow-up Visit
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 10 mIU/mL will be performed and assayed in a certified laboratory OR and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- 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.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, 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 7. 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 participant who becomes pregnant while participating will be withdrawn from the study.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH

guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- 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 participants, as appropriate.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must

be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the SRM.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Liver Safety: Required Actions and Follow-up Assessments

Phase I Liver chemistry evaluation criteria have been designed to assure participant safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry evaluation criteria and required follow up assessments for healthy participants only

<table>
<tr><th colspan="3">Liver Chemistry Evaluation Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3 × ULN
If ALT ≥3 × ULN AND bilirubin[1,2] ≥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="3">Required Actions and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• 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[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, 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 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• 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</td></tr>
</table>

Liver Chemistry Evaluation Criteria	
recommended **If ALT ≥3 × ULN AND bilirubin <2 × ULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 to 72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	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 globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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.
2. 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 participants receiving anticoagulants
3. 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

12.5. Appendix 5: Follow-up for Gastrointestinal Findings

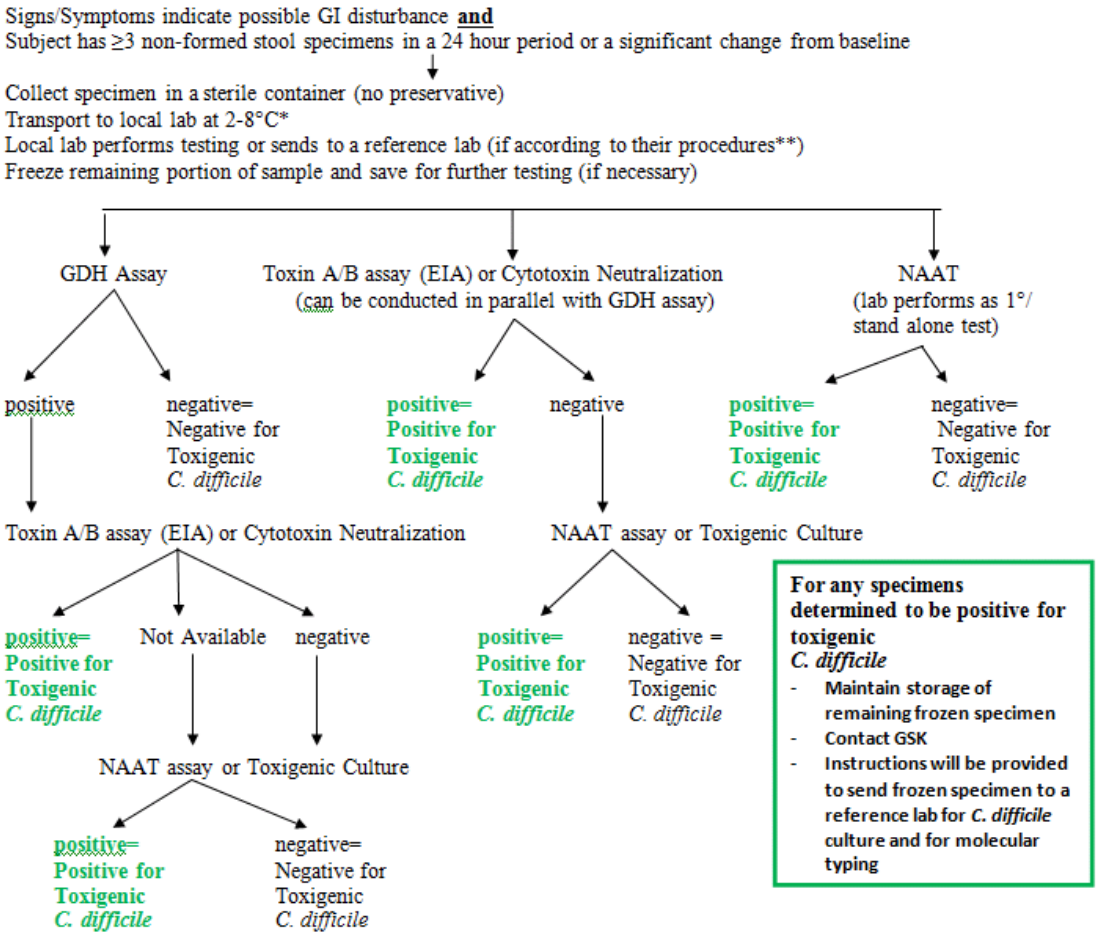
Participants who experience diarrhoea or enteritis should be evaluated with additional fecal occult blood tests and stool cultures as deemed appropriate by the investigator. Any participant with a positive fecal occult blood test should be referred to a gastroenterologist for further evaluation at the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

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

In addition, if the participant meets the clinical criteria outlined in Appendix 6, *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.

12.6. Appendix 6: *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

12.7. Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, serum chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• 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 participant'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 participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that

leads to the procedure is the AE.

- Situations in which 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.

Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

- 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 with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include 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 (healthy participants only) 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 participants receiving anticoagulants. If an INR measurement is obtained, the value is to be recorded on the SAE Form.

Recording AE and SAE

AE and SAE Recording

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

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 Disease (NIAID) Division of Microbiology and Infectious Diseases (DMID) criteria

for adult toxicity assessment (Appendix 10).

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to the investigational product (IP)/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the PPD medical monitor by telephone.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **PPD medical monitor**.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.8. Appendix 8: Clinical Laboratory Tests

Hematology, serum chemistry, urinalysis, and additional parameters to be tested are listed in Table 5.

- The tests detailed in Table 5 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	BUN	Potassium	AST	Total and direct bilirubin
	Creatinine	Sodium	ALT	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Creatine kinase			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Clcr (Section 6.2) • Prothrombin time and prothrombin time international normalized ratio (INR) (Section 7.3) • Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Alcohol (via urine, blood alcohol, or breathalyzer test) and drug screen (via serum, urine, or saliva) to include, at a minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines)			

Laboratory Assessments	Parameters
	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] The results of each test must be entered into the CRF.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 4 All events of ALT ≥3 × upper limit of normal (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).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.9. Appendix 9: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to gepotidacin. They may also be used to develop tests/assays including diagnostic tests) related to gepotidacin or study treatments of this drug class. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to gepotidacin or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on gepotidacin (or study treatments of this class) continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.10. Appendix 10: DMID Adult Toxicity Tables for AE 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 NIAID DMID 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 gm/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 (PT)	1.01 to 1.25 × ULN	1.26 to 1.5 × ULN	1.51 to 3.0 × ULN	>3 × ULN
Activated Partial Thromboplastin (APTT)	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 (AST)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alanine aminotransferase (ALT)	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 (GGT)	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 mm Hg systolic BP. No treatment required	Symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	Requires IV fluids; no hospitalization required	Mean arterial pressure <60 mm Hg 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

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

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°C to 38.5°C or 100.0°F to 101.5°F	38.6°C to 39.5°C or 101.6°F to 102.9°F	39.6°C to 40.5°C or 103°F to 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