TITLE PAGE

Protocol Title: A Phase I, Double-Blind, Two-Part, Sequential Study to Evaluate the Pharmacokinetics of Gepotidacin Tablets in Healthy Adult and Adolescent Participants

Protocol Number: 209611

Compound Number: GSK2140944

Study Phase: Phase I

Short Title: Pharmacokinetics of Gepotidacin Tablets in Adults and Adolescents

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I, Double-Blind, Two-Part, Sequential Study to Evaluate the Pharmacokinetics of Gepotidacin Tablets in Healthy Adult and Adolescent Participants

Short Title: Pharmacokinetics of Gepotidacin Tablets in Adults and Adolescents

Rationale: Single oral doses of gepotidacin (1500 and 3000 mg) were given to patients with gonorrhea in a completed Phase II study, and both doses achieved >95% efficacy; however, in vitro data and pharmacokinetic (PK)/pharmacodynamic modeling revealed that a higher dose would prevent the development of resistance and cover organisms with higher minimum inhibitory concentration (MIC).

The selected total daily dose for gonorrhea is 6000 mg delivered as two 3000 mg doses given either 6 or 12 hours apart in order to keep Cmax under a threshold of 14 μg/mL to mitigate the occurrence of adverse events (AEs) due to acetylcholinesterase (AChE) inhibition (mild and transient AEs of increased salivation, blurred vision, and slurred speech were observed following high intravenous [IV] doses as a 1 or 2 hour infusion during a previous study).

Although total daily oral 6000 mg doses have been given to healthy participants and patients as 2000 mg three times daily (TID) for up to 14 days and daily IV 4500 mg (equivalent to 9783 mg oral dose and based on absolute bioavailability of 46%) doses have been given to healthy participants as TID regimen for up to 10 days, the safety and PK of two 3000 mg doses given either 6 or 12 hours apart have not been characterized previously and gepotidacin has not been administered previously to adolescents. Therefore, this study will support inclusion of adolescents with a body weight ≥40 kg in future Phase III studies and will provide the safety and PK data of two 3000 mg doses separated by the selected dose intervals in Part 1 and Part 2.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part 1 • To evaluate the pharmacokinetics of a single 1500-mg dose and two 3000-mg doses of gepotidacin given 6 and 12 hours apart in adult participants	1500 mg Single Dose • Plasma gepotidacin AUC(0-t), AUC(0-∞), AUC(0-24), AUC(0-48), and Cmax, as data permit 3000 mg Two Doses • Plasma gepotidacin AUC(0-t), AUC(0-τ), AUC(0-24), AUC(0-48), Ro (accumulation ratio), and Cmax, as data permit

Objectives	Endpoints
Part 2 • To evaluate the pharmacokinetics of a single 1500-mg dose and two 3000-mg doses of gepotidacin given at a dosing interval (to be determined) in adolescent participants	1500 mg Single Dose • Plasma gepotidacin AUC(0-t), AUC(0-∞), AUC(0-24), AUC(0-48), and Cmax, as data permit 3000 mg Two Doses • Plasma gepotidacin AUC(0-t), AUC(0-τ), AUC(0-24), AUC(0-48), Ro (accumulation ratio), and Cmax, as data permit
Parts 1 and 2 • To assess the safety of gepotidacin in adult participants and adolescent participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead electrocardiogram readings
Secondary	
Part 1 • To assess the urine pharmacokinetics of gepotidacin following a single 1500-mg dose and two 3000-mg doses of gepotidacin given 6 and 12 hours apart in adult participants	• Urine endpoints include Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit
Part 2 • To assess the urine pharmacokinetics of gepotidacin following a single 1500-mg dose and two 3000-mg doses of gepotidacin given at a dosing interval (to be determined) in adolescent participants	• Urine endpoints include Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit
Parts 1 and 2 • To assess the plasma pharmacokinetics of gepotidacin	• Plasma gepotidacin Tmax, tlag, and t1/2, as data permit

Overall Design: This is a Phase I, double-blind, single-center, randomized, sequential, two-part study. Part 1 is being conducted to evaluate the PK of the gepotidacin tablets in healthy adult participants. Part 2 will evaluate the PK of the gepotidacin tablets in healthy adolescent participants.

Part 1: Pharmacokinetics in Healthy Adult Participants

Part 1 is a 3-period, fixed-sequence study that will assess the PK of a single 1500-mg dose (Period 1) and two 3000-mg doses of gepotidacin at Hours 0 and 12 (Period 2) and Hours 0 and 6 (Period 3) in healthy adult participants.

Participants will be randomly assigned to receive either all active treatment (gepotidacin) or placebo for all 3 periods. Approximately 17 participants will be randomized (in a 14:3 ratio) to receive a single dose of gepotidacin 1500 mg (Treatment A) or matching placebo (Treatment B) in Period 1, gepotidacin 3000 mg separated by 12 hours (Treatment C) or matching placebo (Treatment D) in Period 2, and gepotidacin 3000 mg separated by 6 hours (Treatment E) or matching placebo (Treatment F) in Period 3 to obtain 12 evaluable participants on active treatment and 2 evaluable participants on placebo.

Participants will participate in 3 treatment periods, and blood and urine samples will be collected for PK analysis of gepotidacin concentrations up to 48 to 60 hours after dosing.

This will be a two-part study in which the PK and safety data will be reviewed after completion of Part 1 before enrolling participants into Part 2. The dosing interval in Part 2, Period 2 will be based on the PK, safety, and tolerability data from Part 1.

Part 2: Pharmacokinetics in Healthy Adolescent Participants

Part 2 is a 2-period, fixed sequence study that will assess the PK of a single 1500-mg dose (Period 1) of gepotidacin and two 3000-mg doses (Period 2) of gepotidacin in healthy adolescent participants. The two 3000-mg doses will be separated by a time interval that will be determined based on data from Part 1. The number of PK samples and the PK sampling time points may be modified based on the adult PK data from Part 1.

Participants will be randomly assigned to receive either all active treatment (gepotidacin) or placebo for both periods. Approximately 17 participants will be randomized (in a 14:3 ratio) to receive a single dose of gepotidacin 1500 mg (Treatment A) or matching placebo (Treatment B) in Period 1, and gepotidacin 3000 mg (Treatment G) or matching placebo (Treatment H) in Period 2 to obtain 12 evaluable participants on active treatment and 2 evaluable participants on placebo.

The interval for the two 3000-mg doses in Period 2 will be between 6 hours and 12 hours based on the PK and safety results from Part 1.

For Part 2 only, there may be a 7-day interval between doses in Period 1 and Period 2 to accommodate the adolescent population school schedule. Treatment Period 1 and Treatment Period 2 may be separated by no more than 10 days.

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

Disclosure Statement: This is a sequential clinical pharmacology study that is masking the participant and investigator to assigned treatment.

Number of Participants: Approximately 17 adult participants will be randomly assigned to study intervention in Part 1 to ensure 12 evaluable participants on study drug with evaluable primary PK parameters and 2 participants on placebo with evaluable safety measurements. In Part 2, approximately 17 adolescent participants will be randomly assigned to study intervention to ensure 12 evaluable participants on study drug with evaluable primary PK parameters and 2 participants on placebo with evaluable safety measurements.

Intervention Groups and Duration: The treatments will be as follows:

Part 1 - Adult Participants

- Treatment A: Single dose 1500 mg (Period 1)
- Treatment B: Matching placebo (Period 1)
- Treatment C: Two 3000 mg doses given at Hour 0 and Hour 12 (Period 2)
- Treatment D: Two matching placebo doses given at Hour 0 and Hour 12 (Period 2)
- Treatment E: Two 3000 mg doses given at Hour 0 and Hour 6 (Period 3)
- Treatment F: Two matching placebo doses given at Hour 0 and Hour 6 (Period 3)

Note: All doses will be taken after a standard meal.

Part 2 - Adolescent Participants

- Treatment A: Single dose 1500 mg (Period 1)
- Treatment B: Matching placebo (Period 1)
- Treatment G: Two 3000 mg doses (Period 2; exact dosing interval to be determined after Part 1 is complete)
- Treatment H: Two matching placebo doses (Period 2; exact dosing interval to be determined after Part 1 is complete)

Note: All doses will be taken after a standard meal.

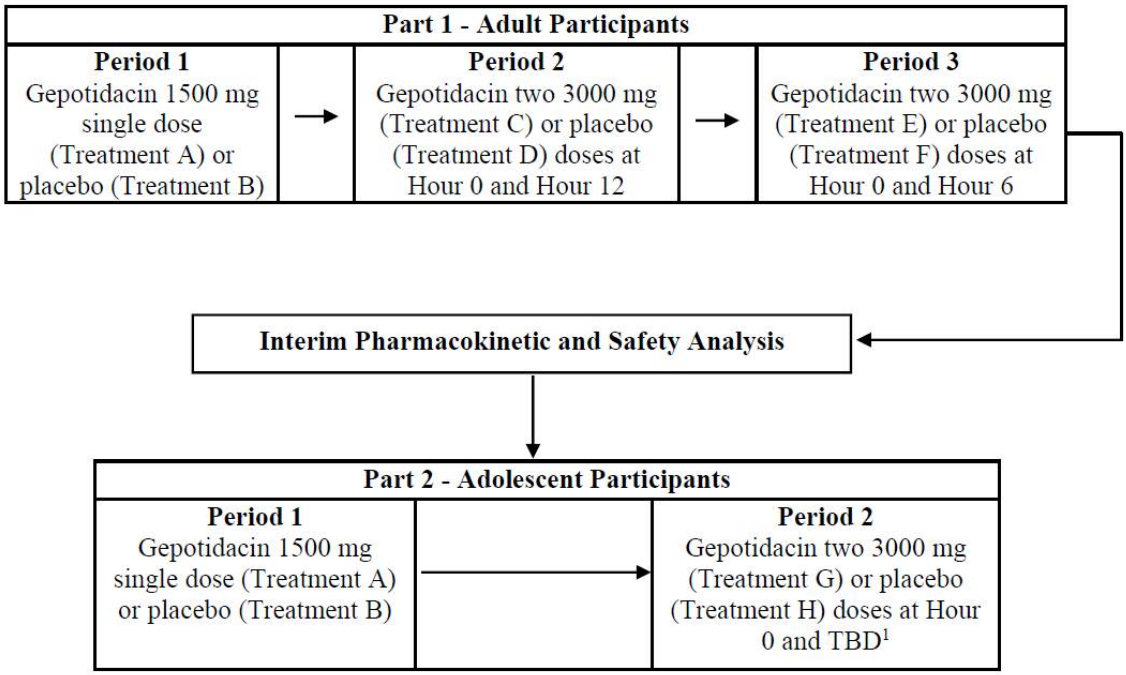
The duration of the study, including Screening, is approximately 47 days for Part 1, and 52 days for Part 2.

Data Monitoring Committee: No

1.2. Schema

A summary of the overall study design is presented in Figure 1.

Figure 1 Study Design Schematic



TBD = to be determined.

1. Exact dosing interval will be determined after interim analysis.

Note: Participants will be randomized in in a 14:3 ratio in order to obtain 12 evaluable participants on active treatment and 2 evaluable participants on placebo.

1.3. Schedule of Activities (SoA)

Table 1 Screening Visit - Parts 1 and 2

Procedure	Screening (up to 28 days before Day -1)
Outpatient visit	X
Informed consent/assent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination including height and weight[1]	X
Laboratory assessments (hematology, chemistry, urinalysis)	X
12-lead electrocardiogram	X
Vital sign measurements[2]	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Serum pregnancy test	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status; Part 1 only)	X
Drug, alcohol, and cotinine screen	X
HIV, Hepatitis B and C screening	X
Serious adverse event review	X

HIV = human immunodeficiency virus.

1 A full physical examination will include at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

2 Respiratory rate and oral temperature collected at Screening only.

Table 2 Schedule of Activities - Part 1 (Adult Participants)

Procedure[1]	Check -in	Treatment Period 1 (Days)				Treatment Period 2 (Days)				Treatment Period 3 (Days)			Follow-up (7 [±3] days after last dose) or Early Termination	Notes
	–1	1	2	3	4	5	6	7	8	9	10	11		
Confined to clinic	X	X	X	X	X	X	X	X	X	X	X	X		
Inclusion and exclusion criteria	X													Recheck clinical status before study intervention
Brief physical examination[2]	X											X	X	
Pregnancy test	X												X	Urine pregnancy test (if WOCBP), as appropriate (see Table 10)
Drug, alcohol, and cotinine screen	X													See Table 10
Laboratory assessments	X				X				X			X	X	Including serum chemistry, hematology, and urinalysis (see Appendix 2)
12-lead ECG[3]	X	X	X	X		X	X	X		X	X	X	X	See Table 3, Table 4, and Table 5 for timing of assessments

Procedure[1]	**Check -in**	**Treatment Period 1 (Days)**				**Treatment Period 2 (Days)**				**Treatment Period 3 (Days)**			**Follow-up (7 [±3] days after last dose) or Early Termination**	**Notes**
	–1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
ECG Holter monitoring[4]	X	X	X		X	X	X		X	X	X			See Table 3, Table 4, and Table 5 for timing of assessments
Vital signs	X	X	X	X		X	X	X		X	X	X	X	See Table 3, Table 4, and Table 5 for timing of assessments
Study intervention		X				X				X				See Table 3, Table 4, and Table 5 for time points
Blood collection for pharmacokinetics		X	X	X		X	X	X		X	X	X		See Table 3, Table 4, and Table 5 for time points
Urine collection for pharmacokinetics		X	X	X		X	X	X		X	X	X		See Table 3, Table 4, and Table 5 for time points
AE/SAE review	X	←==========											X	
Concomitant medication review	X	←==========											X	

AE = adverse event, ECG = electrocardiogram, SAE = serious AE; WOCBP = woman of childbearing potential.

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

2 A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

3 Triplicate 12-lead ECGs will be measured on Day -1.

4 ECG Holter monitoring will begin approximately 12 hours prior to first dose until 24 hours after first dose of each treatment period.

Table 3 Safety and PK Assessments - Part 1, Period 1 (Adult Participants)

Procedure[1]		**Treatment Period 1 Time point (hours)**													
	Predose	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Holter monitoring	X	X													
Vital signs	X				X	X			X		X	X	X	X	X
Study intervention		X													
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK collection[3]	X	X				X			X	X	X	X	X	X	X

ECG = electrocardiogram; PK = pharmacokinetic.

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

2 Triplicate 12-lead ECGs will be measured at predose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (predose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours.

Table 4 Safety and PK Assessments - Part 1, Period 2 (12-Hour Dose Interval, Adult Participants)

Procedure[1]	Treatment Period 2 Time point (hours)																							
	Predose	0	0.5	1	1.5	2	2.5	3	4	6	8	12	12.5	13	13.5	14	14.5	15	16	18	20	24	36	48	60
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Holter monitoring	X	X																							
Vital signs	X				X	X			X		X	X			X	X				X		X	X	X	X
Study intervention		X										X													
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK collection[3]	X	X				X			X	X	X	X				X			X	X	X	X	X	X	X

ECG = electrocardiogram; PK = pharmacokinetic.

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

2 Triplicate 12-lead ECGs will be measured at predose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (predose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 14 hours, 14 to 16 hours, 16 to 18 hours, 18 to 20 hours, 20 to 24 hours, 24 to 36 hours, 36 to 48 hours, and 48 to 60 hours.

Table 5 Safety and PK Assessments - Part 1, Period 3 (6-Hour Dose Interval, Adult Participants)

Procedure[1]	Treatment Period 3 Time point (hours)																						
	Predose	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**	**10**	**12**	**14**	**18**	**24**	**36**	**48**	**60**
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Holter monitoring	X	X																						
Vital signs	X				X	X			X				X	X			X		X	X	X	X	X	X
Study intervention		X								X														
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK collection[3]	X	X				X			X	X				X			X	X	X	X	X	X	X	X

ECG = electrocardiogram; PK = pharmacokinetic.

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

2 Triplicate 12-lead ECGs will be measured at predose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (predose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 10 hours, 10 to 12 hours, 12 to 14 hours, 14 to 18 hours, 18 to 24 hours, 24 to 36 hours, 36 to 48 hours, and 48 to 60 hours.

Table 6 Schedule of Activities - Part 2 (Adolescent Participants)

Procedure[1]	Check-in	Treatment Period 1 (Days)			Check-in[2]	Treatment Period 2 (Days)			Follow-up (7 [±3] days after last dose) or Early Termination	Notes
	–1	1	2	3	–1	1	2	3		
Confined to clinic	X	X	X	X[3]	X	X	X	X[3]		Treatment Period 1 and Treatment Period 2 may be separated by 7 days but no more than 10 days.
Inclusion and exclusion criteria	X				X					Recheck clinical status before study intervention
Brief physical examination[4]	X				X			X	X	
Pregnancy test	X				X				X	Urine pregnancy test (if WOCBP), as appropriate (see Table 10)
Drug, alcohol, and cotinine screen	X				X					See Table 10
Laboratory assessments	X			X	X			X	X	Including serum chemistry, hematology, and urinalysis (see Appendix 2)
12-lead ECG[5]	X	X	X	X	X	X	X	X	X	See Table 7, Table 8, and Table 9 for timing of assessments
ECG Holter monitoring[6]	X	X	X		X	X	X			See Table 7, Table 8, and Table 9 for timing of assessments
Vital signs	X	X	X	X	X	X	X	X	X	See Table 7, Table 8, and Table 9 for timing of assessments
Study intervention		X				X				See Table 7, Table 8, and Table 9 for time points
Blood collection for pharmacokinetics		X	X	X		X	X	X		See Table 7, Table 8, and Table 9 for time points

Procedure[1]	**Check-in**	**Treatment Period 1 (Days)**			**Check-in**[2]	**Treatment Period 2 (Days)**			**Follow-up (7 [±3] days after last dose) or Early Termination**	**Notes**
	–1	**1**	**2**	**3**	**–1**	**1**	**2**	**3**		
Urine collection for pharmacokinetics		X	X	X		X	X	X		See Table 7, Table 8, and Table 9 for time points
AE/SAE review	X	←==========→							X	
Concomitant medication review	X	←==========→							X	

AE = adverse event, ECG = electrocardiogram, SAE = serious AE; WOCBP = woman of childbearing potential.

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

2 Check-in procedures only necessary if participant leaves the clinic between Treatment Period 1 and Treatment Period 2.

3 Participants may be discharged from the clinic after the Hour 48 assessments.

4 A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

5 Triplicate 12-lead ECGs will be measured on Day -1 (before each treatment period).

6 ECG Holter monitoring will begin approximately 12 hours prior to first dose until 24 hours after first dose of each treatment period.

Table 7 Safety and PK Assessments - Part 2, Period 1 (Adolescent Participants)

Procedure[1]		Treatment Period 1 Time point (hours)													
	Predose	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Holter monitoring	X	X													
Vital signs	X				X	X			X		X	X	X	X	X
Study intervention		X													
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK collection[3]	X	X				X			X	X	X	X	X	X	X

ECG = electrocardiogram; PK = pharmacokinetic.

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

2 Triplicate 12-lead ECGs will be measured at predose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (predose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours.

Note: The number of PK samples and the PK sampling time points may be modified based on the adult PK data from Part 1.

Table 8 Safety and PK Assessments - Part 2, Period 2 (if 6-hour dose interval is selected, Adolescent Participants)

Procedure[1]	Treatment Period 2 Time point (hours)																					
	Predose	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**	**10**	**12**	**14**	**18**	**24**	**36**	**48**
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Holter monitoring	X	X																					
Vital signs	X				X	X			X				X	X			X		X	X	X	X	X
Study intervention		X								X													
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK collection[3]	X	X				X			X	X				X			X	X	X	X	X	X	X

ECG = electrocardiogram; PK = pharmacokinetic.

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

2 Triplicate 12-lead ECGs will be measured at predose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (predose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 10 hours, 10 to 12 hours, 12 to 14 hours, 14 to 18 hours, 18 to 24 hours, 24 to 36 hours, and 36 to 48 hours.

Note: The number of PK samples and the PK sampling time points may be modified based on the adult PK data from Part 1.

Table 9 Safety and PK Assessments - Part 2, Period 2 (if 12-hour dose interval is selected, Adolescent Participants)

Procedure[1]	Treatment Period 2 Time point (hours)																							
	Predose	0	0.5	1	1.5	2	2.5	3	4	6	8	12	12.5	13	13.5	14	14.5	15	16	18	20	24	36	48
12-lead ECG[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Holter monitoring	X	X																						
Vital signs	X				X	X			X		X	X			X	X				X		X	X	X
Study intervention		X										X												
Blood PK sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK collection[3]	X	X				X			X	X	X	X				X			X	X	X	X	X	X

ECG = electrocardiogram; PK = pharmacokinetic.

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

2 Triplicate 12-lead ECGs will be measured at predose. Single 12-lead ECGs will be measured at all other time points.

3 Urine collection intervals include 0 (predose), 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 14 hours, 14 to 16 hours, 16 to 18 hours, 18 to 20 hours, 20 to 24 hours, 24 to 36 hours, and 36 to 48 hours.

Note: The number of PK samples and the PK sampling time points may be modified based on the adult PK data from Part 1.

- In Part 2, Period 2, the timing and number of planned study assessments, including safety, pharmacokinetic (PK), or other assessments may be altered during the course of the study based on data from Part 1 (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 as the result of emerging PK data from Part 1 must be documented and approved by the GlaxoSmithKline (GSK) study team and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF)/assent. The changes will be approved by the competent authorities (CA) and the ethics committee (EC) before implementation.

2. INTRODUCTION

Gepotidacin (GSK2140944) is a first in class, novel triazaacenaphthylene antibacterial that inhibits bacterial type II topoisomerases. It has activity versus key pathogens, including drug-resistant strains associated with a range of conventional and biothreat infections and is being developed with intravenous (IV) and oral formulations.

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

2.1. Study Rationale

Single oral doses of gepotidacin (1500 and 3000 mg) were given to patients with gonorrhea in a completed Phase II study, and both doses achieved >95% efficacy; however, in vitro data and pharmacokinetic (PK)/pharmacodynamic modeling revealed that a higher dose would prevent the development of resistance and cover organisms with higher minimum inhibitory concentration (MIC).

The selected total daily dose for gonorrhea is 6000 mg delivered as two 3000 mg doses given either 6 or 12 hours apart in order to keep Cmax under a threshold of 14 µg/mL to mitigate the occurrence of adverse events (AEs) due to acetylcholinesterase (AChE) inhibition (mild and transient AEs of increased salivation, blurred vision, and slurred speech were observed following high IV doses as a 1 or 2 hour infusion during a previous study).

Although total daily oral 6000 mg doses have been given to healthy participants and patients as 2000 mg three times daily (TID) for up to 14 days and daily IV 4500 mg (equivalent to 9180 mg oral dose and based on absolute bioavailability of 46%) doses have been given to healthy participants as TID regimen for up to 10 days, the safety and PK of two 3000 mg doses given either 6 or 12 hours apart have not been characterized previously and gepotidacin has not been administered previously to adolescents. Therefore, this study will support inclusion of adolescents with a body weight ≥40 kg in future Phase III studies and will provide the safety and PK data of two 3000 mg doses separated by the selected dose intervals in Part 1 and Part 2.

2.2. 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.

A detailed description of the chemistry, pharmacology, efficacy, and safety of gepotidacin is provided in the Investigator's Brochure [GlaxoSmithKline Document Number CM2010/00033/06].

2.3. 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.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) Gepotidacin		
Gastrointestinal (GI) Effects Based on nonclinical data, gastrointestinal effects were mild ulceration of the nonglandular mucosa and minimal erosion and/or mural inflammation of the glandular mucosa in stomach (rat, oral study); moderate cecal ulceration and minimal colonic erosion (rat, IV study); and vomiting (dog). Lower gastrointestinal effects (soft stools, flatulence, and diarrhea) are among the most common AEs reported in gepotidacin clinical studies.	Gastrointestinal effects observed in gepotidacin clinical studies, both Phase I studies and the Phase II ABSSSI study, included diarrhea (very common, ≥10%) and flatulence (common; ≥1% and <10%); all nonserious and mild in severity (see Section 6 of the Investigator's Brochure). In the Phase II urogenital gonorrhea study, the most frequently reported gastrointestinal AEs overall were diarrhea, flatulence, abdominal pain, and nausea. Comparing the treatment groups, the incidence of diarrhea and nausea was higher in the 3000-mg treatment group and incidence of flatulence was higher in the 1500-mg treatment group. Few occurrences of *Clostridium difficile* have been reported in clinical studies (see Section 6 of the IB). Of the 282 healthy participants in Phase I studies who have received gepotidacin, *C. difficile* was reported in 8 participants, including 2 elderly participants in association with soft stools or diarrhea. In the Phase I renal impairment and hepatic impairment studies and in the Phase II ABSSSI, urogenital gonorrhea, and uUTI studies, no cases of *C. difficile*-associated diarrhea were reported.	Exclusion criterion and close monitoring of clinical parameters and AEs will be conducted to mitigate and assess GI effects. Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Appendix 7. Participant evaluation criteria: Participants experiencing Grade 3 or Grade 4 AEs will be followed as appropriate until resolution of the AE (see Section 7.1.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. No changes in QRS or QTc of clinical concern have been seen in the clinic (Phase I studies, including renal impairment and hepatic impairment studies, and Phase II ABSSSI and uUTI [acute cystitis] studies) (see Section 6 in the IB). There were electrocardiographic changes noted in a Phase I hepatic impairment study. The majority of participants with severe hepatic impairment had both predose and maximum postdose ECG parameter QTcB and QTcF values of <450 to ≤479 msec throughout the study. Cardiovascular events reported in the Phase II urogenital gonorrhea study were ECG ST segment elevation and palpitations (1 participant each) in the 1500-mg treatment group and tachycardia (1 participant) in the 3000-mg treatment group.	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 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 7.1.2).
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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Rash/Hypersensitivity	A fine, mild, generalized pruritic macular skin rash was seen in 3 of 6 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 7.1.4).

bpm = beats per minute; ABSSSI = acute bacterial skin and skin structure infection; AE = adverse event; Cmax = maximum concentration; ECG = electrocardiogram; IB = Investigator's Brochure; IV = intravenous; ΔΔQTcF = placebo-corrected change-from-baseline in corrected QT interval using the Fridericia formula; QTc = corrected QT interval; QTcB = QT interval corrected for heart rate according to Bazett; QTcF = interval corrected for heart rate according to Fridericia; uUTI = uncomplicated urinary tract infection.

2.3.2. Benefit Assessment

Since this Phase I study is being conducted in healthy adult and adolescent participants, 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.

2.3.3. Overall Benefit: Risk Conclusion

The risk of 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.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Part 1 • To evaluate the pharmacokinetics of a single 1500-mg dose and two 3000-mg doses of gepotidacin given 6 and 12 hours apart in adult participants	1500 mg Single Dose • Plasma gepotidacin AUC(0-t), AUC(0-∞), AUC(0-24), AUC(0-48), and Cmax, as data permit 3000 mg Two Doses • Plasma gepotidacin AUC(0-t), AUC(0-τ), AUC(0-24), AUC(0-48), Ro (accumulation ratio), and Cmax, as data permit
Part 2 • To evaluate the pharmacokinetics of a single 1500-mg dose and two 3000-mg doses of gepotidacin given at a dosing interval (to be determined) in adolescent participants	1500 mg Single Dose • Plasma gepotidacin AUC(0-t), AUC(0-∞), AUC(0-24), AUC(0-48), and Cmax, as data permit 3000 mg Two Doses • Plasma gepotidacin AUC(0-t), AUC(0-τ), AUC(0-24), AUC(0-48), Ro (accumulation ratio), and Cmax, as data permit
Parts 1 and 2 • To assess the safety of gepotidacin in adult participants and adolescent participants	• Adverse events, clinical laboratory tests, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead electrocardiogram readings

Objectives	Endpoints
Secondary	
Part 1 • To assess the urine pharmacokinetics of gepotidacin following a single 1500-mg dose and two 3000-mg doses of gepotidacin given 6 and 12 hours apart in adult participants	• Urine endpoints include Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit
Part 2 • To assess the urine pharmacokinetics of gepotidacin following a single 1500-mg dose and two 3000-mg doses of gepotidacin given at a dosing interval (to be determined) in adolescent participants	• Urine endpoints include Ae total, Ae(t1-t2), AUC(0-τ), AUC(0-24), AUC(0-48), fe%, and CLr of gepotidacin, as data permit
Parts 1 and 2 • To assess the plasma pharmacokinetics of gepotidacin	• Plasma gepotidacin Tmax, tlag, and t1/2, as data permit

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I, double-blind, single-center, randomized, sequential, two-part study. Part 1 is being conducted to evaluate the PK of the gepotidacin tablets in healthy adult participants. Part 2 will evaluate the PK of the gepotidacin tablets in healthy adolescent participants.

Part 1: Pharmacokinetics in Healthy Adult Participants

Part 1 is a 3-period, fixed-sequence study that will assess the PK of a single 1500-mg dose (Period 1) and two 3000-mg doses of gepotidacin at Hours 0 and 12 (Period 2) and Hours 0 and 6 (Period 3) in healthy adult participants.

Participants will be randomly assigned to receive either all active treatment (gepotidacin) or placebo for all 3 periods. Approximately 17 participants will be randomized (in a 14:3 ratio) to receive a single dose of gepotidacin 1500 mg (Treatment A) or matching placebo (Treatment B) in Period 1, gepotidacin 3000 mg separated by 12 hours (Treatment C) or matching placebo (Treatment D) in Period 2, and gepotidacin 3000 mg separated by 6 hours (Treatment E) or matching placebo (Treatment F) in Period 3 to obtain 12 evaluable participants on active treatment and 2 evaluable participants on placebo.

Participants will participate in 3 treatment periods, and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the Schedule of Activities (SoA; see Section 1.3).

This will be a two-part study in which the PK and safety data will be reviewed after completion of Part 1 before enrolling participants into Part 2. The dosing interval in Part 2, Period 2 will be based on the PK, safety, and tolerability data from Part 1.

Part 2: Pharmacokinetics in Healthy Adolescent Participants

Part 2 is a 2-period, fixed sequence study that will assess the PK of a single 1500-mg dose (Period 1) of gepotidacin and two 3000-mg doses (Period 2) of gepotidacin in healthy adolescent participants. The two 3000-mg doses will be separated by a time interval that will be determined based on data from Part 1. The number of PK samples and the PK sampling time points may be modified based on the adult PK data from Part 1.

Participants will be randomly assigned to receive either all active treatment (gepotidacin) or placebo for both periods. Approximately 17 participants will be randomized (in a 14:3 ratio) to receive a single dose of gepotidacin 1500 mg (Treatment A) or matching placebo (Treatment B) in Period 1 and gepotidacin 3000 mg (Treatment G) or matching placebo (Treatment H) in Period 2 to obtain 12 evaluable participants on active treatment and 2 evaluable participants on placebo.

The interval for the two 3000-mg doses in Period 2 will be between 6 hours and 12 hours based on the PK and safety results from Part 1.

Participants will participate in 2 treatment periods, and blood and urine samples will be collected for PK analysis of gepotidacin concentrations according to the SoA (see Section 1.3).

For Part 2 only, there may be a 7-day interval between doses in Period 1 and Period 2 to accommodate the adolescent population school schedule. Treatment Period 1 and Treatment Period 2 may be separated by no more than 10 days.

4.2. Scientific Rationale for Study Design

Although total daily oral 6000 mg doses have been given to healthy participants and patients as 2000 mg TID for up to 14 days and daily IV 4500 mg (equivalent to 9180 mg oral dose and based on absolute bioavailability of 46%) doses have been given to healthy participants as TID regimen for up to 10 days, the safety and PK of two 3000 mg doses given either 6 or 12 hours apart have not been characterized previously and gepotidacin has not been administered previously to adolescents; this study will support inclusion of adolescents with a body weight ≥40 kg in future Phase III studies and will provide the safety and PK data of two 3000 mg doses separated by the selected dose intervals in Part 1 and Part 2.

Both adult and adolescent (≥12 to <18 years of age) eligible participants will be enrolled in this double-blinded study. Adolescent participants will only be enrolled if allowed per the study site's IRB and national regulatory guidelines, and enrollment will be contingent upon such approvals. Adolescent assent forms and adult consent forms will be developed with oversight from local governing IRB (see Appendix 3).

Part 1 is being conducted to evaluate the pharmacokinetics, safety, and tolerability of the gepotidacin tablet.

Part 2 will evaluate the pharmacokinetics, safety, and tolerability of the gepotidacin tablet in adolescent participants. Testing gepotidacin in this specific population will provide PK, safety, and tolerability information needed for their inclusion in future pivotal Phase III studies.

4.3. Justification for Dose

Selection of dose and dosing frequency for this study is justified based on observed safety efficacy and PK data following single oral dosing (1500 to 3000 mg), repeat oral twice daily (BID; 1500 to 2300 mg) and TID dosing (1500 to 2000 mg) in previous studies. In addition, exposures higher than anticipated in this study were achieved following single IV dosing of 1800 mg equivalent to an oral dose of 3913 mg (absolute bioavailability is 46%) and repeat IV dosing of 1500 mg TID for 10 days (equivalent to an oral daily dose of approximately 9180 mg).

Based on PK modeling, gepotidacin will be administered for gonorrhea as two single oral 3000-mg doses, given either 6 or 12 hours apart with a minimum body weight of 40 kg, to provide higher daily systemic exposures that allow coverage of *Neisseria gonorrhoeae* isolates with higher gepotidacin MIC values, which are likely to be observed in the global Phase III study and reduce the risk of resistance emergence. Less than 3% of the population is expected to exceed the Cmax threshold of 14 µg/mL.

In the current study, gepotidacin will be administered as a single oral 1500-mg dose and 2 oral 3000-mg doses. The two 3000-mg doses, given either 6 or 12 hours apart in Part 1 and at the selected dose interval in Part 2, compared with the single 1500-mg dose, are expected to provide valuable PK and safety data to guide Phase III studies and the prescribing information for the gepotidacin tablet.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the final date on which data were or are expected to be collected.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled visit shown in the SoA (see Section 1.3) for the last participant in the study.

5. STUDY POPULATION

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

If participants prematurely discontinue the study, additional replacement participants may be recruited at the discretion of the sponsor in consultation with the investigator. Replacement participants will be assigned to the same randomization sequence as the participant who discontinued.

5.1. Inclusion Criteria

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

Age

1. Participant in Part 1 must be ≥18 to ≤64 years of age inclusive, at the time of signing the informed consent.
2. Participant in Part 2 must be ≥12 to <18 years of age inclusive, at the time of signing the informed consent/assent.

Type of Participant and Disease Characteristics

3. Participants who are healthy as determined by the investigator or medically qualified designee based on medical evaluation including medical history, physical examination, clinical laboratory tests, vital sign measurements, and 12-lead electrocardiogram (ECG) results <450 millisecond (msec). A participant with clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the investigator feels and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

4. Body weight ≥40 kg and body mass index (BMI) within the range 18.5 – 32.0 kg/m^2 (inclusive).

Sex

5. Male and/or female

a. Female Participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 5 for at least 30 days prior to dosing until completion of the Follow-up Visit. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a highly sensitive negative pregnancy test before the first dose of study intervention.

Informed Consent

6. Capable of giving signed informed consent/assent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the ICF/assent and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Clinically significant abnormality in the past medical history or at the Screening physical examination 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 cardiac, hepatic, renal, neurologic, gastrointestinal (GI), respiratory, hematologic, or immunologic disease.
2. Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study intervention, 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. Use of any systemic antibiotic within 30 days of Screening.
5. Within 2 months before Screening, either a confirmed history of *Clostridium difficile* diarrhea infection or a past positive of *C. difficile* toxin test.
6. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
7. History of drug and/or alcohol abuse within 6 months before Screening, as determined by the investigator, or has a positive drug screen at Screening or upon admission to the clinic.
8. History of sensitivity to any of the study drug, components thereof, or a history of drug or other allergy that, in the opinion of the investigator or GSK medical monitor contraindicates their participation.
9. History of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinic uses heparin to maintain intravenous cannula patency).

Prior/Concomitant Therapy

10. Participants must abstain from taking prescription or nonprescription drugs (except for hormonal contraceptives and/or acetaminophen), vitamins, and dietary or herbal supplements, unless specified in Section 6.5, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to study intervention 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 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 starting study intervention.
12. Participant has participated in a clinical trial and has received an investigational product prior to gepotidacin administration within 30 days, 5 half-lives, or twice the duration of the biological effect of investigational product (whichever is longer).

Diagnostic assessments

13. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention.
14. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN).
15. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. History of any kidney disease or current or chronic history of impaired renal function as indicated by an estimated creatinine clearance <60 mL/min.
17. A positive test for human immunodeficiency virus antibody.
18. History of regular alcohol consumption within 6 months of screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full strength beer, 470 mL of light beer, 30 mL of spirits, or 100 mL of wine.
19. Urinary cotinine level indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months before Screening.
20. Clinically significant abnormal findings in serum chemistry, hematology, or urinalysis results obtained at Screening or Day -1.
21. Baseline corrected QT interval using the Fridericia formula (QTcF) of >450 msec.

Other Exclusions

22. Participant has donated 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.

23. Participant is unable to comply with all study procedures, in the opinion of the investigator.
24. Participant should not participate in the study, in the opinion of the investigator or sponsor.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- All doses of study intervention (gepotidacin or placebo) should be after food consumption (a standard meal) and with approximately 240 mL of water. Up to 480 mL of water is allowed if the participant has difficulty swallowing multiple tablets.
- Prior to the morning dose, participants will fast (no food or drink except water) for approximately 8 to 10 hours before dosing and will receive a standard meal 30 minutes prior to dose. Participants should consume this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 2 hours after dosing. Standard meals will be provided during the study treatment period at times that do not interfere with study procedures.
- For doses scheduled to occur 6 or 12 hours after the initial dose, participants will have the standard meal in the morning and will receive another standard meal (similar in calorie content and similar ratios of protein, carbohydrates, and fat as the previous meal) prior to the second dose. Participants should consume this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 2 hours after dosing.
- 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.
- No water is allowed until 2 hours after dosing, unless administered under the investigator's direct order for treatment of an AE. Water is allowed ad libitum at all other times.
- Standard meals will be provided during the study dosing period at specified times.

5.3.2. 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.
- Use of tobacco products will not be allowed from 3 months before Screening until after the final Follow-up visit.

5.3.3. 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 the study (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled 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, any protocol deviations, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants should be assigned a new participant number for every screening/re-screening event.

6. STUDY INTERVENTION

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

6.1. Study Interventions Administered

Intervention Name	Gepotidacin Tablets, 750 mg	Placebo (Matched to Gepotidacin Tablets)
Type	Tablets containing gepotidacin mesylate (GSK2140944E) and inactive formulation excipients	Unit-dose gepotidacin placebo-to-match tablet
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	750 mg	Not applicable
Dosage Level(s)	Part 1, Period 1: 2 x 750 mg single dose Each dose should be taken after food consumption and with water Part 1, Periods 2 and 3: 4 x 750 mg two doses given either 6 or 12 hours after first dose (6000 mg total daily dose) Each dose should be taken after food consumption and with water Part 2, Period 1: 2 x 750 mg single dose Each dose should be taken after food consumption and with water Part 2, Period 2: 4 x 750 mg two doses given at an interval to be determined after review of safety and PK data from Part 1 (6000 mg total daily dose) Each dose should be taken after food consumption and with water	Part 1, Period 1: Administer 2 tablets as a single dose Each dose should be taken after food consumption and with water Part 1, Periods 2 and 3: Administer 4 tablets (two doses); second dose given either 6 or 12 hours after first dose Each dose should be taken after food consumption and with water Part 2, Period 1: Administer 2 tablets as a single dose Each dose should be taken after food consumption and with water Part 2, Period 2: Administer 4 tablets (two doses) given at an interval to be determined after review of safety and PK data from Part 1 Each dose should be taken after food consumption and with water

Route of Administration	Oral	Oral
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Gepotidacin will be provided in high-density polyethylene (HDPE) bottles. Each bottle will be labeled as required per country requirement.	Placebo will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention 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 intervention are provided in the Study Reference Manual (SRM).

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study. The study treatment taken during the study will be double-blind. An unblinded pharmacist will dispense study intervention. Neither the participant nor immediate study personnel (i.e., investigators, PPD staff) will know which study treatment the participant is receiving. Participants who are randomly assigned to receive placebo will receive a matching placebo form of the active treatment. The matching placebos will look identical to the active form.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

In Part 1 and Part 2, participants will be randomized in a 14:3 ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

Unblinded monitors and in the event of a quality assurance audit, the auditor will be allowed access to unblinded study intervention records at the site to verify that randomization/dispensing has been done accurately.

A participant will be withdrawn if the participant's intervention code is unblinded by the investigator. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

To protect the safety of participants, GSK safety medical monitor may remain unblinded to participant treatment throughout the study and will monitor safety data in real time.

Limited members of GSK staff (e.g., statistician, pharmacokineticist, and medical monitor) will be unblinded to study treatment at the end of Part 1 in order to determine which dosing frequency to take forward to Part 2.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study Intervention 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 study site staff.
- When participants are dosed at the site, they will receive study intervention 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 intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. 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.

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

Hormonal contraceptives and/or acetaminophen, at doses of ≤2 grams/day, are 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.

6.6. Dose Modification

The interval for the two 3000-mg doses in Part 2, Period 2 will be between 6 hours and 12 hours based on the PK and safety results from Part 1.

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from GSK (gepotidacin or placebo) after completion of the study because only healthy participants are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

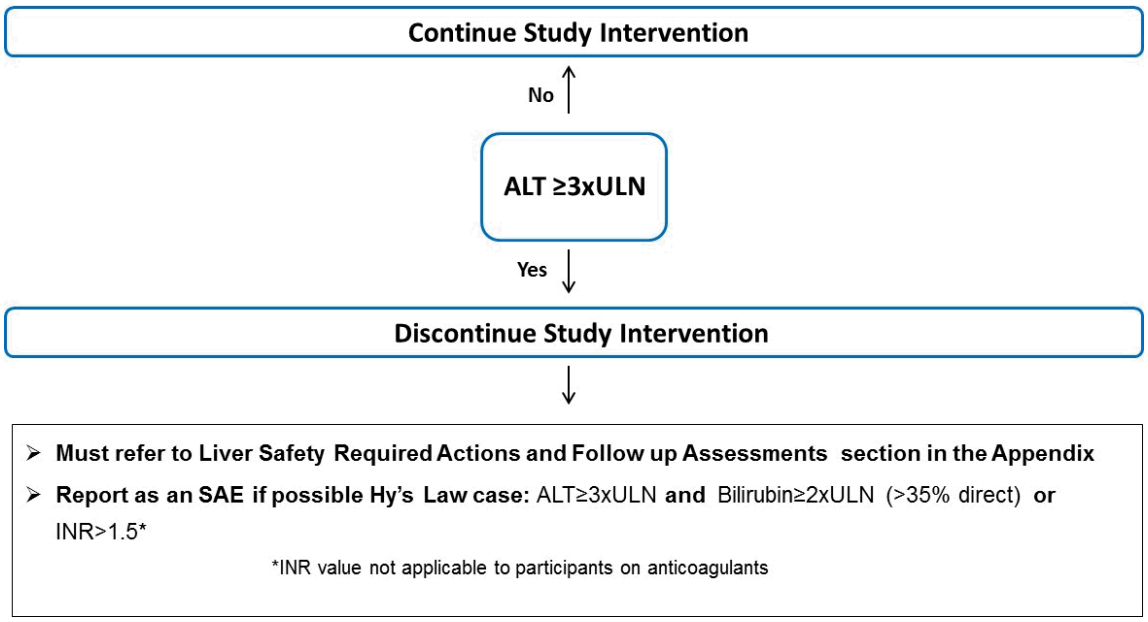
7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA (see Section 1.3) for data to be collected at the time of discontinuation of study intervention.

7.1.1. Liver Chemistry Stopping Criteria

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Appendix 6 for required Liver Safety Actions and Follow-up Assessments.

7.1.2. QTc Stopping Criteria

A participant who meets the following bulleted criteria based on triplicate ECG readings will be withdrawn from study treatment:

- Corrected QT (QTc) >500 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle-branch block, follow the discontinuation criteria listed below:

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

- 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 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 ECG readings obtained over a brief (e.g., 5 to 10 minute) recording period.

See the SoA (see Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.3. Gastrointestinal Evaluation Criteria

If a participant meets the criteria in Appendix 7, *C. difficile* toxin testing should be conducted.

7.1.4. 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).

7.2. Participant Discontinuation/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.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (see Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

7.3. 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 3.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (see Section 1.3).
- 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 intervention.
- 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/assent 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.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.2.1. Physical Examinations

- A full 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.

8.2.2. 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. Oral temperature and respiratory rate will be collected at Screening only. Each measurement will be recorded in the eCRF.

8.2.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- Twelve-lead ECGs will be performed with the participant in a semi-supine position after a rest of at least 10 minutes.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession but no more than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5 to 10 minutes) recording period.
- ECG Holter monitoring will be obtained as outlined in the SoA (see Section 1.3). The Holter monitoring data will be sent to GSK and may be analyzed at a later date.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (see Section 1.3) 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 that 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 participation in the study or 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 2, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any qualified 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 intervention or the study, or that caused the participant to discontinue the study (see Section 7).

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

- All SAEs will be collected from the signing of the ICF/assent until the Follow-up Visit at the time points specified in the SoA (see Section 1.3).
- All AEs will be collected from the start of intervention until the Follow-up Visit at the time points specified in the SoA (see Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of 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 4. 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 after the conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- 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 4.
- 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.

8.3.3. 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 2.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an 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.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention 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 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

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

GlaxoSmithKline does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AEs/SAEs 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 intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

8.5. Pharmacokinetics

- The PK blood and urine samples will be collected for measurement of plasma and urine concentrations of gepotidacin at the time points indicated in the SoA (see Section 1.3). The volume of blood required for each PK sample is approximately 3 mL for Part 1, and approximately 2 mL for Part 2. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- Processing, storage, and shipping procedures for blood and urine samples are provided in the SRM and/or laboratory manual.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no formal research hypothesis that will be statistically tested in this study.

9.2. Sample Size Determination

The PK parameter sample size for this study was based on feasibility; however, justification has been considered. For the 1500 mg single-dose regimen, the closest reference study was BTZ116778, with 1500 mg oral dose (immediate-release capsule) taken in fed state, resulting in a coefficient of variation (CV) for AUC(0-∞) and Cmax of 21.5% and 40.3% respectively. Precision has been evaluated for a range of plausible sample sizes of 10, 12, and 15 participants exposed to the active dose (see table). The precision of sample size of 12 is deemed sufficient for the primary PK endpoint in this study. With 12 participants, the upper limit of the 95% confidence interval for AUC(0-∞) and Cmax will be approximately 14.5% and 28.0% above the geometric means, respectively.

There were 2 studies similar to the 3000 mg BID (at 6- or 12-hour intervals) dosing regimen. BTZ114595 studied PK profile after a 3000 mg single dose in the fasted state, with CV for AUC(0-∞) and Cmax being 31.5% and 36.0%, respectively. BTZ116576 studied the 2-hour postdose concentration following a 3000 mg single dose in the fed state, with CV for the concentration being 42.9%. The estimate of AUC(0-∞) CV was higher after 3000 mg than the 1500 mg dose; however, AUC(0-∞) appeared less variable than Cmax consistently across doses, indicating that Cmax should be the main

consideration for precision. Despite slight differences in dosing regimens, both 3000 mg single-dose studies indicated the variability of Cmax approximately 40%, consistent with that of the 1500 mg single dose. Therefore, sample size justification for the 1500 mg single dose is also applicable for the 3000 mg dose.

	Distance from 95% CI Upper Limit to the Geometric Mean (given numbers of participants exposed to the active dose)		
	n=10	n=12	n=15
AUC (0-∞) CV=21.5%	16.4%	14.5%	12.5%
Cmax CV=40.3%	32.0%	28.0%	24.0%
CI = confidence interval; CV = coefficient of variation.			

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	**Description**
Enrolled	All participants who sign the ICF/assent.
Randomized	All participants who are randomized.
Safety	All participants who take at least 1 dose of study intervention. This population will be used for all demographic and safety summaries.
PK	Participants who receive at least 1 dose of gepotidacin and have evaluable postdose plasma concentration data for gepotidacin. This primary analysis population will be used in the assessment and characterization of PK concentrations (summary tables and figures).
PK Parameter	All participants in the PK population who received gepotidacin for whom valid and evaluable plasma PK parameters are derived for gepotidacin. This primary analysis population will be used in the assessment and characterization of PK parameters (summary and analysis tables and figures).

9.4. Statistical Analyses

9.4.1. Pharmacokinetic Analyses

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

Plasma:

AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of the last quantifiable concentration
AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
AUC(0-τ)	Area under the concentration-time curve from time 0 (predose) to time tau (tau = 12 and 6 for Part 1, Periods 2 and 3, respectively; for Part 2, tau will be between 6 and 12)
AUC(0-24)	Area under the concentration-time curve from time 0 (predose) to 24 hours postdose administration following the first dose
AUC(0-48)	Area under the concentration-time curve from time 0 (predose) to 48 hours postdose administration following the first dose
Cmax	Maximum observed concentration
Ro	Accumulation ratio, calculated as: Ro for AUC = AUC(0-6) after second 3000 mg dose divided by AUC(0-6) after the first 3000 mg dose Ro for Cmax = Cmax after second 3000 mg dose divided by Cmax after the first 3000 mg dose
t1/2	Terminal phase half-life
tlag	Lag time before observation of drug concentrations in sampled matrix
Tmax	Time to reach maximum observed plasma concentration

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 time intervals of predose, 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 36 hours, 36 to 48 hours, and 48 to 60 hours (Period 2 and Period 3) after dosing
AUC(0-τ)	Area under the concentration-time curve from time 0 (predose) to time tau (tau = 12 and 6 for Part 1, Periods 2 and 3, respectively;

	for Part 2, tau will be between 6 and 12)
AUC(0-24)	Area under the concentration-time curve from time 0 (predose) to 24 hours postdose administration following the first dose
AUC(0-48)	Area under the concentration-time curve from time 0 (predose) to 48 hours postdose administration following the first dose
fe%	Percentage of the given dose of drug excreted in urine, calculated as: fe% = (Ae total/Dose) × 100%
CLr	Renal clearance of drug, calculated as: Ae total/AUC(0-t)

Plasma 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 CV) will be presented by Study Part and treatment. Mean and individual plasma concentration versus time profiles will be presented graphically on linear and semilogarithmic scales.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical analysis of the safety data will be conducted.

The details of the statistical analyses of safety and PK data will be provided in the reporting and analysis plan (RAP).

9.4.3. Other Analyses

Not applicable.

9.5. Interim Analyses

Preliminary plasma PK and safety results from participants in Part 1 will be reviewed by the sponsor before enrolling participants into the next part of the study. The dosing interval to be used when two gepotidacin doses are given in Part 2, Period 2 will be determined after a review of the PK and safety results from Part 1. The number of PK samples and the PK sampling time points may be modified based on the adult PK data from Part 1.

An ad hoc review of 12-lead ECG data may be performed between Part 1, Period 2 and Part 1, Period 3.

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AChE	acetylcholinesterase
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 (predose) extrapolated to infinite time
AUC(0-24)	area under the concentration-time curve from time 0 (predose) to 24 hours post dose administration following the first dose (plasma or urine)
AUC(0-48)	area under the concentration-time curve from time 0 (predose) to 48 hours post dose administration following the first dose (plasma or urine)
AUC(0-t)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (plasma or urine)
AUC(0-τ)	area under the concentration-time curve from time 0 (predose) to time tau (plasma or urine)
BID	twice daily
BMI	body mass index
CA	Competent Authorities
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CLr	renal clearance of drug
Cmax	maximum observed concentration
CONSORT	Consolidated Standard of Reporting Trials
CV	coefficient of variation
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
fe%	percentage of the given dose of drug excreted in urine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GSK	GlaxoSmithKline
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act

HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
MIC	minimum inhibitory concentration
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
Ro	accumulation ratio
SAE	serious adverse event
SD	standard deviation
SoA	schedule of activities
SRM	Study Reference Manual
τ	tau is the dosing interval in hours
t1/2	terminal phase half-life
TID	three times daily
tlag	lag time before observation of drug concentrations
Tmax	time to reach maximum observed plasma concentration
ULN	upper limit of normal
uUTI	uncomplicated urinary tract infection
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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing should be conducted at the time points indicated in the SoA (see Section 1.3).
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 10 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count Red Blood Cell Count Hemoglobin Hematocrit	Red Blood Cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry [1]	Blood urea nitrogen Creatinine Glucose (fasting) Potassium Sodium Magnesium	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Total and direct bilirubin Creatine phosphokinase Calcium	Chloride Carbon dioxide Total protein Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood, leukocyte esterase, or protein is abnormal)		

Laboratory Assessments	Parameters
Other Screening Tests	• Serology: HIV-1 and -2 antigen/antibody immunoassay, Hepatitis B surface antigen (HBsAg), Hepatitis C (Hep C antibody) • Alcohol, cotinine, and drug screen (to include at minimum amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Pregnancy • Follicle-stimulating hormone • Fecal occult blood test and stool cultures as appropriate for gastrointestinal adverse events (Appendix 7).

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6. All events of ALT ≥3 ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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).

Laboratory results that could unblind the study will not be reported to the investigative site or other blinded personnel until the study has been unblinded.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. 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/assent form, 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/IEC
  - 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

10.3.2. Financial Disclosure

Investigators and subinvestigators 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.

10.3.3. Informed Consent/Assent 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.
- Adolescent participants should be asked for their written assent to participate in the study.
- As applicable, the IRB will be consulted before assent form development for guidance around age-appropriate groupings and any specific IRB requirements or local laws for conducting and documenting assent.
- 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.

10.3.4. 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.

10.3.5. 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.

10.3.6. 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.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.3.7. 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.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- 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/assent, 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/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.

10.3.8. 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.

10.3.9. 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 intervention development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical 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 intervention 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 intervention 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 NOT 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.

10.4.2. 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).

An SAE is defined as any untoward medical occurrence that, at any dose:
o Results in death
o 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.
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.
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.
Is a congenital anomaly/birth defect
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.

Cardiovascular and Gastrointestinal Adverse Events of Special Interest

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

Cardiovascular Events:	**Gastrointestinal Events:**
• Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization	• Nausea • Vomiting • Dysphagia • Abdominal pain • Diarrhea • Flatulence • Feces soft • Constipation

10.4.3. Recording and Follow-Up of 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 (see Appendix 8).

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 intervention 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 intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) 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.

10.4.4. 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 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 medical monitor by telephone.
- Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit

this information to the 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 in SRM.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

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

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the 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, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.

10.5.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
• Sexual abstinence • *Note: 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 intervention. 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.*
• **ACCEPTABLE METHODS[d]**
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.
e. Male condom and female condom should not be used together (due to risk of failure with friction).

10.5.3. 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 male participants who receive gepotidacin.
- 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.
- The female 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 for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 intervention by the investigator, will be reported to GSK as described in Appendix 4. 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.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

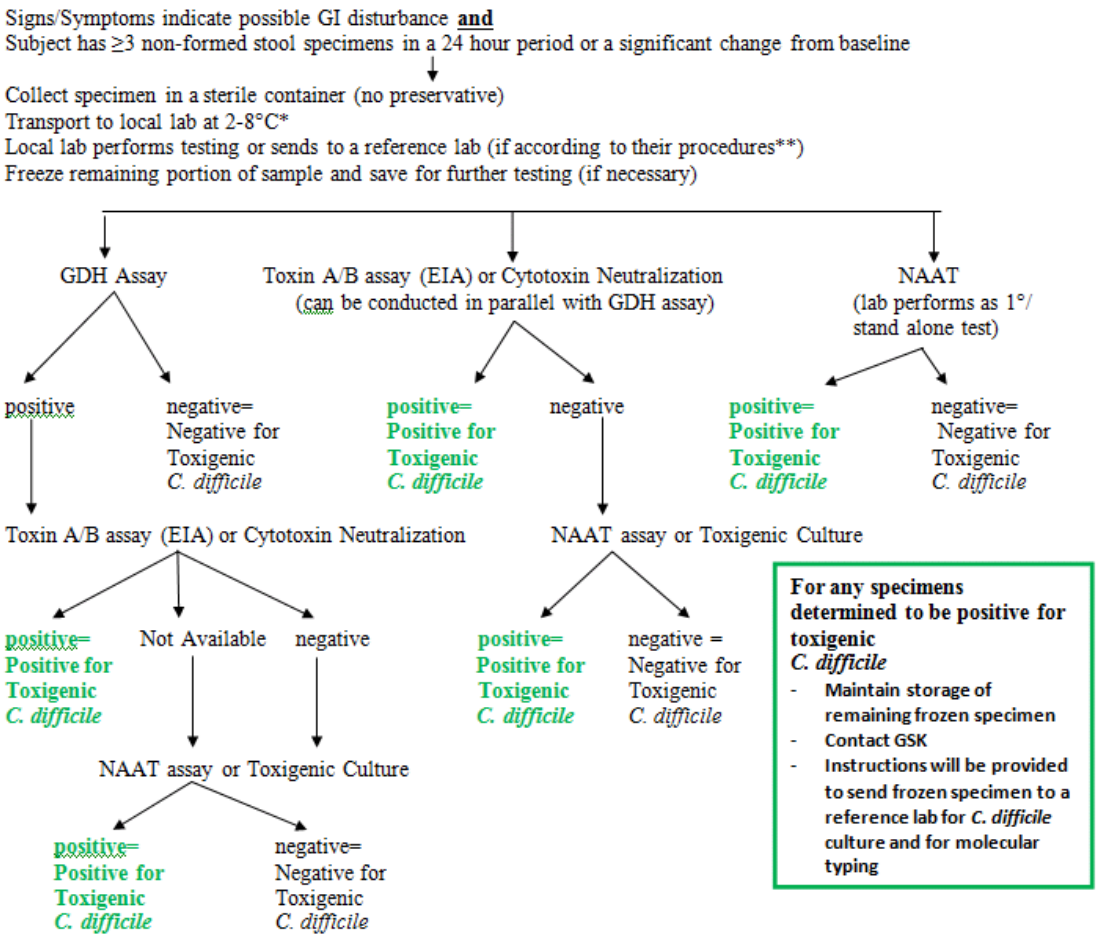
Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• 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, stabilize, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilize, or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR</td><td>• Viral hepatitis serology[3]
• Obtain international normalized ratio (INR) and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR</td></tr>
</table>

Liver Chemistry Stopping Criteria	
≤1.5:	**>1.5:**
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize, or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized 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 intervention for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. 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 ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible "Hy's Law"), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: Hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing), and Hepatitis E IgM antibody.
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.7. Appendix 7: *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

Note: This algorithm is subject to investigator discretion when the clinical presentation and time course of diarrhea (e.g., during or within 12 hours immediately after dosing) do not fit the Clostridium difficile associated diarrhea definition; consideration should be given to diarrhea occurring in this early time frame to be suggestive of a cholinergic effect.

10.8. Appendix 8: Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment

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

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

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

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the Division of Microbiology and Infectious Diseases (DAIDS) and modified to better meet the needs of participants in Division of Microbiology and Infectious Diseases (DMID) trials (November 2007).
- For parameters not included in the following Toxicity Tables, study sites should refer to the "Guide for Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.

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 /mm^3	750 to 999 /mm^3`	500 to 749 /mm^3	<500 /mm^3
Platelets	75,000 to 99,999 /mm^3	50,000 to 74,999 /mm^3	20,000 to 49,999 /mm^3	<20,000 /mm^3
White Blood Cells	11,000 to 13,000 /mm^3	13,000 to 15,000 /mm^3	15,000 to 30,000 /mm^3	>30,000 or <1000 /mm^3
% 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 mmHg systolic BP. No treatment required	Symptoms due to orthostatic hypotension or BP decreased by <20 mmHg systolic; correctable with oral fluid treatment	Requires IV fluids; no hospitalization required	Mean arterial pressure <60 mmHg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion; pain; EKG changes	Tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	Microscopic/occult	Mild, no transfusion	Gross blood loss; 1 to 2 units transfused	Massive blood loss; >3 units transfused

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

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

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

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

IV=intravenous.

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

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

ADL=activities of daily living.

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

N/A=not applicable.

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic reaction	Pruritus without rash	Localized urticarial	Generalized urticarial; angioedema	Anaphylaxis
Headache	Mild, no treatment required	Transient, moderate; treatment required	Severe; responds to initial narcotic therapy	Intractable; requires repeated narcotic therapy
Fever: oral	37.7 to 38.5°C or 100.0 to 101.5°F	38.6 to 39.5°C or 101.6 to 102.9°F	39.6 to 40.5°C or 103 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

11. REFERENCES

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